


**PUTTING A PAUSE
ON PELVIC PAIN:
NUTRITION AND
SUPPLEMENTAL
HIGHLIGHTS**

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NHAND 2020



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DISCLOSURES

- Has received compensation for occasional industry-sponsored webinars and educational presentations:
 - 2020: NutraBioceuticals, Gaia
- Co-principal for Thrivers, LLC, an educational company that hosts a weekly health and wellness radio show for consumers and which receives industry sponsorship
 - 2020: Kyowa Hakko, Dr Ohhria Probiotics, Hyatt Life Sciences
- Has received research funding:
 - Pharmavite (2020)

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TOPICS

- Quick overview of chronic pelvic pain pathways relevant to modification by nutrition and dietary supplements.
- Gain familiarity with core dietary approaches with evidence of pain modification effects.
- Explore the evidence for specific dietary supplements which may modify chronic pelvic pain.

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PELVIC PAIN: CENTRALIZED PAIN

- Chronic pelvic pain (continuous or intermittent pain x 3-6 months) affects 1 in 5 reproductive aged women.
- Pelvic pathology does not necessarily correlate with degree of pelvic pain.
- Central pain amplification is a component of chronic pelvic pain resulting in generalized heightened pain sensitivity (hyperalgesia)
 - Begins with persistent peripheral nociception (most commonly from **inflammation** or lesions) leading to:
 - **Hyperresponsiveness** of dorsal horn spinal neurons via N-methyl-D-aspartic (NMDA) receptors - and / or -
 - Upregulated nociceptive processing within the brain (**catastrophizing**)
- Evidence of pain centralization in women with chronic pelvic pain is high prevalence of co-morbid conditions:
 - headaches are found in over 50%
 - IBS, vulvodynia and/or chronic fatigue syndrome are found in 20%

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PAIN CENTRALIZATION IS AFFECTED BY MULTIPLE FACTORS

- Peripheral tissue injury or lesion leads to increased NGF and inflammatory mediators (ie TNF- α) which cause increased sensory nerve growth and sensitization.
- Pain ascends via spinal cord nociception
- Increased cognitive pain perception as well as impaired pain inhibition are influenced by central cortisol levels (HPA axis activation), mood-induced changes in neurotransmitters, overlay of cognitive reasoning, and genetics (e.g. polymorphisms in ANS receptors)

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SUMMATION MODEL FOR PELVIC PAIN

- Many patients with pelvic pathologies resulting in pain report symptom aggravation with consumption of certain foods
- This may be the result of **neuronal crosstalk between colon and pelvic organ**
- Spatial summation: **multiple sensory inputs are summed together within the CNS and perceived at a greater intensity than each stimulus alone.**
- Spatial summation and temporal summation (repetitive stimulation over time causes greater pain from otherwise nonpainful stimuli via peripheral and/or central sensitization) \rightarrow IC pain

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FACTORS ASSOCIATED WITH MORE SEVERE CHRONIC PELVIC PAIN

- Cross sectional data from prospective cohort of 656 premenopausal women <50y with chronic pelvic pain and/or endometriosis
- These factors contribute to pain by increasing inflammation and by influencing pain centralization

TABLE 6
Factors Independently associated with severity of chronic pelvic pain

Risk factors	b	95% CI	t Test	P
BMI ^a	0.05	0.01–0.09	2.28	.023
Abdominal wall pain ^b	0.77	0.23–1.31	2.81	.005
Pelvic floor (levator ani) tenderness ^b	0.76	0.24–1.29	2.66	.004
Pain Catastrophizing Scale ^b	0.05	0.03–0.07	5.37	<.001
Painful bladder syndrome ^b	0.57	0.09–1.04	2.35	.019
Smoking ^c	0.68	0.01–1.36	1.90	.049
Family history of chronic pain ^d	0.55	0.03–1.07	2.00	.038
History of adult sexual assault ^d	0.71	0.02–1.39	2.03	.043

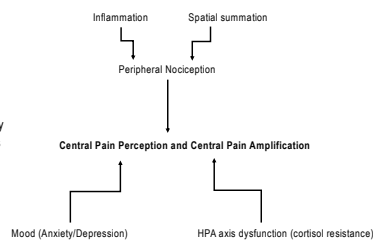
95% CI, 95% confidence interval.
^aContinuous variable. ^bBinary variable (yes vs no). ^cBinary variable (yes vs other, see "Materials and Methods").
^dYusef et al. Severity of chronic pelvic pain. Am J Obstet Gynecol 2016.

Yusef A, et al. Am J Obstet Gynecol. 2016;215(6):760.e1-14

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NUTRITIONAL PAIN TARGETS

- Anti-inflammation to reduce peripheral pain sensitization
- Address spatial summation, specifically gut-induced pain stimulation as well as pain from pelvic organ pathology
- Reduce anxiety and depression
- Address HPA axis dysfunction



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ANTI-INFLAMMATION (REDUCE PERIPHERAL NOCICEPTION)

- Anti-inflammatory diet
- Flavonoids
- Diet & Endometriosis
- Diet & Dysmenorrhea
- Obesity, Inflammation & Diet

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ANTI-INFLAMMATORY DIET

- The anti-inflammatory (AI) diet is an eating pattern that is associated with reduced chronic inflammation.
- In contrast to the standard Western diet which is replete with foods high in:
 - saturated fatty acids
 - trans fatty acids
 - sodium
 - refined carbohydrates
 - ultra-processed foods
- the AI diet is high in:
 - monounsaturated and omega-3 polyunsaturated fatty acids from marine sources and nuts
 - vegetable and seed fiber
 - legumes
 - whole grains
 - lean protein
 - spices

Wilcox DC, et al. Mech Ageing Dev. 2014;136-137:148 10

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ANTI-INFLAMMATORY DIET PYRAMID

The pyramid is divided into several sections with the following labels and descriptions:

- RED WINE**: 1-2 glasses a day
- TEA**: 2-3 cups a day
- HEALTHY SWEETS**: 1-2 squares a day
- OTHER SOURCES OF PROTEIN**: 1-2 servings a day (e.g., eggs, tofu, poultry, fish, beans)
- EDIBLE ASIAN MUSHROOMS**: 1-2 servings a day
- WHOLE-BODY FOODS**: 1-2 servings a day (e.g., nuts, seeds, whole grains)
- FISH & SHELLFISH**: 1-2 servings a week
- HEALTHY FATS**: 1-2 servings a day (e.g., olive oil, avocado, nuts)
- VEGETABLES**: 3-4 servings a day
- WHOLE & CRACKED GRAINS**: 3-4 servings a day
- PASTA**: 1-2 servings a day
- BEANS & LEGUMES**: 1-2 servings a day
- FRUITS**: 2-3 servings a day

<https://www.drweil.com/diet-nutrition/anti-inflammatory-diet-pyramid/dr-weils-anti-inflammatory-food-pyramid/> 11

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ANTI-INFLAMMATORY EFFECTS: MEDITERRANEAN DIET + OLIVE OIL

- In a controlled study, randomly assignment of 112 older subjects with diabetes or > or =3 CVD risk factors to 3 dietary intervention groups:
 - Med-Diet with supplemental virgin olive oil (VOO)
 - Med-Diet with supplemental nuts
 - Low-fat diet
- One hundred six participants (43% women; average age: 68 y) completed the 3 mo. study.
- C-reactive protein decreased only after the Med-Diet with Virgin Olive Oil (P < 0.05)

Mena et al. Am J Clin Nutr. 2009;89(1):248. 12

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FLAVONOIDS: KEY ANTI-INFLAMMATORY COMPONENTS OF AI DIET

Flavonoids

Surb Y.J. Journal Nutr. 2005;135: 2993S-3001S.

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FLAVONOIDS INHIBIT NF-KB & PRO-INFLAMMATORY CYTOKINES

- **Flavonoids (all)**: NF-kB and AP-1 mediate the expression of cytokines and cell studies have found flavonoids to inhibit NFkB by 43%-69%
- **Quercetin [onions, apples]**: reduces IL-1, IL-6, IFN-gamma and TNF-alpha in LPS stimulated macrophages (150mg x 6 weeks)
- **Sesamin [sesame]**: blocks NFkB activation
- **Luteolin [celery, green peppers]**: reduces IL-1, IL-6, and TNF-alpha in microglial cells and monocytes stimulated with LPS
- **Black raspberry [ellagic acid]**: decreases IL-6 and TNFa (750mg x 12 weeks)
- **Curcumin [turmeric]**: inhibits NFkB activation, TNFa, and COX and activates p53 by inhibiting MDM2
- **Resveratrol [grapes, peanuts]**: inhibits NFkB
- **Epigallocatechin gallate (EGCG) [green tea]**: inhibits NFkB

Pal S, et al. J Inflamm. 2014;11:23. Egert S, et al. Br J Nutr. 2009;102:1065.
 Leiva-Lopez N, et al. Int J Mol Sci. 2016;17:921. Jeong HS, et al. J Med Food. 2016;19(4):346.

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NUTRIENT INTAKE AND ENDOMETRIOSIS


- Systematic review of 12 studies¹ of women with image confirmed endometriosis and studying the effect of a nutrient or diet on endometriosis-related symptoms.
- Review notes that in an Australian national online survey², up to 76% of women with endometriosis use self-management strategies, consisting of diverse self-care and lifestyle choices, such as meditation, exercise and nutrition.
- Almost half (44%) of the women use dietary strategies, such as a gluten-free or vegan diet, with an effectiveness rating of 6.4 out of 10.
- Overall quality of included studies was low to very low due to small size, lack of control groups, heterogeneous patient group or heterogeneous intervention.

1. Huijs E, Nap A. RBMO. 2020;41(2):317.
 2. Armour M, et al. BMC Complement Altern Med. 2019;19:17

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DIET AND PRIMARY DYSMENORRHEA

- Systematic review of 38 included observational studies
- The increased consumption of fruits and vegetables as the sources of vitamins and minerals had inconsistent effects on dysmenorrhea (2/4 showed inverse relationship and 2/4 showed no relationship)
- Coffee did not have any effect on dysmenorrhea (7 studies); 3 studies found increased dysmenorrhea in association with coffee
- Milk and dairy products have positive associations with less menstrual pain in 4 studies
- Higher consumption of sugar in 3 studies had a significant relationship with increased risk of dysmenorrhea.
- Limitation of this review was the methodological heterogeneity of studies

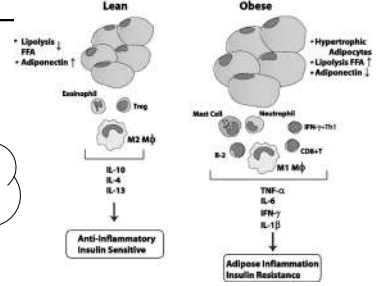


Bajalan Z, et al. Gynecol Obstet Invent. 2019;84:209. 19

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INFLAMMATION IN ASSOCIATION WITH OBESITY

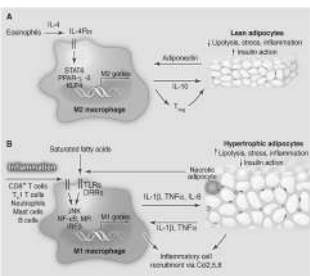
Macrophages respond to the cytokine environment in which they reside. Thus systemic conditions influence the tissue microenvironment.



<http://dx.doi.org/10.1186/s12973-019-1603-2> 20

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INSULIN RESISTANCE: MEDIATING FACTOR BETWEEN OBESITY & INFLAMMATION



Van Kruijsdijk RC, et al. Cancer Epidemiol Biomarkers Prev. 2009;18:2569-78. 21

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DIETARY INFLUENCES ON INSULIN RESISTANCE

Table 1. Metabolic effect of various dietary restriction regimes in C57BL/6 mice and insulin-resistant humans

Parameter	FGF21		IGF-1		Insulin		Glucose		SHBG		Body weight	
	Mouse	Human	Mouse	Human	Mouse	Human	Mouse	Human	Mouse	Human	Mouse	Human
Starvation	↑	↑	↓	↓	↓	↓	↓	↓	↑	↑	↓	↓
Calorie restriction	/a	/a	↓a	↓a	↓ab	C ↓b	↓b	↓ab	/b	/b	↓	↓
Protein-deficient diet, isocaloric	↑	↑	↓	↓	↓	↓	↓	↓	—	—	↓	↓
Protein-deficient diet, hypocaloric	↑	↑	↓	↓	↓	↓	↓	↓	—	—	↓	↓
KD, isocaloric	—	—	—	—	—	—	—	—	↑	↑	↑	↑
KD, hypocaloric	/a	/a	↓a	↓a	↓	↓	↓	↓	↑	↑	↓	↓

Abbreviations: SHBG, sex hormone-binding globulin; FGF21, fibroblast growth factor 21; KD, ketogenic diet. C, mainly dependent on the degree of protein restriction; /b, mainly dependent on the degree of CHO restriction. The protein-deficient diet is defined as a diet containing < 10% protein. The KD is assumed to contain > 10% protein.

Common denominator across the most successful diets = **low calorie diets!**

Klement RJ and Fink MK. *Oncogenesis*. 2016;5:e193.

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ALTERNATE-DAY FASTING

Day	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Fast	Ad libitum	Ad libitum	Ad libitum	Ad libitum	Ad libitum	Ad libitum	Ad libitum
Fast	Ad libitum	Ad libitum	Ad libitum	Ad libitum	Ad libitum	Ad libitum	Ad libitum

IER Intermittent Fasting Schedule Example

Day	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Fast	Ad libitum	Ad libitum	Ad libitum	Ad libitum	Ad libitum	Ad libitum	Ad libitum
Fast	Ad libitum	Ad libitum	Ad libitum	Ad libitum	Ad libitum	Ad libitum	Ad libitum

COMPARISON BETWEEN IER, IF AND CER DIETS

- Intermittent Energy Restriction (IER) commonly restricts caloric intake by 50%-70%, typically for 2-3 days per week
- Intermittent Fasting (IF) is commonly overnight, alternate day, or 2-3 consecutive days fasting per week
- Continuous Energy Restriction (CER) is commonly a 20% reduction in caloric intake that results in 5% to > 30% weight reduction
- All diets reduce fat stores and thus lower levels of mitogens such as insulin, IGF-1, estradiol, androgens, TNF α , IL-6, leptin, decreased kinase signaling, and increased adiponectin.

Harvie M and A Howell. *Proc Nutr Soc*. 2012;71:263-75.

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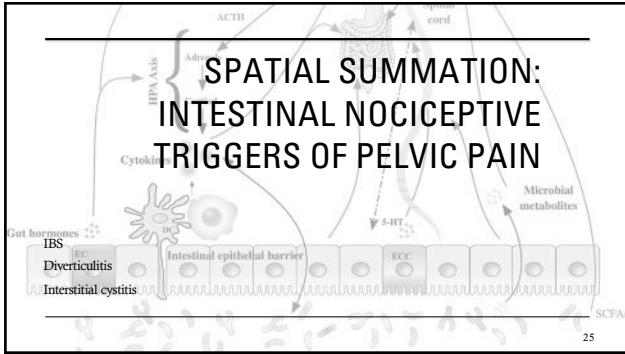
IER VS. CER AND WEIGHT

- In 107 overweight pre-menopausal women, 2d of a 70% ER (2.71MJ/d) on restricted days and 5d Mediterranean-type diet per week was compared to an isocaloric 25% energy restricted diet for 6 months.
- Both diets resulted in reduced body fat, by 6.4 (SD 1.5) kg in IER compared to 5.6 (SD 1.3) kg in CER diet (P = 0.34)
 - Reduction in fasting insulin and insulin resistance in both groups but greater in IER
 - Reductions in leptin, hsCRP, total and LDL cholesterol, TG in both groups
 - Increases in SHBG and IGF-BP1 and IGF-BP2 in both groups
- IER (4.18 MJ for 4 d with 3 d regular diet/week) v. CER (6.0-7.0 MJ/d) among 51 men with type 2 diabetes and showed equivalency between the diets in terms of weight change and fasting insulin.

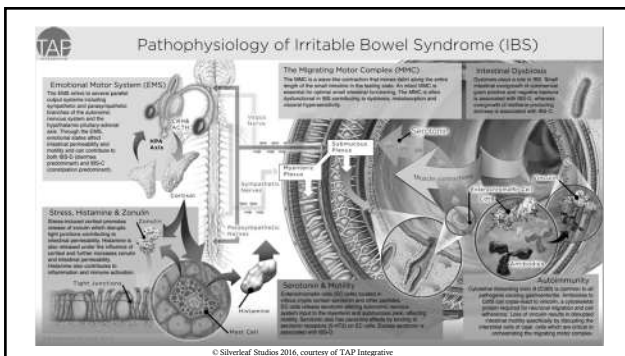
Harvie MN, et al. *Int J Obes (Lond)*. 2011;35(5):714-27.
Ash S, et al. *J Obes Relat Metab Disord*. 2003;27:797-802.

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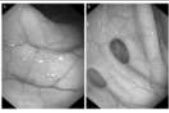
IBS: DIETARY INTERVENTIONS

- Food timing
 - Meal spacing of at least 4 hours apart to allow for complete migrating motor complex (MMC) intestinal sweep¹
- Mindful eating with complete mastication
- Elimination diets
 - Elimination/challenge diet of common intolerances (wheat, dairy, soy, corn, sugar) or based on food allergy testing
 - FODMAP² restriction diet (for IBS-D); short term (4-8weeks) to identify offending saccharides and facilitate optimizing digestion.²
 - Effective symptom relief per findings from 7 systematic reviews/meta-analyses³
 - FODMAP: Fermentable Oligo-, Di and Monosaccharides And Polyols
 - FODMAPs are poorly absorbed increase intestinal transit time and undergo fermentation in colon, producing gas and distension
- Increase fiber and hydration (for IBS-C)

1. Takahashi T. J Smooth Muscle Res. 2013;4999.
 2. Halmos E. Gastroenterol. 2014; 146(1):67.
 3. Ovi S, et al. Complement Ther Medicine. 2019;43:73.

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DIVERTICULITIS (WOMEN)



- 60% of people >70y have diverticulosis.
- Diverticulitis = acute inflammation of diverticulosis
- Study out of NHS cohort (prospective cohort of 121,700 female nurses ages 30-55y).
 - Cohort = 50,019 women were free of diverticulitis at baseline
 - 4,343 incident cases confirmed with medical record review
 - Food intake assessed every 4 years with Food Frequency Questionnaire
- Highest quintile of fiber intake from fruit and cereals (not vegetables) was associated with a 24% reduced incidence of diverticulitis [0.86 (95% confidence interval: 0.78–0.95; P-trend=0.002)]
- Each daily serving of apple, pear, prunes and/or whole fruit was associated with a 5% reduced risk of diverticulitis [0.95 (0.92–0.98; P-trend<0.001)]

Ma W, et al. Am J Gastroenterol. 2019;114:1531. 28


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DIVERTICULITIS (MEN)

- Prospective cohort study of 46,295 out of Health Professionals Follow-Up Study free of diverticulosis and diverticulitis.¹
 - Diet assessed by Food Frequency Questionnaire every 4 years
 - Over 894,468 person years of follow-up, there were 1063 incidences of diverticulitis
- Men in the highest quintile of Western dietary pattern* had 55% increased risk of diverticulitis compared to men in the lowest quintile. [1.55 (95% CI, 1.20-1.99)]
 - *high in red meat, refined grains, and high-fat dairy
- Men with the highest prudent diet* score had a 26% decreased risk of diverticulitis compared to the lowest (multivariate hazard ratio, 0.74; 95% CI, 0.60 - 0.91).
 - *high in fruits, vegetables, and whole grains
- Prospective cohort of 46,418 men out of Health Professionals Follow-Up Study free of diverticulosis and diverticulitis.²
 - Empiric Dietary Inflammatory Pattern (EDIP) score was calculated for each participant every 4 years from their FFQ
 - Over 992,589 person years of follow-up, 1110 cases of diverticulitis
- Men in the highest quintile of dietary inflammatory scores had a 31% increased risk of diverticulitis and the association did not differ by BMI or activity level.
 - Anti-inflammatory dietary pattern: high intake of green leafy vegetables, dark-yellow vegetables, coffee, and tea, and low consumption of red meat, processed meat, refined grain, and sugary beverages
- In a nested case-control study, pre-diagnostic plasma CRP and IL6 were each associated with the risk of diverticulitis.

1. Strate LL, et al. Gastroenterology. 2017;152:1023.
2. Ma W, et al. Clin Gastroenterology. 2020;18(10):2228. 29

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FIBER DURING ACTIVE DIVERTICULOSIS

- Systematic Review and Meta-analysis
 - 9 studies included in the review
 - 4 studies included in the meta-analysis
 - Adults age 57-70y
- Dietary inositol fiber supplementation improved stool weight (MD: 42 g/day, P < 0.00001; GRADE level of evidence: low), but had no significant effect on gastrointestinal symptoms (SMD -0.13, P = 0.16; GRADE level of evidence: low) or stool transit time (MD: -3.70; P = 0.32; GRADE level of evidence: low).
 - Quality of evidence low due to heterogeneity of study interventions (bran, psyllium, unspecified)
- This review conditionally recommends a high dietary fiber diet for older adults with asymptomatic or uncomplicated symptomatic diverticular disease


Eberhardt F, et al. Maturitas. 2019; 130:57. 30

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FOOD TRIGGERS AND INTERSTITIAL CYSTITIS

- Over 90% of patients with interstitial cystitis/bladder pain syndrome report sensitivities to various foods.¹
- A stimulus from the colon in response to food combined with bladder stimulus are summed to generate pain when either one alone would be insufficient to evoke pain.²
- Colonic stimulation in response to food occurs:
 - Activation of mechanoreceptors from bulky foods
 - Activation of pain fibers in gut from capsaicin
 - Activation of acid-sensing receptors from tomato, citric acid in juices etc
 - Activation of specific receptors such as caffeine receptors

1. Friedlander JI, BJU International. 2012;109:1784
 2. Klumpp D, Rudick C. Nature Clinical Practice Urology. 2008;5(9):494



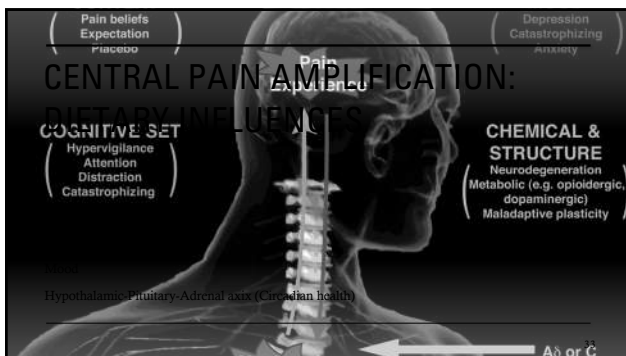
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DIETARY TRIGGERS OF INTERSTITIAL CYSTITIS / BLADDER PAIN SYNDROME

- Web-based questionnaire provided to 20,000 members of the Interstitial Cystitis Association²
- 598 IC/bladder pain syndrome participants
 - 91% female
 - The questionnaire assessed the effect of 344 different foods, drinks, supplements, ingredients/spices, and general food categories on urinary frequency, urgency, and/or pelvic pain symptoms using a Likert response scale.
- Foods that worsened symptoms included: citrus fruits, tomatoes, coffee, tea, carbonated and alcoholic beverages, spicy foods, artificial sweeteners, and vitamin C
- Most items in the survey had no effect on symptoms.
- Limitations:
 - Diagnoses of IC/Bladder pain syndrome were not confirmed.
 - Self-selection bias: individuals with more severe symptoms and/or with food sensitivities may have been more motivated to participate

1. Bassaly R, et al. Female Pelvic Med Reconstr Surg. 2011;17:36.

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DIETARY IMPACTS ON MOOD (CENTRAL PAIN AMPLIFICATION)

- Cross-sectional RCT x 2 weeks, N=39 adults
- Primary outcome measures: Depression Anxiety Stress Scales (DASS) and Profile of Mood States (POMS) questionnaires
- 3 diet groups:
 - Omnivore (consumed meat and/or poultry at least once daily)
 - Fish (no meat or poultry and consumed 3-4 servings seafood weekly)
 - Vegetarian (no animal products except for dairy)
- Mood scores were unchanged for OMN or FISH participants, but stress and confusion scores improved for VEG participants.

Beezhold B and C Johnston. Nutr J. 2012;11:9. 34

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HEALTHY DIET PATTERN CORRELATES WITH IMPROVED MOOD/LOWER ANXIETY

- Based on a questionnaire of diet and a psychological assessment tool (n=1,046 women, ages 20-50)¹
 - Traditional diet (vegetables, fruit, meat, fish, whole grains) was associated with lower odds for depression, dysthymia and anxiety.
 - Western diet (processed and fried foods, refined grains, sugar, beer [this was done in Australia, after all!]) was associated with higher psychological distress
 - Difficult to interpret – is the poor diet a result of higher distress, or vice versa?
- A Mediterranean style diet results in improved mood and cognition in a period as short as 10 days!²

1. Jacka FN, et al. Am J Psychiatry. 2010;167(3):305-11.
2. Lee J, et al. Nutrition. 2015;31(9):647-52. 35

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DIETARY INFLUENCES ON HPA AXIS: FAT & CARB CONSUMPTION

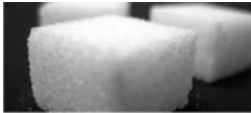
- A disturbed HPA axis is associated with abdominal fat distribution and a higher content of fat and saturated fatty acids in the diet.
- Women who chose a dietary pattern closer to the Mediterranean diet, with high monounsaturated fatty acid intake, showed lower levels on HPA axis disturbance.
- Activation of the HPA axis following the ingestion of large amounts of carbohydrates occurs specifically in women with the abdominal obesity phenotype.

Caraci-Prato M, et al. Endocrinol (Oxf). 2007;148(6):2145-9.
Varrault V, et al. Clin Endocrinol Metab. 2002; Aug;57(8):884-8. 36

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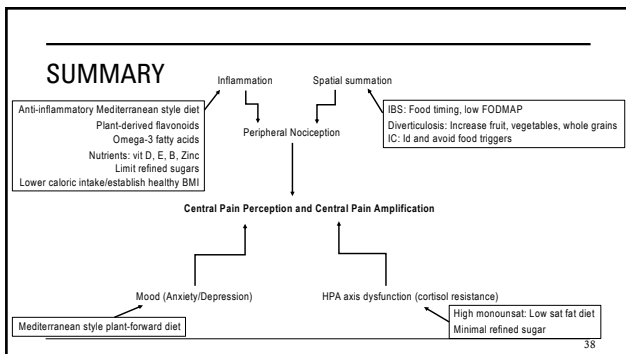
SUGAR AND HPA AXIS HEALTH

- Glucose intake amplifies cortisol response to psychosocial stress and smoking in healthy young men, while low blood glucose levels prevents the stress-induced activation of the hypothalamus pituitary adrenal (HPA) axis.



Gonzalez-Bono E, Horm Behav. 2002 May;41(3):328-33. 37

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DIETARY SUPPLEMENTS FOR CHRONIC PELVIC PAIN

- PUFAs
- Vit D
- NAC and ALA
- Vit E
- Curcumin
- Ginger
- Chamomile
- Saffron
- Peppermint
- Adaptogens
- Phosphatidylserine
- L-theanine
- St Johns Wort

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DIETARY SUPPLEMENT PAIN TARGETS

- Anti-inflammation to reduce peripheral pain sensitization
- Address spatial summation, specifically gut-induced pain stimulation as well as pain from pelvic organ pathology
- Reduce anxiety and depression
- Address HPA axis dysfunction

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POLYUNSATURATED FATTY ACIDS (PUFA): ANTI-INFLAMMATION

- Systematic Review and Meta-analysis on PUFA supplementation and chronic pain*
 - studies included if chronic pain was defined per the International Association for the Study of Pain
 - Funnel plot and Egger's test showed no evidence for publication bias (P = 0.30).
- 5 observational studies
 - One showed a protective effect of PUFA
- 46 interventional studies
 - Pooled random effects SMD of -0.40 (95% CI -0.58, -0.22) (0 = absence of effect)
 - Substantial heterogeneity with design, quality and study population so random effects analysis was done
 - Effect was strongest for dysmenorrhea (SMD -0.82, 95% CI -1.21, -0.43)
 - Omega-3 supplementation had strongest effect of the PUFAs (SMD -0.47, 95% CI -0.68 to -0.26)
 - Effect was stronger for low doses (-0.55, 95% CI -0.79, -0.30)
 - Effect was strongest in short term supplementation studies (-0.56, 95% CI -0.86, -0.25)
- Omega-3 PUFAs (EPA and DHA) inhibit the arachidonic acid pathway, leading to decreased production of eicosanoids and other inflammatory cytokines (TNF- α , IL 1, and IL 6).
- Omega-3 PUFAs also inhibit pain signaling, increase release of β -endorphins and resolvins

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Preco-Dominquez J, et al. Pain Physician. 2016;19:521.

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OMEGA-3 FATTY ACIDS AND VITAMIN D: ENDOMETRIOSIS

- 6-month DBRPCT of 147 young women, ages 12-25 with surgically confirmed endometriosis
- Randomized to 2000IU vitamin D, 1000mg fish oil or placebo
 - Primary outcome: Pain measured by VAS
 - Secondary outcomes: CoL, Pain catastrophizing, and pain medication usage
 - Compliance was assessed with serum 25(OH)D and omega-3 fatty acids
- All 3 study arms demonstrated improvements in pain severity with "worst pain in the last month" mean VAS scores improving from baseline to 6 mo*:
 - placebo (8.0 to 4.4, P value=0.07)
 - vitamin D (7.0 to 5.5, P value=0.02)
 - fish oil (5.9 to 5.2, P value=0.39)
- However, a statistically significant change applying a P value <0.05 was noted only in the vitamin D arm.
- The odds of a clinically meaningful change in pain score for in the vitamin D group between the baseline and 6-mo time points were 2 times greater than for those in placebo and fish oil groups, however the CI was wide.
- CoL improved in all groups without significance differences between groups.
- Catastrophic thinking score improved in all groups, but as statistically improved from baseline only in vitamin D group.
- Limitations: Small sample size, participants were not not low (<20ng/mL) in vit D at baseline, and 1000mg fish oil may be insufficient

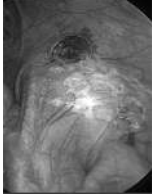
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Nadler JL, Am J Clin Nutr. 2020;112:229.

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VIT D AND ENDOMETRIOSIS-RELATED PAIN AFTER SURGERY

- DBRCT of 39 women with endometriosis treated by laparoscopy, scores of at least 3 for dysmenorrhea and/or pelvic pain at 8 weeks after surgical treatment. ¹
- Randomized to 50,000iu vitamin D3 weekly x 12 weeks or placebo.
 - Anti-inflammatory actions of vit D: 1,25(OH)₂D₃ helps maintain self-tolerance and prevents immunoinflammatory tissue damage by damping adaptive immune system responses through polarizing CD4+ Tcells towards TH2 and Th17 regulatory types ²
- Following the treatment with vitamin D or placebo, there were no differences in severity of pelvic pain (p=0.24) and dysmenorrhea (p=0.45) between vit D and placebo.
- Study limitations:
 - Serum vit D was not ascertained at baseline or after treatment.
 - Vitamin D may only be effective for those who are vit D deficient
 - Dose was not adjusted to serum level and may have been too high or too low (vit D has diminishing returns with high supplementation levels in other studies)



1. Almassinokiani F, et al. Medical Science Monitor. 2016;22:4960
 2. Lang PO, et al. Osteoporos Int. 2012. DOI 10.1007/s00198-012-2204-6

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VIT D AND PRIMARY DYSMENORRHEA

- Out of 683 consecutive admissions to the study center in Turkey, 184 women, ages 18-25y, with primary dysmenorrhea were randomly allocated to dysmenorrhea group and 184 women (same age range) without dysmenorrhea were randomly allocated to control group.
- The dysmenorrhea group had significantly less consumption of dairy products (p=0.001), lower serum calcium (p=0.001), lower serum vitamin D (p=0.001) and higher serum parathyroid hormone (p=0.001) than those of the control group.
- The dysmenorrhea patients with vitamin D deficiency (<12 ng/mL) (45%) had significantly higher VAS scores (p =0.001) than dysmenorrheic patients with normal 25OHD.
- Depression, irritability, mood swings, fatigue, headache and breast tenderness were significantly more frequent in the vitamin D deficiency group (p<0.05 for all).
- Study limitations:
 - Study was conducted throughout a year so seasonal variations in vit D were not taken into account
 - Laparoscopy was not conducted so some underlying pelvic pathologies that cause pain could not be ruled out

Karacin O, et al. Taiwanese J Obstet Gynecol. 2018;57:58.

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VIT D AND DYSMENORRHEA

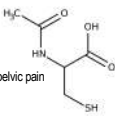
- 100 women, ages 18-30 with primary dysmenorrhea and no other pelvic disorders with serum 25OHD less than 30ng/mL (Turkey)
 - The 25(OH)D level was insufficient in 23% (21 and 29 ng/mL), deficient (10and 20 ng/mL) in 45%, and severely deficient (below10 ng/mL) in 32% of the patients.
- Treatment: Each participant took 8 – 23 drops (800iu – 2,300iu) daily x 2 months according to baseline serum 23OHD with goal to achieve 30ng/mL.
 - Following 2months of replacement, maintenance of 6 drops (600iu) vit D3 provided x 1 month
- The mean VAS score was higher among patients with severe 25(OH)D deficiency compared to other patients (p = 001).
- The ratio of patients with severe pain was higher in the group with severe 25(OH)D deficiency compared to other groups
- A significant decrease was observed in the VAS score for all groups after the replacement therapy, while the decrease in the VAS score was higher in the severely deficient 25(OH)D group compared to the insufficient and deficient 25(OH)D groups (p< 001):
- Of the patients who had severe pain before the replacement therapy, after vit D, 81% had moderate pain and 13% had mild pain (5% had no change in pain)

Kucukceran H, et al. Gynecol Endocrinology. 2019;35(10):53.

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N-ACETYL CYSTEINE, ALPHA LIPOIC ACID, BROMELAIN, ZINC: ANTI-INFLAMMATION



- N= 398 patients with endometriosis diagnosed by surgery or imaging with endometriosis-associated pelvic pain (EAPP) >3 on VAS who wished to become pregnant so were not using hormonal treatments
 - Mean age 34.6y ± 7.2y
 - 55% nulliparous
 - 93% moderate or intense EAPP (VAS >6)
- Intervention: Oral tablets containing N-acetylcysteine (600mg), alpha lipoic acid (200mg), bromelain (25mg), zinc (10mg) x 6 months
- At baseline, the mean VAS score for pain was 6.68 ± 1.97 and 86.4% needed NSAIDs to control pain, with 13.6% needing NSAIDs continuously each day.
- At 6 months, the mean VAS score for pain was 3.52 ± 1.91 and 37.4% were taking NSAIDs, of whom 1.3% were required this medication continually each day.
- Changes at both 3 and 6 months were statistically significant (p < 0.0001)
- 52 patients withdrew from the study; 27 due to pregnancy and 25 due to uncontrolled pain, NV.

Letic I, et al. Eur J Obstet and Gynecol and Reproductive Biology. 2018;228:221

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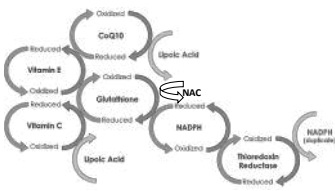
NAC AND ENDOMETRIOSIS

- An observational study of 92 women with US-confirmed ovarian endometriosis compared oral NAC x 3 months to no treatment prior to laparoscopy.
 - NAC: 600mg TID x 3 consecutive days each week
 - NAC treated women had reduction in cyst mean diameter (-1.5mm) compared to an increase in untreated women (+6.6mm).
 - Also, in NAC treated women, a greater number of cysts reduced in size and fewer increased in size
- Dyspareunia and chronic pelvic pain were similar in the two groups at enrollment.
- Pain was significantly reduced in the NAC- treated group at the end of observation, with a decrease of 55% in dysmenorrhea (P = 0.001), of 50% in dyspareunia (P = 0.027) and of 59% in chronic pelvic pain (P = 0.015)
 - Strength of pain data is limited due to lack of placebo group
- Twenty-four NAC-treated patients—versus 1 within controls—cancelled scheduled laparoscopy due to cysts decrease/disappearance and/or relevant pain reduction (21 cases) or pregnancy (1 case).

Porpora MG, et al. Evid Based Complement Alternat Med. 2013;2013:240702

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MECHANISM OF ACTION LINKED TO NAC AND ALA



- Oxidative stress has a pathophysiological role in endometriosis and endometriosis associated pelvic pain.
- Both n-acetyl cysteine and alpha lipoic acid have antioxidative actions: ¹
 - Increase glutathione production
 - Eliminate reactive oxygen species and peroxide radicals
- Both NAC and ALA have anti-inflammatory actions, inhibiting IL-8 and IL-6 and TNFα.²

- Ray K, et al. Pain. 2015;156(3):528
- Agostinis C, et al. Mediators Inflamm. 2015;2015:918089

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VITAMIN E AND VITAMIN C: ENDOMETRIOSIS-RELATED PAIN

- Oxidative stress, especially in the peritoneal fluid, plays an etiologic role in endometriosis.
 - Vit E reduces lipid peroxidation and vit C helps to recycle oxidized vit E back to reduced (antioxidative) vit E.
- RPCT of 59 women, ages 19-41 with endometriosis-related pelvic pain and infertility
 - Randomized to placebo or vitamin E (1200iu) and vitamin C (1000mg) daily x 8 weeks prior to surgery.
 - Pain scales administered at baseline and every 2 weeks.
 - Inflammatory markers were measured in the peritoneal fluid at time of surgery
- Chronic "everyday" pain improved in 43% of vit E/C group compared to 0 in placebo (p = 0.0055)
- Dysmenorrhea decreased in 37% of Vit E/C group compared to 1% of placebo
- Dyspareunia decreased in 24% of patients in Vit E/C group compared to 0 in placebo
- Peritoneal fluid had significantly decreased T-cell expression (p<0.002), IL-6 (p<0.056) and monocyte chemotactic protein (p<0.016) in the Vit E/C group compared to control group.

Santanam N, et al. Translational Res. 2013;161(3):189.

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CURCUMIN: ANTI-INFLAMMATORY EFFECTS FOR PRIMARY DYSMENORRHEA

- Given the central role of prostaglandins in inflammatory pain (esp. PGE2) in dysmenorrhea, turmeric is of interest as it blocks COX-2, thereby inhibiting PGE2 production
- DBRCT of 128 university students with dysmenorrhea and BMI <30.
- Randomized to:
 - Turmeric: 500mg x 2 days before menstruation and continued x 3 days after menstruation
 - Mefenamic acid NSAID: 250mg x 2 days before menstruation and continued x 3 days after menstruation
 - Turmeric + Mefenamic acid: same regimen x 5 days
 - Placebo x same regimen x 5 days
- Baseline characteristics and distribution of mild, moderate and severe pain was comparable between groups
- Mefenamic and turmeric each significantly and comparably decreased pain compared to placebo (no change in pain in placebo group) [p = 0.04 for each]
- Mefenamic + curcumin was the most effective compared to placebo [p=0.02]



Hesami S, et al. J Gynecol Obstet Hum Reprod. 2020. <https://doi.org/10.1016/j.jogoh.2020.101840>

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DIETARY SUPPLEMENTS FOR PRIMARY DYSMENORRHEA

- Cochrane review of 27 RCTs (3101 women).
 - 22 studies conducted in Iran
- Interventions included 12 different herbal medicines (German chamomile (*Matricaria chamomilla*), cinnamon (*Cinnamomum zeylanicum*, *C. verum*), Damask rose (*Rosa damascena*), dill (*Anethum graveolens*), fennel (*Foeniculum vulgare*), fenugreek (*Trigonella foenum-graecum*), ginger (*Zingiber officinale*), guava (*Psidiumguajava*), rhubarb (*Rheum emodi*), uzara (*Xysmalobium undulatum*), valerian (*Valeriana officinalis*), and zataria (*Zataria multiflora*) and five non-herbal supplements (fish oil, melatonin, vitamins B1 and E, and zinc sulphate) in a variety of formulations and doses.
- Comparators included other supplements, placebo, no treatment, and NSAIDs
- All evidence was low or very low quality due to small sample sizes, failure to report study methods and inconsistency

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DIETARY SUPPLEMENTS: DYSMENORRHEA

- Supplements vs. placebo or no treatment:
 - Vit E, 2 RCTs: no evidence for effectiveness
 - Dill, Guava, Fennel: trend towards effectiveness, but not statistically significant
 - Fenugreek, Fish oil, Ginger, Valerian, vit B1, Zataria (Middle Eastern thyme-like plant), Zinc: Limited evidence of effectiveness
- Supplements vs. NSAIDs
 - Equivalency between NSAIDs and dill, fennel, guava, rhubarb, and valerian
 - Limited evidence that chamomile was more effective than NSAIDs
- Supplements vs. Supplements
 - No difference in effectiveness between ginger and zinc sulphate
 - Vit B1 may be more effective than fish oil
- Authors conclude that there is no high-quality evidence to support the effectiveness of any dietary supplement for dysmenorrhea and evidence of safety is lacking. Supplements for which low quality evidence is suggestive of benefit include: **fenugreek, ginger, valerian, zataria, zinc sulphate, fish oil, vitamin B1.**

Pattaninum P, et al. Cochrane Database Sys Rev, 2016;2016(3)

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GINGER FOR PRIMARY DYSMENORRHEA

- Systematic Review and Meta-analysis included 6 trials
 - 5 studies in Iran, 1 study in India
 - 5/6 studies included women with moderate – severe symptoms only
 - 4 studies excluded secondary dysmenorrhea
 - Sample sizes of ginger intervention arm ranged from 25 – 61
 - All trials tested ginger as crude dry ginger powder with daily dosage ranging from 750mg – 2000mg
 - Most common dosing schedule was x 1= 3 days of menstruation; one study used 4 days and one study used 5 days
 - Ginger vs placebo in 3 trials; ginger vs NSAIDs in 2 trials; remainder ginger vs. control
 - Pain was measured using VAS scale in 4 studies, other pain scales used in remaining 2 studies
- Risk of bias was high in most studies



Chen, CX, et al. Evidence-based Complement Alternative Med. 2016. doi.org/10.1155/2016/6295737

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GINGER FOR PRIMARY DYSMENORRHEA

Study or subgroup	Ginger		Placebo		Weight	Mean difference IV, random, 95% CI	Mean difference IV, random, 95% CI
	Mean	SD	Mean	SD			
Khadri 2013	6.81	1.7	10	7.11	1.12	34.4%	-2.10 [-2.98, -1.22]
Kabirian et al. 2012	3.12	2.09	29	6.28	3.02	46.2%	-1.61 [-2.36, -0.86]
Karaffi et al. 2014	6.2	1.4	47	7.13	1.3	45.3%	-0.93 [-1.48, -0.38]
Total (95% CI)	141		122		100.0%	-1.21 [-2.43, -0.06]	

Heterogeneity: $\tau^2 = 0.47$; $I^2 = 84$; $\text{df} = 2$ ($P < 0.0005$); $I^2 = 79\%$
 Test for overall effect: $Z = 3.47$ ($P = 0.0005$)


FIGURE 3 Forest plot for ginger versus placebo, pain severity (0-10 cm VAS).

Study or subgroup	Std. mean difference	SE	Weight	Std. mean difference IV, random, 95% CI	Std. mean difference IV, random, 95% CI

FIGURE 4 Forest plot of ginger versus NSAID (Specifically mafenamic acid), pain severity.

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CHAMOMILE: PMS

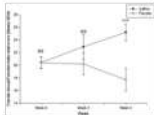

- Systematic Review that included 8 RCTs.
- Chamomile has anti-inflammatory effects (inhibits COX-2), anti-spasmodic effects, anti-anxiety effects.
- Reduces central pain amplification (reduces sympathetic activation, modulates dopamine and serotonin)
- Overall results:
 - One study found chamomile is more effective than placebo
 - Two trials found chamomile to be more effective than mefenamic acid
 - Remaining trials used untreated menstruation as control and found chamomile to relieve dysmenorrhea over control
 - Effective doses ranged from 20-30 drops chamomile extract, 250-400 mg capsule and 2 cups of chamomile tea
 - Study sizes ranged from 30 to 118, with most studies enrolling 60-90 women
- Limitations:
 - Significant heterogeneity of study design, intervention and outcomes
 - Overall quality of studies is low

Khalesi Z, et al. J Pharmacopuncture. 2019;22(4):204 55

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SAFFRON: ANTI-NOCICEPTIVE EFFECTS

- Decreases peripheral nociception
 - Active constituents include crocin, crocetin, safranal and picrocrocin
 - Animal models show anti-nociceptive effects¹
- Decreases pain and improves sexual function among women with fluoxetine-induced sexual dysfunction²
 - 4-week RDBPCT of 34 women with favorable response (greater than 50% reduction in depression) to fluoxetine (40mg) x > 6 weeks. Sexual dysfunction present at baseline (minimum of 16 on Female Sexual Function Index)
 - Randomized to saffron 15mg (1.65-1.75 mg crocin) twice daily or placebo
 - Saffron was particularly effective in improving the arousal (p=0.028), lubrication (p=0.035), and pain domains of FSFI (p = 0.016).
 - Safety was the same as placebo





1. Forouzanfar F, Hosseinzadeh H, Iranian J Basic Med Sci, 2018;21(4):347
 2. Kashani L, et al. Hum Psychopharmacol Clin Exp. 2013;28:54 56

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ADDRESSING SPATIAL SUMMATION: IBS PEPPERMINT


- Systematic review and meta-analysis of enteric-coated peppermint oil capsules
- RCTs of at least 2 weeks duration = 9 studies (726 patients)
- Peppermint oil was superior to placebo for:
 - Global improvement of IBS symptoms (5 studies, 392 patients, relative risk 2.23; 95% confidence interval, 1.78-2.81)
 - Improvement in abdominal pain (5 studies, 357 patients, relative risk 2.14, 95% confidence interval, 1.64-2.79)
- Most common adverse event was transient heartburn



Khanna R, et al. J Clin Gastroenterol. 2014;48(6):585.

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BOTANICALS: IBS



- Systematic Review and Meta-analysis of 33 RCTs
 - 17 evaluated peppermint oil
 - 15 evaluated other botanicals
 - 1 evaluated peppermint oil in one arm and anise seed oil in the other arm.
- Peppermint oil is both efficacious and well-tolerated in the short-term management of IBS
 - Risk of Bias: low risk for most studies; high risk for 2 studies
- Overall, 224 of 351 (64%) subjects assigned to the peppermint oil group had improved global IBS symptoms compared to 106 of the 333 (32%) subjects in the control groups (RR = 1.95, 95% CI 1.46 to 2.62, P < 0.00001). The number needed to treat with peppermint essential oil for one patient to experience improvements in their global IBS symptoms = 4 (95% CI 2.2 to 5.5).
- For IBS-related abdominal pain, the pooled analysis for the ITT population included 207 subjects. Overall, 67% subjects in the peppermint oil group had improved IBS-related abdominal pain compared to 30% subjects in the control groups (RR = 2.14, 95% CI 1.56-2.94, P < 0.00001). The number needed to treat with peppermint essential oil for one patient to experience improvements in their IBS-related abdominal pain = 3 (95% CI 2-4).
- Aloe vera juice (aloin = laxative is removed) also demonstrated efficacy in reducing global IBS symptoms, with the number needed to treat with aloe extracts for one patient to experience improvements in their global IBS symptoms = 6 (95% CI 2.9 to 50.0).

Hawrelak JA, et al. Complement Ther Med. 2020;48:102233.

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PEPPERMINT AND CARAWAY



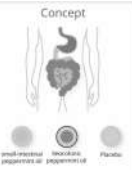
- Systemic review of DBRCTs using Menthacarin®, a proprietary peppermint/caraway-oil-combination for IBS-associated symptoms
 - Menthacarin contains 90mg peppermint oil and 50mg caraway oil
- Pain intensity values decreasing by 50–75% on average during 28 days of treatment in patients (p<0.05)

Madsich A, et al. Wien Med Wochenschr. 2019;169:149–155

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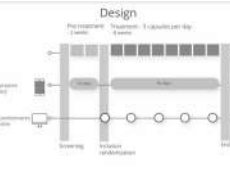
PEPPERMINT OIL IN IBS

Concept



small intestinal peppermint oil
placebo

Design



Randomized, double-blind, placebo-controlled trial

Main results

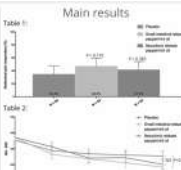
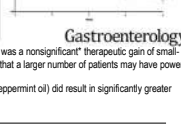


Table 1: Abdominal Pain Response Rate (%)

Group	Response Rate (%)
Peppermint oil	~12.4%
Placebo	~12.4%

Table 2: Abdominal Discomfort and Severity of Abdominal Pain




Gastroenterology

- 189 Patients with IBS (Rome IV)
- Mean age 34.0 years
- 77.8% female, 57.7% primary care
- Primary outcome: Abdominal Pain Response rate %
- Secondary outcomes, e.g.: IBS-symptom severity system (IBS-SSS)
- % responders did not differ significantly between either peppermint oil group or placebo although there was a nonsignificant therapeutic gain of small-intestinal-release peppermint oil over placebo of 12.4%, corresponding to an NNT of 8. [authors note that a larger number of patients may have powered the study sufficiently to show statistical significance]
- The small-intestinal-release peppermint oil (representative of conventionally available enteric coated peppermint oil) did result in significantly greater reduction in abdominal discomfort and severity of abdominal pain.
- No serious AE, but peppermint oil was associated with belching, and hicc in 6.4%

Wooten ZRM, et al. Gastroenterology. 2020;158(1):123.

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GINGER IN IBS

- 28-day DBRCT of 45 patients with IBS
 - Received either oral 1g, 2g or placebo daily
 - Ginger extract contained 2.29 mg/g of gingerols and 6-shogaols
- Response rates:
 - Placebo = 57.1%
 - 1g ginger = 46.7%
 - 2g ginger = 33.3%
- Adequate relief reported by 53.3% in all groups.
- Side effects in 36% of placebo vs. 17% of ginger groups
- This trial failed to show benefit of ginger over placebo.

Van Tilbur MA, et al. Complement Ther Med. 2014;22(1):17.

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GINGER: MOTILITY EFFECTS

- Ginger accelerates gastric emptying time, relieving symptoms of dyspepsia
 - Wu KL, et al. Eur J Gastroenterol Hepatol. 2008;20(5):436
- Ginger improves intestinal transit while reducing hyperperistalsis
 - Hasimoto K, et al. Planta Med. 2002;68(10):936
- Gingerol and shogaol are weak inhibitors of 5-HT(3) receptors antineurokininergic activities of this receptor in the intestines
 - Abdel-Aziz H, et al. Eur J Pharmacol. 2006;530(1-2):136

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GINGER: ANTI-INFLAMMATORY EFFECTS

- **Migraine headaches:** 250mg ginger at onset of headache (DBRCT of 100 patients)
 - Maghbooli M, et al. Phytother Res. 2014;28(3):412.
- **Dysmenorrhea:** 250mg ginger every 6 hours (DBRCT of 125 women)
 - Maghbooli M, et al. Phytother Res. 2014;28(3):412.
- **Osteoarthritis:** 750mg ginger daily for 12 weeks (DBRCT of 60 patients)
 - Paramdeep G. Ind J Physiol Pharmacol. 2013;57(2):177.
- **Tuberculosis:** 3g ginger for 1 month (DBRCT of 69 patients)
 - Kukiemi RA and Deshpande AR. J Complement Integr Med. 2016;13(2):201.
- **Individuals at increased risk for colorectal cancer:** 2g ginger daily for 28 days (pilot trial of 20 patients)
 - Zick SM, et al. Mol Carcinog. 2015;54(9):908.

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HPA AXIS REGULATION: ADAPTOGENIC HERBS

HPA Axis

- Innocuous
- Have a normalizing action, irrespective of the direction of the pathologic state
- One key mechanism of adaptogens is to restore intracellular glucocorticoid receptor (GR) sensitivity in the brain, and thereby reinstating negative feedback.
 - In the brain, GR activation inhibits genes that encode for CRH and ACTH.
- Adaptogenic plants:
 - Inhibit FKBP5. FKBP5 reduces the affinity of glucocorticoids to GR and delays translocation to the nucleus. Inhibited FKBP5 restores intracellular GR activation with resultant inhibition of CRH and ACTH
 - Inhibit of COMT (catechol-O-methyl transferase) which otherwise degrades cortisol in the region of GR receptors

Gaffney B. Med Hypotheses. 2011;54(5):567-72
Zannas AS. Neuropsychopharmacology. 2016;41:261-74
Verjze S. Planta Med. 2018;84(9-10):696.

64

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PANAX GINSENG

- A classic adaptogen – builds stamina and resilience
- Decreases adrenal hypertrophy, corticosteroid production and hyperglycemia, reduces the extent of alarm reaction and prevents or delays the exhaustive phase of the stress response.
- Clinically studied to:
 - Reduce fatigue
 - Duan L. Sys Rev/Meta-analysis. 2019. PMID: 29624410
 - Reduces unstable angina (freq and duration)
 - Sys Rev/Meta-analysis. 2018. PMID: 30166105
 - Reduces muscle inflammation after exercise
 - Hou CW. 2015. PMID: 25617625
 - Improves insulin sensitivity
 - De Souza L. 2015. PMID: 25446600
 - Increases Th1 and NK cell immunity
 - Ma J. 2014. PMID: 25618966
 - Cho YJ. 2014. PMID: 25297058

Not considered safe w/ PCP or in children

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PANAX GINSENG

- Ginsenosides are stimulating
- Panax has demonstrated blood sugar stabilizing, immune enhancing, cognitive restoring actions
- Panax is particularly indicated for fatigue
- DBRPCT of 90 adults with chronic fatigue took 20% ethanol extract of Panax at 1g, 2g or placebo per day x 4 weeks
- Self-rated fatigue improved significantly in those taking ginseng in both dosages with the 2g resulting in greater objective improvement.

Kim H. PLoS One. 2013;8(4):e61271

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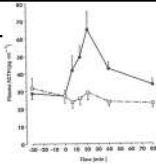
WITHANIA SOMNIFERA (ASHWAGANDHA)

- Ashwagandha - restorative, calming
- Exerts a calming, anxiolytic, slightly sedative effect, while also supporting cognition, and thereby rests and restores the health of the nervous system and person overall. It is best suited to individuals who are debilitated and who suffer from nervous exhaustion, weakness and anemia.
- 300mg full spectrum concentrated ashwagandha extract twice daily or placebo. The ashwagandha group experienced significant reduction in all measures of stress compared to placebo (p<0.0001) and experienced reduced cortisol level (27.9% reduction) compared to placebo (7.9% reduction) (p=0.0006)
 - Chandrasekhar K, 2012. PMID: 23439798
- Thirty-nine patients with ICD-10 classified anxiety disorders were randomized to receive an ethanolic extract of *Withania somnifera* or placebo. The study indicated benefit of ashwagandha at 6 weeks, with 88% of ashwagandha subjects showing reduction in anxiety compared to 50% of the placebo subjects. Ashwagandha was well-tolerated.
 - Andrade C, 2000. PMID: 21407860

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PHOSPHATIDYLSERINE

- Derived from soy or sunflower lecithin
- Supplemental phosphatidylserine reduces ACTH, CRH and cortisol levels
 - Also reduces epinephrine and norepinephrine
 - Donates choline and supports dopamine production
- RPCT: 4 groups of 20 subjects x 3 weeks and then exposed to a mental and emotional stressor (standardized stress test):
 - 400mg, 600mg, 800mg soy-derived PS or placebo
 - Primary Outcome measure: Spielberger State Anxiety Inventory stress subscale
- 400mg blunted serum ACTH and cortisol and exerted a positive effect on emotional responses to the stress test.
 - Larger doses did not result in the same effects.



Hellhammer J. et al. Stress. 2004;7(2):119-26. 68

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NEUROTRANSMITTER NUTRIENT CO-FACTORS

Tryptophan

↓

Iron, Calcium, Folic acid

↓

5-HTP

↓

Vitamin C, Vitamin B6

↓

Serotonin

Tyrosine

↓

Iron, Vitamin B6, Folic acid

↓

L-Dopa

↓

Vitamin B6, Magnesium

↓

Dopamine

↓

Vitamin C, Copper

↓


Norepinephrine

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L-THEANINE: ANXIOLYTIC & MILD SEDATIVE EFFECTS

- L-theanine (γ-glutamyl-ethylamide) is a unique amino acid present almost exclusively in the tea plant (*Camellia sinensis*) (1-2% of dry weight of tea leaves) ¹
- 200mg generates alpha waves in the central nervous system, exerts GABAergic actions and reduces neuroexcitation by inhibiting glutamatergic neurons - typically within 30 minutes of ingestion (causing an anxiolytic effect characterized as a relaxed yet alert state). ²




- L-theanine Monograph. Altern Med Rev. 2005 Jun;10(2):136-8.
- Rao TP, et al. J Am Coll Nutr. 2015;34(5):436.

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ST JOHN'S WORT: ANTIDEPRESSANT EFFECTS

- 2016 meta-analysis of 35 RCTs (6993 patients with major depressive disorder) of at least 4 weeks in duration comparing SJW to placebo or active comparator (1)
 - SJW was associated with more treatment responders than placebo (relative risk [RR] 1.53, 95% confidence interval [CI] 1.19 - 1.97)
 - Compared to antidepressants, SJW participants were less likely to experience adverse events (OR 0.67, CI 0.56 - 0.81) with no difference in treatment effectiveness (RR 1.01, CI 0.90 - 1.14)
- 2017 meta-analysis of 27 RCTs (3808 patients with mild-to-moderate depression) with study duration between 4 - 12 weeks. (2)
 - St John's wort demonstrated comparable response (pooled RR 0.983, 95% CI 0.924-1.042, p<0.001) and remission (pooled RR 1.013, 95% CI 0.892-1.134, p<0.001) rate, and significantly lower discontinuation/dropout (pooled OR 0.587, 95% CI 0.478-0.697, p<0.001) rate compared to standard SSRIs.
 - The pooled SMD from baseline HAM-D scores (pooled SMD -0.068, 95% CI -0.127 to 0.021, p<0.001) also support its significant clinical efficacy in ameliorating depressive symptoms.



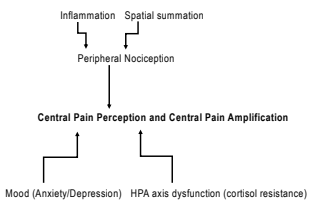
- Apaydin EA, et al. Syst Rev. 2016;5(1):148.
- Ng QX, et al. J Affect Disord. 2017;210:211.

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CONCLUSIONS

- Anti-inflammation, Antioxidation and Anti-nociception**
 - Omega-3 Fatty Acids
 - Vit D
 - N-Acetyl cysteine
 - Alpha lipoic acid
 - Vitamin E
 - Curcumin
 - Ginger
 - Chamomile
 - Saffron
- Spatial Summation**
 - BS: peppermint, ginger
- Decrease Central Pain Amplification**
 - HPA axis regulation
 - Adaptogenic herbs i.e. Panax ginseng, Withania somnifera
 - Phosphatidylserine
 - Mood support
 - Nutrient co-factors, L-theanine, St John's Wort



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