# DIETARY SUPPLEMENTS REVIEW

**Charles W Fetrow, PharmD**

Clinical Pharmacist

Senior Care Consultant Group

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# OBJECTIVES

- Recognize history, philosophies & concerns w/ Dietary Supplement industry
- Review select popular DS & associated claims, efficacy & safety data
- Identify resources & references to enable HCP to educate themselves
- Provide perspective w/ respect to “informed” counseling for patients

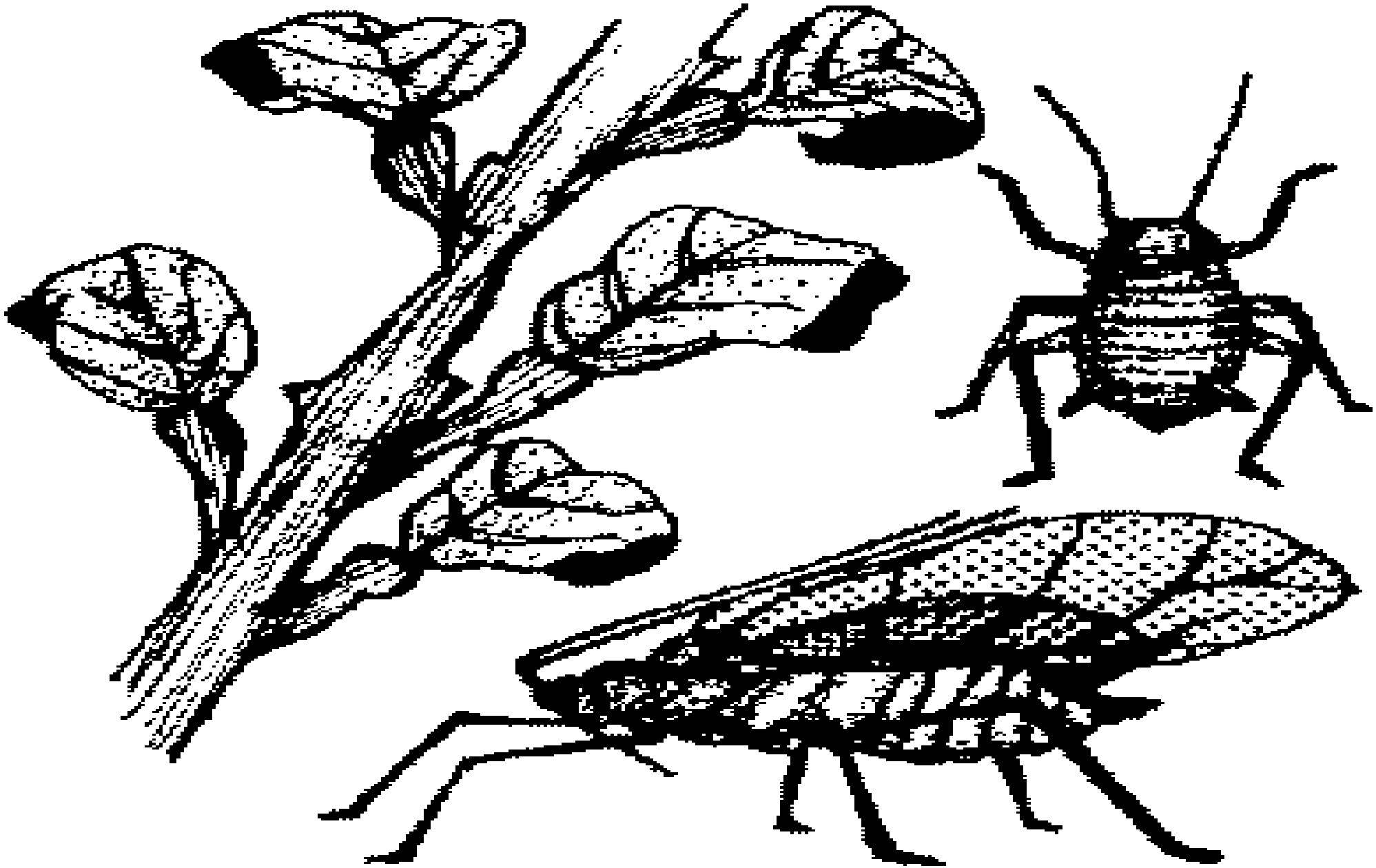
# DIETARY SUPPLEMENTs

## SUPPLEMENT

- TAKEN TO ENHANCE / INCREASE AN ALREADY EXISTING ENDOGENOUS SUPPLY (aka: NUTRACEUTICALS)

## ADJUVANT

- TAKEN TO ENHANCE EXISTING PHYSIOLOGIC PROCESSES; EXOGENOUS COMPOUND / UNIQUE TO BODY (BOTANICALS)



# Unintentional vs. Intentional Adulteration

## Unintentional

- Already exists in entity to extent which can cause harm

- Expressed in product as a result of some aspect of manufacturing process

- Most “contamination” is unintended event

## Intentional

- Necessary substance is in short supply or expensive

- Supplier wishes to create / intensify effect

Cole MR, Fetrow CW . Adulteration of dietary supplements Am J Health Syst Pharm. 2003 Aug 1;60(15):1576-80

# Potential Problems with Dietary Supplements

- Extracts have many active components
- Misidentification of plant
- Selection of wrong part of plant
- Inadequate / Unknown stability
- Contamination (incl. herbicide/pesticide/fungicide residues)
- Adulteration
- Mislabeling

# Health Risks of Herbals

**OBVIOUS HEALTH RISKS**

-ADRs (may be insidious)
-Drug Interactions rarely known
-Exposure to unnecessary compounds
-Typically unknown effect in pregnancy / breastfeeding

**UNFORESEEN HEALTH RISKS**

-Unproven herbs delay time to proven Rx
-Often lacking consensus on administration (Multiple Manufacturers)

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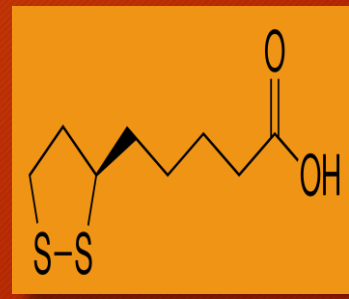
# Alpha Lipoic Acid

- Antioxidant (amphiphilic)
  - ↑ Glu disposal
  - chelates heavy metals from bloodstream
  - reduces oxidized Vits A, C, GSH
  - Improves endothelial cell dysfunction
  - Reduces oxidative stress post-exercise
  - appetite suppressant
  - Inhibits atherosclerosis
  - nootropic
  - assists multiple signal transduction pathways (insulin, Nuclear Factor Kappaβ, Nitric Oxide & cellular apoptosis)

# Alpha Lipoic Acid




(aka: Thioctic Acid, 1,2 dithiolane-3-pentanoic acid, di-hydro-lipoic acid (reduced form)

- Co-factor in mitochondria for pyruvate dehydrogenase & α-ketoglutarate dehydrogenase enzymes of oxidative metabolism

  Discovered in 1937 / isolated in 1951 from cow liver

  1st therapeutic use – Amanita Phalloides Poisoning - Germany 1959

- Dietary Sources: spinach, broccoli, tomato, brussel sprouts & meats
- Healthy mammalian mitochondria synthesize low to adequate (?) amounts
- Synthesized as a racemic compound; **R-αLA (active)** >>> S-αLA (not present in nature)
  - F = 40%, ↓ absorption w/ food intake; liquid forms > solid
  - Crosses BBB, primarily liver metabolism

# Alpha Lipoic Acid (Frontiers ?)

Vitamins C & E & ALA 600mg/day ↓ oxidative stress & improved endothelial cell fxn in brachial artery of elderly adults

Rats: ↑ BMD & ↓IL-6 & TNFα in E2-deficient rats

2 small, open-label trials w/ 600mg/d slows Alzheimer's

Preliminary success in NAFLDz

NIDDM: minor, not necessarily significant improvements in HgbA1c & FPG

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# Alpha-Lipoic Acid (Peripheral Neuropathy)

## 2 meta-analysis reviewed data in 2012

- **4 RCTs** (N = 653) ALA vs PLAC in NIDDM – PN
- 30% ↓ in Symptoms (↓ 2 points on 15 pt scale) Baseline score ≥ 4

  ALA 600 mg PO x 3-5 wks vs PLAC = Not Significant (2 trials)

  **ALA 600 mg IV** x 3 wks vs PLAC = (- 2.8; CI -4.2 to -1.5, $p < 0.05$) (2 trials)

  Int J Endocrinol. 2012; 2012:45:62-79
- **15 RCTs** (N = 1058) DPN

  ALA IV 300-600 mg vs PLAC ( - 4; CI – 5.9 to – 2.7; $p < 0.05$)
- Less stringent criteria; smaller sample sizes;

  Eur J Endocrinol. 2012; 167(4):465-471

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# Alpha Lipoic Acid (Concerns)

- Pro-Oxidant effects at higher concs → Exacerbate nephrotic syndrome in rats
- GI ADRs & thiamine deficiency (↑↑ doses ALA)
- Nausea, pruritis, skin ulceration, & bronchitis
- Refractory Seizures assoc w/ ALA toxicity
- Case Reports: Insulin Autoimmune Syndrome (spontaneous hypoglycemia, ↑↑ Insulin concs & insulin Abs)
  Asian heritage predisposition (ALA in combo w/ Vitamin B) Endokrynol Pol 2020;10.5603/EPa2019.0065
- ALA inhibits conversion T4 → T3 (↓ deiodinase fxn 22%) Arzneimittelforschung 1991;41(12):1294-8

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# Alpha Lipoic Acid (Rec)

1) Diet Modifications & Aerobic Exercise (↓ weight)

2) Vit B12 > **ALA** > acetyl L – carnitine > Vit D3

Baute V et al. Curr Treat Options Neurol 2019;21(9):44

DPN: ALA 200 – 400 mg PO TID

Cost: 0.08 – 0.41 cents/100 mg www.consumerlabs.com/alphalipoicacid

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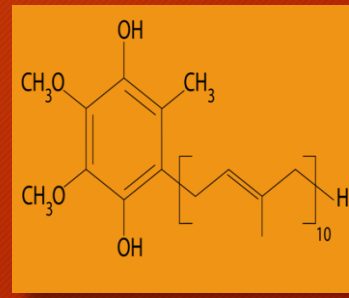
# Co Enzyme Q10 (CoQ10)




Ubiquinone

Naturally occurring anti-oxidant

Made in heart, liver & kidneys

Blood concs ↑ to 60 yo then ↓ levels of 20's

Converted to Ubiquinol - less conversion with age

MOTIVATION

To replenish low levels in myocardium of CHF

To replenish decline in levels which occurs with statin use

To increase "energy"

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# CoEnzyme Q10

- Low bioavailability problematic; ↑ with Fats or Oils in GI tract
  - Polysorbate 80 (↑ absorption)
    - Dosage Forms: 30 mg – 400 mg
- Idebenone (Contaminant)
- MitoQ® - Cation ↑ absorption; Renal damage in mice Gottwald Physiol Rep 2018
- Ubiquinol also available as supplement
  - COST: 100 mg → $ 0.34 - $1.13 www.consumerlab.com/reviews/CoQ10-Ubiquinol-Supplements-Review/CoQ10

# CoQ10 in CHF

## Meta Analysis

- 13 trials chosen (120 total)
- 100 mg po Day vs PLACEBO
- Pooled Mean Net $\Delta$ = $\uparrow$ in EF 3.67% (CI 1.6-5.7)
- Pooled Mean Net $\Delta$ NYHA = NS (CI -0.66-0.06)

- Varying formulations CoQ10 employed
- Small Study Sizes (N = 6 - 69 subjects)
- No data Mortality / Hospital Admissions

Fotina AD Am J Clin Nutr 2013;97: 268-75

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# CoQ10 in CHF (Q-SYMBIO) 2014

- MODERATE – SEVERE CHF
- RCT N = 420
- 100 mg po TID vs PLACEBO for 2 yrs

- ALL SHORT TERM ENDPTS (16 WKS) = NS
- LONG TERM COMPOSITE EVENT (2 YRS)
  - 15% Rx vs 26% PLAC (p = 0.003, 50% ↓ CI 32%-80%)
- CV Mortality
  - 9% Rx vs 16% PLAC (p = 0.026, 51% CI 28%-92%)
- Hospital Admits
  - 8% Rx vs 14% PLAC (p = 0.033, 51% ↓ CI 27%-95%)

Study funded in part by supplement Manufacturers

Significant effects gone 3 months after COQ10 discontinuation

Mortensen SA JACC 2014;2:6:641-9

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# CoQ10 in Statin Myalgia 2014

- STATIN USE & MILD-MODERATE MYALGIA > 6 MOS

- DB,RCT N = 50 (Age 45-60y)
- 50 mg (H20 SOLUBLE) po BID vs PLACEBO for 30 DAYS
- EVAL: 2 Pain Scores (PSS & PIS)

- ↓ MYALGIA / PAIN INTENSITY (PSS) AFTER 30 DAYS ($p < 0.001$, -33.1 vs -0.4)
- ↓ symptoms seen in 75% subjects
- CPK ↑ slightly in both groups (NS)

*(Historically…)* Subjective *over-estimation* of Statin-Myalgia is well documented
Previous trials support (2) and conflict (2)

**Investigators: "If after 30 days & no benefit → D/C Supplement"**

Skarlovnik A, et al. Med Sci Monitor 2014;20:2183-2188

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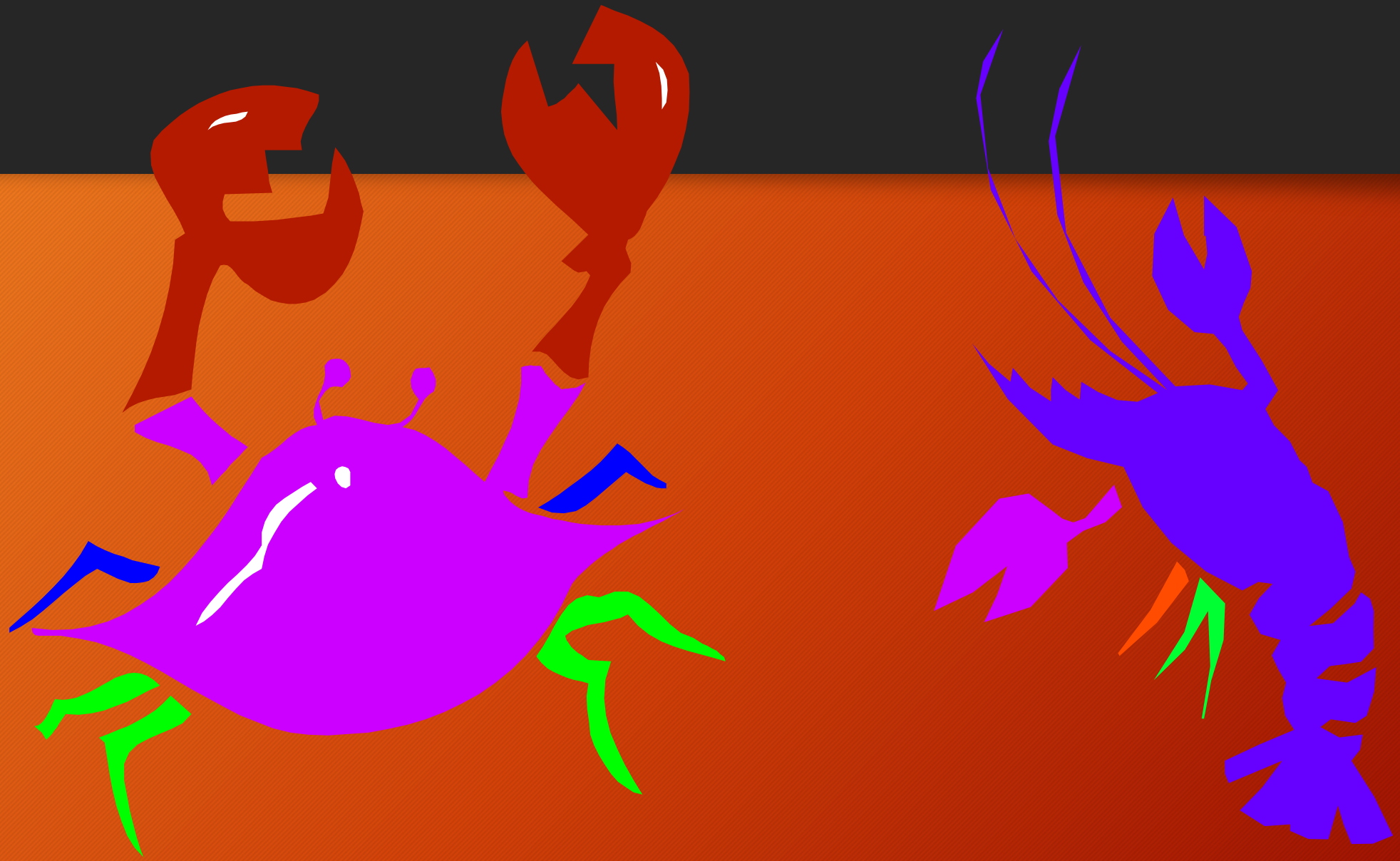
# CoEnzyme Q10

- ADRs (1%) → Loss appetite, heartburn, GI effects including nausea & diarrhea
  - Reports of transient hypotensive effect but not therapeutically useful
  - Reports of insomnia if taken too close to bedtime
- Case Report: Insulin Autoimmune Syndrome Kusano, J Rural Med 2019
- Not evaluated in pregnancy or breast feeding
- **Clinically relevant drug interaction with warfarin**
  - Structurally similar to Vitamin K
  - COST: 100 mg → $ 0.07 - $2.12 www.consumerlab.com/reviews/CoQ10-Ubiquinol-Supplements-Review/CoQ10



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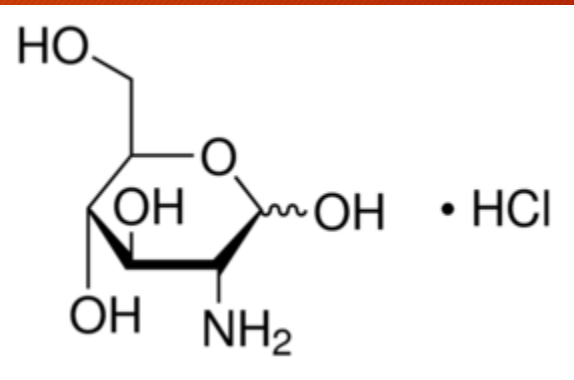
# Glucosamine Sulfate




- Amino monosaccharide
- Natural constituent of Glycosoaminoglycans in articular cartilage matrix
- Glucosamine → "rate-limiting step in Glycosaminoglycan formation"

  -NH2 group always bound (never free in nature) → (salt form)

  Acetylation (seldom used)

  HCL (most common)

  SO4 (hygroscopic & unstable)

  Sulfate → NaCL Patented Process → Crystallized Glucosamine Sulfate (CGS)

  [(Rottapharm, Italy) - Dona® , Viatril-S®, Arthryl®, Xicil®, Osaflexan®, Glusartel®]

  CGS → F = 25% & T1/2 = 15 hrs

CLAIM 2 FAME: "Symptom & structure modifying treatment in OA"

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# Glucosamine Sulfate Knee Osteoarthritis (1998)

- Randomized, double-blind trial N=178
- IBUPROFEN 1200mg/day vs GS 1500mg/day
- At 4wks ; both agents improved Sxs over baseline
- Differences between GS & IBU = NS
- GS > IBU; better tolerated

(Lacks Incl/Excl criteria & Obj tests)

Arzneim-Forsch/Drug Res 1998;48:469-74

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# Glucosamine Sulfate (2001)
# "Slows progression in Knee Osteoarthritis"

- R, DB PLAC CT (N=212) GS 1500mg/QD vs PLAC
  Rescue meds OK; > 50yrs, 1°Knee OA, AC Rheum
- EVAL: Mean joint space medial tibiofemoral joint (digital image analysis) & minimium joint space (visual) @ BASELINE, 1 & 3 yrs
  (Conducted in Liege, Belgium)
- RESULTS (favoring Rx)
  Less Joint space narrowing
  Joint space quantification
  WOMAC

CRITICISMS: ? X-ray technigue; X-ray poor correlation w/ pain & functioning;

Funding: Manufacturer - Rotta Research Labs

Lancet 2001;357:251-6

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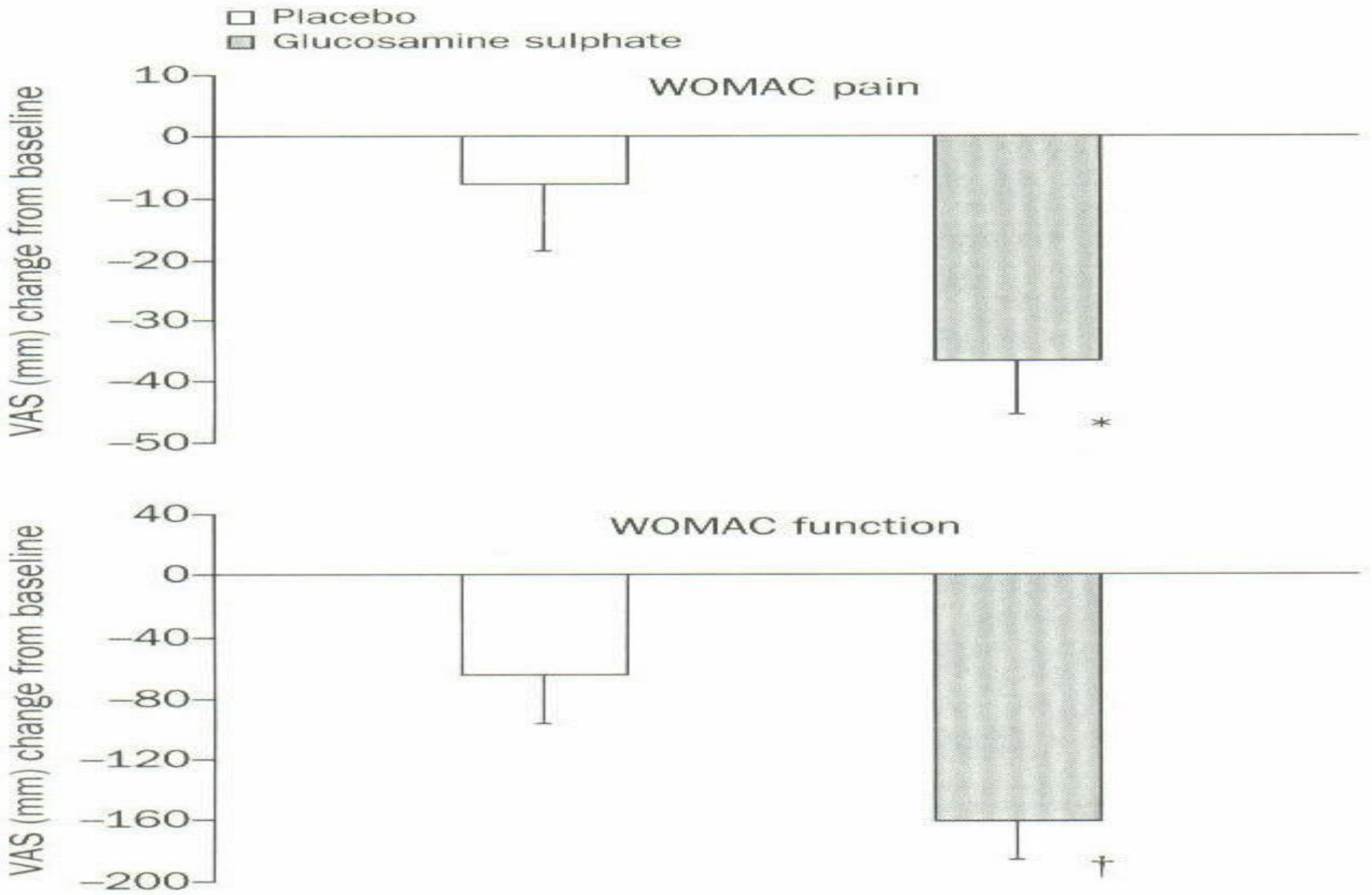


Figure 2: **Intention-to-treat mean (SE) sum of VAS change subscales after 3 years**

Upper: WOMAC pain Lower: WOMAC physical function. *p=0·047; †p=0·020. VAS=visual analogue scale.

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| Adverse event* | Placebo (n=106) | Glucosamine sulphate (n=106) |
|---|---|---|
| Abdominal pain | 18 (17%) | 13 (12%) |
| Dyspepsia | 8 (8%) | 4 (4%) |
| Diarrhoea | 11 (10%) | 10 (9%) |
| Increased blood pressure | 15 (14%) | 15 (14%) |
| Decreased blood pressure | 8 (8%) | 2 (2%) |
| Cardiac failure | 7 (7%) | 4 (4%) |
| Fatigue | 7 (7%) | 10 (9%) |
| Headache | 4 (4%) | 6 (6%) |
| Vertigo | 3 (3%) | 7 (7%) |
| Neuritis | 6 (6%) | 4 (4%) |
| Depressive mood | 7 (4%) | 4 (6%) |
| Allergic episode | 7 (7%) | 4 (4%) |

*Seasonal/infective upper respiratory tract disorders were reported by 49% of patients on placebo and 51% on glucosamine sulphate, and influenza-like symptoms by 23% and 28% with placebo and glucosamine sulphate, respectively.

Table 4: **Proportion of patients reporting adverse events recorded with an at least 5% frequency**

# Glucosamine Salts (since 2001)

- Results replicated x 1

  Pavelka, K.et al. (2002) Glucosamine sulfate use and delay of progression of knee osteoarthritis: a 3-year, randomized, placebo-controlled, double-blind study. Arch Intern Med 2002;162: 2113–2123

- Efficacy called into question . . .
  - Regulatory status, labeling & product availability vary

- "Benefits driven by PATENTED Crystalline Glucosamine Sulfate" (Cochrane Review of 4963 patients in 25 trials)

  Towheed, T., et al. Glucosamine therapy for treating osteoarthritis. Cochrane Database Syst Rev 2:2009:DOI: 10.1002/14651858.CD002946

- European Society for Clinical & Economic Aspects of OA & Osteoporosis

  REC: Glucosamine (Rx) & Chondroitin (1st line) → "Slow onset medium to long term relief of Sx"

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# Glucosamine Sulfate (Safety Data 2012)

Crystalline GS → (RxOnly for OA) 60 countries → ~ 29 million patients

ADRs = GI distress (~ 5%), HA, fatigue & pruritis, rare allergic rxns

Rovati LC et al. Ther Adv Musculoskel Dis 2012;4(3):167-80

- GS causes ↓ in GLU uptake in skeletal muscle – may promote Insulin-resistance

Lancet 1999;354:353-4

- No change in HGA1C values in R, DB, PC 90-day trial of IDDMs

Arch Intern Med 2003;163(13):1587-90

**May interact with warfarin (case reports)**

**Short-term use: GS ≈ NSAIDs / Long term use GS > NSAIDs**

**5 yrs AFTER both 3 yr CGS trials 57% ↓ RR need for joint surgery**

Bruyere O,etal. OsteoarthritisCartilage 2008;16:254-60

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# GLUCOSAMINE (GS) & CHONDROITIN SULFATE (CS)

- LONG TERM STUDIES of CHONDROITIN SULFATE (Lone Rx) ECHO RESULTS SEEN w/ GS
  Both CS & GS have ADR profiles comparable to PLACEBO

- LIMITED EVIDENCE FOR COMBINATION (GS 1500 mg/DAY + CS 800 mg/DAY)
  Fransen M, etal.Glucosamine & chondroitin for knee OA. Ann Rheum Dis 2015;74:851-8

- NO STUDY YET CONDUCTED WITH PHARMACEUTICAL GRADE (Rx) TREATMENTS

* DONA® [(CGS) Mylan Labs} 750 mg caplet 60 ct = $25.51 (www.amazon.com)

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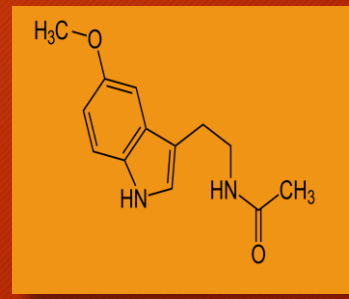
# Melatonin




Ubiquitous natural amphiphilic molecule – found in almost all living & ancient organisms

Primary: Pineal gland secretes ≈ 20 - 30 **MCG** / DAY but also GI tract, bone marrow, platelets & skin

M1 & M2 receptors expressed in various tissues

**EFFECTS: (anti-oxidant / anti-inflammatory / immunomodulator)**

Free-radical scavenger & both direct & indirect antioxidant

Protects against UV-induced formation of ROS

Modulates DNA methylation & histone acetylation

↓ levels on IL-1β, IL-6, TNF-α & CRP in stressed-out rodents J Pineal Res 2014;57:3:280-90

↓ methamphetamine toxicity / ↓ drug-induced renal toxicity & renders treatment-resistant cancers sensitive to various therapeutic agents

J Pineal Res 2016;61(3):253-78

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# Melatonin

***"Circadian rhythm dysfunction known contributor to aging and disease"*** ***(obesity, diabetes, heart dz & depression)***

**Elderly Melatonin-deficient insomniacs** Sleep 1995;18(7):598-60

**Jet lag** (5-10 mg QD 3 days prior to 4 days after) Aviat Space Environ Med 1996;67:520-4

# Melatonin
## Agency for Healthcare Research & Quality Study

"….appears **safe when used for short periods**, at relatively high doses and in various formulations

"Safety over months or even years is unclear"

"Some evidence exists for benefits of melatonin as supplement, AND evidence suggesting **limited or no benefits for most sleep disorders**."

AHRQ Pub # 05-E002-2 /Nov 2004

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# Melatonin

**NIMH-funded Meta-Analysis (2013)** PLoS One. 2013; 8(5): e63773

19 studies of 268 total (1683 subjects)

0.1 – 5 mg po daily

↓ sleep latency → 7.06 mins (CI: 4.37 - 9.75, p < 0.001)

↑ total sleep time → 8.25 mins (CI: 1.74 - 14.75, p = 0.013)

*"Synchronizes circadian rhythm & improves onset, duration & quality of sleep"*

*"Effects appear constant for any given dose or duration"*

*"No evidence for development of tolerance, dependency or hangover"*

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# Melatonin

***Effective in subpopulations:*** children, children with autism, children w/ ADHD, adolescents, depressed adolescents, pre-menstrual syndrome & post-menopausal, elderly & [**patients taking beta-blockers** → Sleep 2012;35:1395-1402]

- Large single oral doses 20-100 mg daily (20 healthy volunteers) produced no significant changes in physiological or biochemical parameters over 24hrs. No significant differences in sleep onset, sleep duration or sleep quality

***Galley HF, et al. J Pineal res 2014;56:427-38***

***ADRs:*** - Day drowsiness(20%), headache(8%), dizziness(4%), nausea(1.5%), hypothermia, agitation, fatigue, mood swings, cognition, confusion, nightmares, skin irritation & palpitations CNS Drugs 2019;33(12):1167-86

- GI Symptoms, Impaired GLU metabolism, ∆s BP/HR & sex hormones, loss of balance in elderly Complement Ther Med 2019;42:65-81

↑ ***Risk of fractures w/ long term use*** Frisher , Age & Ageing 2016

↑ ***Worsening Depression, hallucinations, rage & terror (Mega Dose 250-1200 mg)***

***Case report: (2019) infant twin death w/ melatonin concs 1400 ng/mL (NML = pcg/mL)***

***Case report: (2002) Crohn's Dz exacerbation (3 mg daily x 4 days) D/C → resolution***

FAQs ? Seizures ? Pineal gland suppression ? Nocturnal Asthma ? Organ dysfxn ? Anticoagulant effect ?

DDI: Caffeine & fluvoaxamine ↑ melatonin levels; use w/ CNS-altering agents ?

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# Melatonin (Parasomnias)

- **Parasomnias**

  *Abnormal sleep-related complex movements, behaviors, emotions, perceptions, dreams & autonomic nervous system activity that can result in physical injury & adverse consequences*

  - Further distinquished between REM & NREM parasomnias
  - REM (40-70yrs) – dream enactment often involving violent / inurious behavior during REM; 55% have Hx of injuring themselves or partner
  - NREM (pediatric) – night terrors, somnambulism, confusion during arousals

- Survey of 45 REM-type parasomniacs:

  Melatonin 6 mg equally effective to Clonazepam 0.5 mg

  Melatonin favored due to significantly fewer injuries & fewer adverse effects

  McCarter SJ, et al. Treatment outcomes in REM sleep behavior disorder. Sleep Med 2013;14:237–242

- 4 wk RCT (N = 30) Melatonin SR (2 mg or 6mg) vs PLAC (30 mins before QHS) did not reduce frequency or severity of REM sleep behavior disorder Jun JS, et al. Ann Clin Transl Neurol 2019;6(4):716-22

# Fish Oils (and other sources of EPA & DHA)

Purported Benefits

- mental health
- anti-inflammatory
- muscle maintenance
- cancer prevention
- cognition
- cardiovascular protection (↓ TRIG & . . ?)

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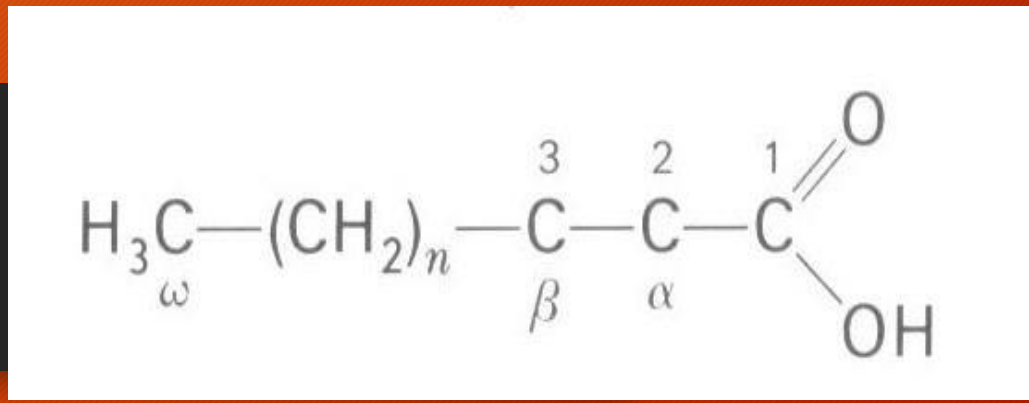
# FATS (Nomenclature)




**Saturated Fats** = One long single chain (R-COOH) – no double bonds

**Solid at normal room temperature (BUTTER)**

Ex: Palmitic Acid 16:0 & Stearic Acid 18:0

**Monounsaturated Fats** = One point of UN-saturation = one double bond

**Liquid at room temperature – solid (or very close) if refrigerated**

Ex: Oleic Acid 18:1

**Polyunsaturated Fats** = Multiple points of Unsaturation – 2 or 3+ double bonds

**Liquid at room temp AND liquid if refrigerated (freezing may solidify)**

Ex: α-linolenic acid **(omega 3)** 18:3 (N-3) (FLAX & CHIA SEEDs)

linoleic acid (omega 6) 18:2 (N-6) Ex: vegetable oils, safflower oil, corn oil, sunflower oil

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# TRANS FATS (BEWARE)

- "Natural" double-bonds always is *CIS* geometry
- High Heat / chemical modifies *CIS* to *TRANS* form
- CRISCO® – Crystallized Cotton Seed Oil (highly processed seed oil)
- TRANS FATS abundant in HIGHLY PROCESSED corn, safflower & soybean oils
- ***Trans-PUFAs*** **worse than "saturated" fats; adversely affect HDL / LDL; ↑ CVDz events**

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# History of Fish Oils (CADz)

- **1929 - EFAs identified in USA:  Evans & Burr**
- **1937 - British physiologist ( H. Sinclair ) suggested deficiencies of EFAs responsible for CADz**
- **1944 - Greenland Eskimos free from ischemic CADz and prone to epistaxis**
- **1956 - "Deficiency of EFAs & atherosclerosis, etc."**
- **1980s - Norway & Japan identified to have similarly reduced rates of MI related to greater fish consumption** (Okinawan eat 2 gms/day)
- Greenland eskimos ate ↑↑ fat (seals, whales & fish); free from CADz  (6-7 gms/day)
  - 7% DHA & Eicosapentaenoic acid (EPA; 20:5 ω-3) & 70% saturated fats
- EPA & DHA synthesized by phytoplankton; scarce or absent in land plants & animals
- Some plants do provide ALA; from which EPA & DHA can be synthesized

# Animal & in-vitro data relating to CADz

- Prevent arrythmias (Vtach & Vfib)
- Stimulate endothelial-derived nitric oxide
- Anti-thrombotic properties
- Hypolipidemic properties
- May impair atherosclerosis
- Prostaglandin & leukotriene precursors
- Anti-inflammatory properties
- Inhibit synthesis of cytokines & mitogens

# *GISSI-Prevenzione Trial*
## Dietary Supplementation ω-3 FAs

- R,DB, PC Italian MC Trial; N = 11,324 patients surviving **recent (w/in ≤ 3 mos) MI**
- **1) Vit E** (300mg/day) or **2) PUFA 1g/day** gelatin capsule (EPA/DHA ratio→ 2:1 ) or **3)** BOTH or **4) PLAC**
  - No age limit, *Excluded*: allergic, known coagulopathy, "unfavorable short-term outlook" (i.e.,severe CHF, Cancer,etc.)
  - Compliance measured by refill monitor; Intent-to-treat analysis; Kaplan-Meier survival curve; 3.5yr follow-up
- *2 combined composite endpts*:
  - 1) all-cause death + Non-fatal MI + Non-fatal stroke; & 2) CV-death + Non-fatal MI + Non-fatal stroke;
  - 2-way (any treatment vs control) & 4-way analysis (each vs control)
- *Results*: *Groups*: 2836 to ω-3; 2830 to Vit E; 2830 to both; 2828 to ∅
  - Median time to randomization after MI = 16 d; baseline demographics well-balanced

Lancet 1999;354(9177):447-55

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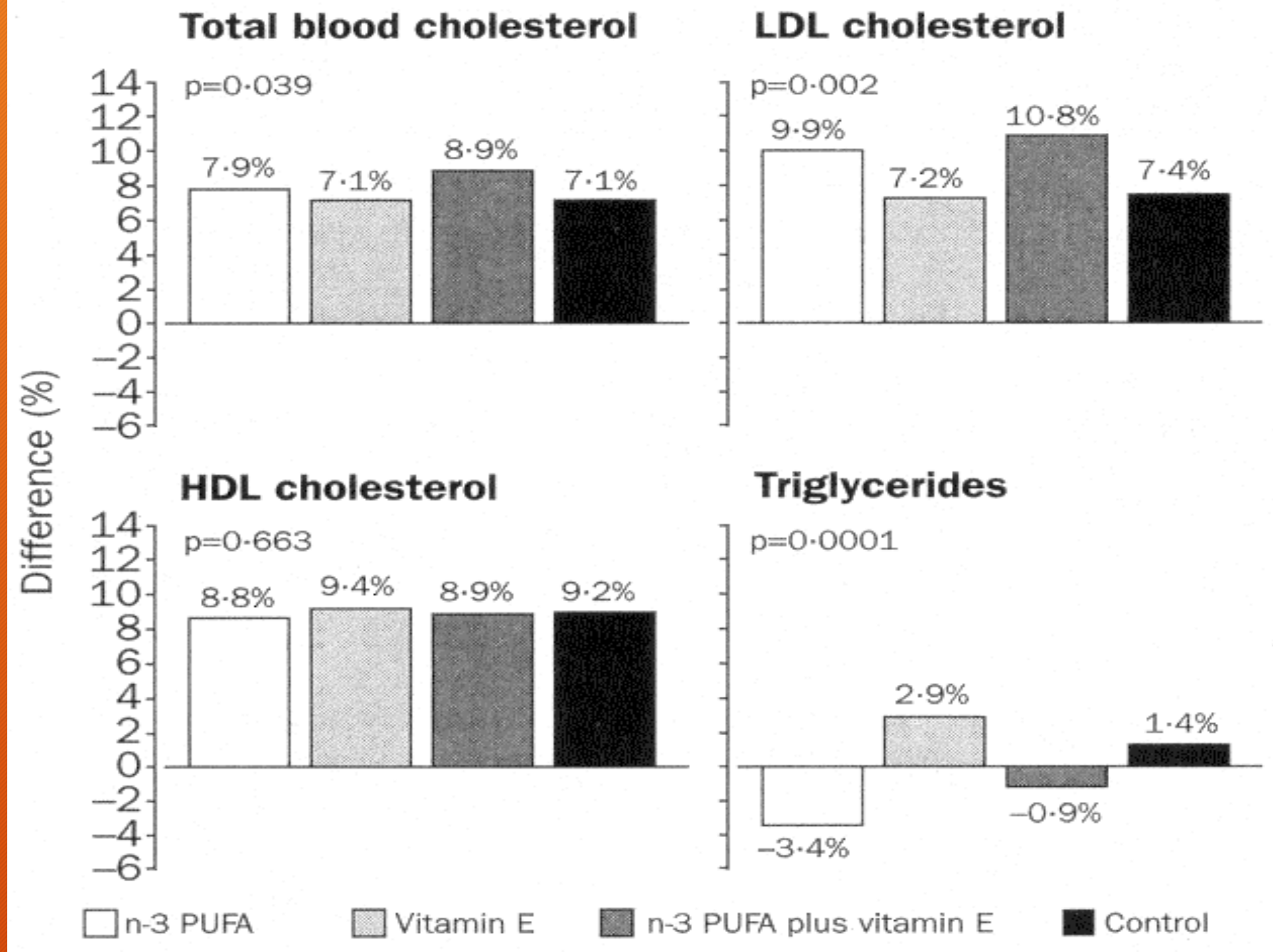


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# *GISSI-Prevenzione Trial*
## Dietary Supplementation ω-3 FAs

*Omega 3 FA Results (Cont')*:

- *2-way analysis*:
- 10% ↓ in risk of combined endpt #1 (p=0.048; CI 1-18%)
- No difference in risk of combined endpt #2 (p = NS)

- *4-way analysis*:
- 15% ↓ in risk of combined endpt #1 (p=0.023; CI 2-26%)
- 20% ↓ in risk of combined enpt #2 (p=0.008; CI 5-32%)

Lancet 1999;354(9177):447-55

# OMEGA 3 FAs FAILURE JAN 2018

## META ANALYSIS

- 10 large RCTs selected (N = 77,917 subjects) Mean Duration 4.4 yrs

  Inclusion: RCT w/ > 500 participants with > 1 yr duration

- **EPA dose 226-1800 mg/day vs PLAC → ALL NS**
  - CV Death (RR 0.93; CI 0.83 - 1.03, p = 0.05)
  - NFMI (RR 0.97; CI 0.87 - 1.08, p = 0.43)
  - Any CHDz Event (RR 0.96; CI 0.90 – 1.01, p = 0.12)
  - Vascular Events (RR 0.97; CI 0.93 – 1.01, p = 0.10)

JAMA Cardiol doi:10.1001/jamacardio.2017.5205

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# Vit D & Omega 3 (EPA 460 / DHA 380) (VITAL Study)

- DB, RCT VitD3 (2000 IU) and/or **FISH OIL 1gm/day** → 25,871 adults
  Age > 50♂, > 55♀ Median Duration Rx = 5.3 yrs
- FISH OIL did NOT ↓ 1° CV composite endpt (AMI, Stroke, CVD death)
  8%↓ = NS (386 vs 419)
- Did ↓ . . . ($p < 0.05$)
  - Total MI (HR, 0.72 [95% CI, 0.59-0.90])
  - PTCA (HR, 0.78 [95% CI, 0.63-0.95])
  - Fatal MI (HR, 0.50 [95% CI, 0.26-0.97])

*CVD event benefit seen w/subjects who consumed < 1.5 fish servings/wk

Circ Res 2020 Jan 3;126(1):112-128

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# Health Benefits of EPA

- ANTIPLATELET EFFECT (SIMILAR TO ASA W/O SIDE EFFECTS)
- ANTI-INFLAMMATORY (RESOLVINS) – RESOLVE INFLAMMATION
- ENHANCES CELLULAR METABOLISM - (EPA INCORPORATION INTO CELL MEMBRANES IMPROVES MEMBRANE FLUIDITY AND ENZYME FXN IN MEMBRANE ENHANCING CELLULAR METABOLISM)

# REDUCE-IT USA (Subgroup analysis)

**VASCEPA®** (icosapent ethyl) **2gms PO BID or PLAC**

**Purified EPA ethyl ester (EPA 960/DHA <40)**

- RCT 8179 statin-Rx pts w/ TRIGs < 500 & healthy LDL w/ CADz or NIDDM

## Subgroup 3146 pts followed for 5 yrs

- 1° CV Composite endpt → 18.2% Rx vs 24.7%, RR 69% CI 59 to 80, p < 0.000001
- 2° CV Composite endpt → 12.1% Rx vs 16.6%, RR 69% CI 57 to 83, p = 0.00008
- All endpts ↓ (AMI, CV death, stroke, total mortality, p < 0.05)

Circulation 2019 Nov 11. doi: 10.1161/CIRCULATIONAHA.119.044440

# Fish Oil (Concerns)

FDA recommends ≤ 3gms day (EPA+DHA) " unless medically necessary "

Krill Oil ≅ Fish Oil → Burps, Nausea, Gas, Bloating, Diarrhea

Slight ↑ in LFTs (common) Am J Clin Nutr 2000;71(1)197

**ADRs** (High Dose) ↓ immunity; ↑ risk Prostate CA, ↑ risk of afib, ↑ Bleeding (> 3g/day), ↑ lipid peroxidation, Impaired lipid & GLU metabolism, ↑ in cholesterol gallstones

Prostaglandins Leukot Essent Fatty Acids. 2013 ; 89(6): 379–390

1) **EAT OILY FISH (2-3 x/wk)**
2) AHA recommends **2 to 4 grams fish oil** (EPA/DHA) for ↑↑ TRIGs
3) **(4g) Vascepa = $10, (4g) Lovaza $7.32, others as low as $1.25/day (take w/ fatty meal)**
4) **Encourage antioxidant ingestion ≈ RDA**

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# Omega-3 Index (O3I)

O3I = EPA + DHA as a % of erythrocyte total fatty acids
(Ideal: 8-12% assoc w/ ↑ heart /brain health)

2 cross sectional studies examining O3I and EPA / DHA / FISH intake

Odds of having "desirable O3I"

44% in highest intake group (≥ 3 fish servings/wk + supplementation)
2% in lowest (no fish & no supplementation)

CONCLUSION:

Eat 3 fish meals /week AND take supplement

Prostaglandins Leukot Essent Fatty Acids 2019 Mar;142:4-10. doi: 10.1016/j.plefa.2019.01.002

# Ω3-FA Content
(per 100g edible raw portion)

High Mercury: Swordfish, Shark, King Mackerel & Tilefish
Fish can also accumulate dioxins & PCBs

| | |
|---|---|
| Mackerel | 1.8-5.3g |
| Herring | 1.2-3.1g |
| Salmon | 1.0-1.4g |
| Tuna/Trout | 0.5-1.6g |
| Halbut | 0.4-0.9g |
| Shrimp | 0.2-0.3g |
| Seaweed | 0.8g |
| Leeks | 0.7g |
| Kale | 0.2g |
| Soybeans | 3.2g |
| Beans (dry) | 0.6g |

| | |
|---|---|
| Walnuts | 3.3g |
| Pecans | 0.7g |
| Almonds | 0.4g |
| Peanuts | 0.2g |
| Peas / Lima | 0.2g |
| Oats | 1.4g |
| Wheat germ | 0.7g |
| Barley | 0.3g |
| Avocados | 0.1g |
| Raspberries | 0.1g |
| Strawberries | 0.1g |

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# Saw Palmetto *(Serenoa repens)*

Small palm tree of Carolinas & Florida

- CLAIMS: 1500 BC Ancient Egypt "urethral obstruction," mild diuretic & urinary antiseptic"

*In-vitro "Finasteride-like" effects (5-alpha reductase inhibitor)*

- Blocks conversion of Testosterone → Dihydrotestosterone
- Competes w/ androgen receptor & ↑ DHT metabolism

- 1990s (conflicting results) Permixon 320 mg ≅ Finasteride 5 mg

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# Benign Prostatic Hyperplasia
## Network Meta Analysis (2020)

HEXANE EXTRACT vs REGULAR EXTRACT vs PLAC vs ALPHA BLOCKERS

22 RCTs (2115 trials identified) (N = 8564)

- EVALs: (3, 6 & 12 mo) Symptom Scores IPSS & Peak Flow

**“No clinically meaningful improvement w/ use of Serenoa repens”**

- SCORING: Terazosin > Silodosin > Alfuzosin > Tamsulosin > Hexane > Regular

Eur Urol Focus 2020 Jan 15. pii: S2405-4569(20)30018-3. doi: 10.1016/j.euf.2020.01.002

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# Saw Palmetto (Sereno Repens)

**ADRs**:(mild, infrequent & reversible) Data collected 24 manufacturers / distributors

abdominal pain, diarrhea, nausea, fatigue, headache, decreased libido & rhinitis

DRUG SAFETY 2009;32(8):637-47

*Hexane extract > regular extract*

*No advantage over existing Rxs* *(Go Alpha Blockers !)*

**HAIR LOSS !!**

**Androgenetic alopecia (N = 10)** "highly positive response to treatment"

J Altern Complement Med 2002 Apr;8(2):143-52

2 year study (AGA): (N = 100) Finasteride 1 mg > Sereno Repens 320 mg

Int J Immunopathol Pharmacol 2012 Oct-Dec;25(4):1167-73

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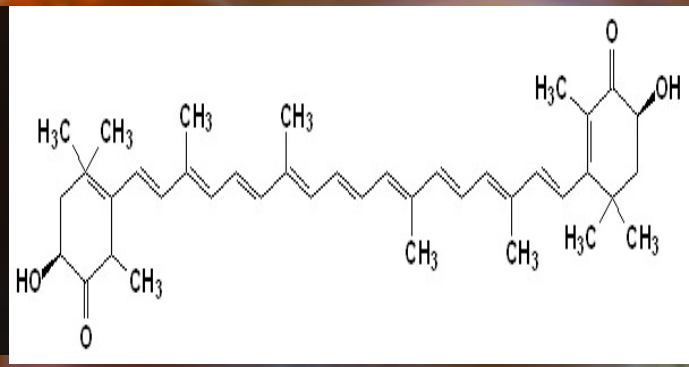
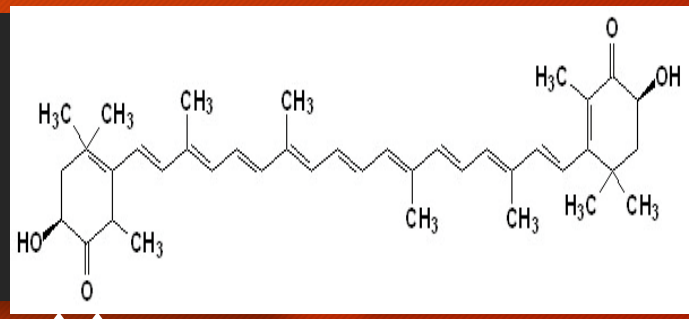
MEMECENTER.COM

# Astaxanthin

HAEMATOCOCCUS PLUIVALIS



# ASTAXANTHIN



- FAT-SOLUBLE CAROTENOID (BETA-CAROTENE, LUTEIN, LYCOPENE, ZEAXANTHIN) ↑↑ANTI-OXIDANT
  (SCAVENGES EXCESS OXIDATIVE MOLECULES THAT WOULD REACT WITH PROTEINS, LIPDS & DNA)
- WILD SOCKEYE > FARMED RAINBOW TROUT > FARMED ATLANTIC SALMON
  - ASTAX APPROVED AS COLOR ADDITIVE IN SALMON FEEDS
  - ABSORPTION ↑ WHEN GIVEN WITH DIETARY FATS/OILS
- LIPOPHILLIC & HYDROPHILLIC → READILY INCORPORATES INTO MEMBRANE
- MITOCHONDRIAL DYSFUNCTION MEDIATOR OF AGING AND AGE-RELATED DISEASE
  - LINKED TO TYPE 2 DM & INSULIN RESISTANCE
  - INSUFFICIENT LIPID OXIDATION → ACCUMULATION OF LIPID EXCESS → INSULIN RESISTANCE
  - Rodents: ASTAX improves GLU metabolism via GLUT4 regulation & inhibits tissue glycation

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# ASTAXANTHIN RODENT /IN-VIVO /IN-VITRO

- ANTIOXIDANT
- UV PROTECTION
- ANTI-INFLAMMATORY
- ANTI-DIABETIC
- ↓ MYOCARDIAL DAMAGE (PRE-TREATMENT)
- ↓ MUTAGENSIS & ↓CARCINOGENESIS
  - INHIBITED GROWTH OF FIBROSARCOMA, BREAST, PROSTATE & EMBRYONIC CANCER CELLS
- ENHANCED IMMUNITY
- NEUROPROTECTION
- ↑ GASTRIC MUCOSA PROTECTION
- IMPROVED BLOOD RHEOLOGY (20 Adults @ 6 mg/DAY x 10 days)
- EXERCISE PERFORMANCE
- AGE-RELATED MACULAR DEGENERATION (27 Adults @ 4 mg/DAY w/ other antioxidants)

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# ASTAXANTHIN in NIDDM

- ASTAXANTHIN (8 mg/day) vs PLACEBO in TYPE 2DM RCT (N = 44) for 8 weeks
- EVALUATED

  ADIPONECTIN, FRUCTOSAMINE & GLUCOSE, VISCERAL BODY FAT MASS, BLOOD PRESSURE, SERUM TRIGLYCERIDE, VLDL, CHOL
- AT 8 WEEKS

  PLASMA ASTAX CONCS ↑ from non-existent to 0.01 μmol/L

  ↑ ADIPONECTIN, ↓ VISCERAL BODY MASS, ↓ TRIG & VLDL, ↓ FRUCTOSAMINE, ↓ SBP ($p < 0.05$)
  - Marginal ↓ GLU & ↑ HDL

Mashhadi NS, et al. Asia Pac J Clin Nutr 2018;27(2):341-6

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# Turmeric & Curcumin

Turmeric (*Curcma Longa*)

- Ancient Spice from Ginger family of plants
- Asian Medicinal Folklore → antioxidant, anti-inflammatory, antimutagenic, anticancer, antimicrobial

Curcumin

- Poor absorption, rapid metabolism & elimination
- Piperine ↑ curcumin absorption 2000% Shoba G, Planta Med 1998;64:353-6
- FDA → Curcuminoids → GRAS
- Blocks NF-κβ, free radical scavenger, ↑ SOD concs, COX -, etc . . .

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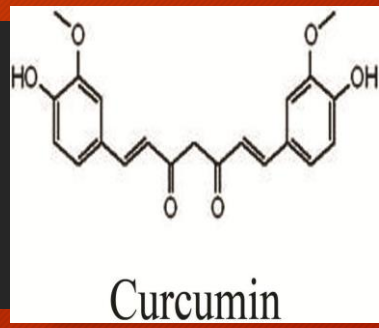
# Curcumin in OA




- Follow up trial to prior Meriva® vs PLAC pilot Belcaro, Panminerva Med 2010;52:55-62

  Meriva® - patented phosphatidylcholine-curcuminoid supplement - Manufacturer: Indena, SpA (Alme, Italy)
- Primary Knee OA (N = 100) healthy non-surgical candidates

  Add-On Rx: 500 mg po BID (200 mg curcumin) vs PLAC x **8 months**
- EVAL
  - Functional Impairment, OA symptoms, Physical Performance, Inflam Markers, Other OA Rx
- RESULTS
  - Karnofsky & WOMAC scores, Treadmill Distance, Inflam Markers, all favored Rx ($p < 0.05$)
  - Use of NSAIDs & other drugs, interventions, costs, all favored Rx ($p < 0.05$)

Belcaro Altern Med Rev 2010;15(4):337-44

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# Curcumin - Inflammatory Markers Effect

| | Rx GRP | Rx GRP | CONTROL | CONTROL |
|---|---|---|---|---|
| * p < 0.05 | Start | 8 mos | Start | 8 mos |
| sCD40L (ng/mL) | 2.47 | 1.39* | 2.34 | 2.46 |
| IL-1β (pg/mL) | 0.88 | 0.31* | 0.92 | 0.89 |
| IL-6 (pg/mL) | 1.38 | 1.01* | 1.36 | 1.39 |
| sVCAM-1 (ng/mL) | 644 | 456* | 652 | 641 |
| ESR (mm/hr) | 35.23 | 26.23* | 37.59 | 36.63 |
| Treadmill Distance (meters) | 77.3 m (15-188) | 344.4 m (113-478)* | 82.3 m (19-210) | 156 m (46-383)* |

200 mg Curcumin vs PLAC for 8 mos
N = 100 healthy Knee OA subjects
Beclaro Alt Med Rev 2010;15(4):337-44

**Unrelated trial 6 wk duration failed to show beneficial effects in cytokines but still showed benefit via VAS & WOMAC**
Panahi, Phyother Res 2014;28:1625-31

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# Meta Analysis of Curcumin in Joint Arthritis 2016

- 8 articles met criteria of 29 identified (N = 45-124 subjects)
- Eval concluded low to moderate risk of bias
- Conclusion:

> *"evidence that 8-12 weeks of standardized turmeric extracts (1000 mg / day curcumin) treatment can reduce arthritis symptoms (pain and inflammation-related symptoms) and result in similar improvements in symptoms as either ibuprofen or diclofenac . . . . turmeric extracts and curcumin can be cautiously recommended for alleviating the symptoms of arthritis, especially osteoarthritis."*

Daily JW et al. J Med Food 2016;19:717-29

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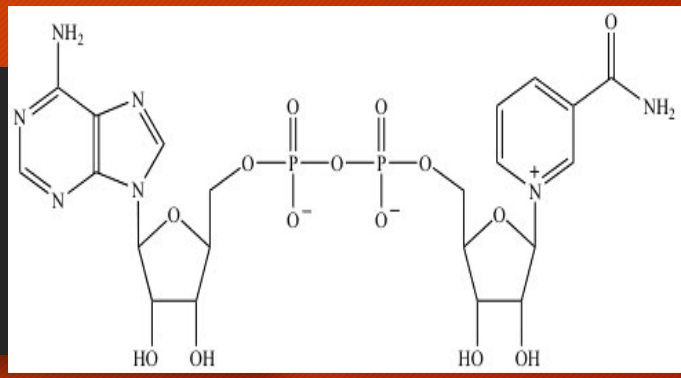
# Turmeric / Curcumin

- ADRs
  - Mega doses have been studied (up to 12,000 mg /day)
  - Most Common: Diarrhea, nausea, headache, rash, yellow stool & ↑ AlkPhos & ↑ LDH
  - Can worsen gallbladder disease (↑ contractions) Rasyid, Asia Pac J Clin Nutr 2002
  - Case reports ↑ LFTs / liver injury accumulating (~ 5%) Lukfahr BMJ Case Report 2018
  - Curcumin inhibits platelet aggregation (in-vitro & in-vivo) Shah Biochem Pharmacol 1999
  - Kidney Stones ? - Some products contain oxalates American Urologic Association 2017
  - High doses (> 2000 mg/day) may bind iron & ↓ absorption Tuntipopipat Int J Food Sci Nutr 2009
  - Conflicting reports on CYP 3A4 metabolism

# Nicotinamide adenine dinucleotide **NAD** & Nicotinamide riboside (precursor) **NR**



- Prelim evidence NR supplementation ↑ serum NAD+ levels (NIAGEN®)
- Possibility ? improve disease assoc w/ mitochondrial dysfunction

- 40 middle-age, obese, insulin-resistant men
- NR 1000 mg vs PLACEBO x 12 weeks
  - Skeletal Muscle Biopsy
  - High-resolution respirometry on muscle fiber
  - Protein abundance & mRNA expression
- Levels of NAMPT decreased by 14% w/ NR
- NO CHANGE: NAD+ levels, mitochondrial protein abundance, respiratory capacity, mitochondrial fractional area or network morphology

Dollerup OL et al. J Physiol 2019;Nov 11 /10.1113/JP278752

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# Relative Risk Drug – DS Interactions

*Am Fam Physician* 2017;96(2):101-107

| HIGHER RISK | |
|---|---|
| Goldenseal (Hydrastis Canadensis)<br>Inhibits CYP 2D6 & 3A4 | Multiple drugs potentially effected (psych, cardiac, opiates, warfarin, etc.) |
| St John's Wort (Hypericum perforatum)<br>Potent inducer of P-gp & CYP3A4 | ↓ effectiveness: cyclosporine (Sandimmune), tacrolimus (Prograf), warfarin (Coumadin), protease inhibitors, irinotecan (Camptosar), theophylline, digoxin, venlafaxine, and oral contraceptives; |
| **LOWER RISK** | |
| Black Cohosh | May ↓ effectiveness of statins; single report of ↑ LFTs with atorvastatin |
| Garlic (P-gp Inducer) | ↓ effectiveness: colchicine, digoxin, doxorubicin, quinidine, rosuvastatin, tacrolimus verapamil |
| Ginkgo Biloba | Potential ↑ bleeding risk with warfarin (antiplatelet effect) |
| Kava Kava<br>Possible effect multiple CYP450 enzymes | Caution using CNS depressants, such as benzodiazepines, or alcohol, because of the increased risk of drowsiness and motor reflex depression. d/c Kava ≥ 5 days before surgery w/ anesthesia |
| Green Tea<br>Inhibitor P-gp, OATP1A1, or OATP1A2 | Caution with ↑ concs / effectiveness of statins, fluoroquinolones, some beta blockers, imatinib, & antiretrovirals |
| Saw Palmetto, Cranberry, Valerian, Milk Thistle | Minor, if any effect (theorized) and/or little to nothing reported |

# Dietary Supplements
## General Perspective

- **Potential for benefit, must be proven with well-designed DB, RCTs**
- **Standardized dosage forms are required**
- **Data often too preliminary for therapeutic application**

  ***(Exceptions: Terminal Dz or Severe Morbidity with no reasonable allopathic Rx)***
- **Clinical research to be promoted**
- **ADRs should be reported to MEDWATCH 1-800-332-1088**
- **HCPs require education to ensure informed decision-making of patients**

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# Patient Counseling

- Mandate disclosure of  ALL medication
- Reinforce “self-empowerment” towards individual health improvement
- Discuss herbal “body of evidence”
- Explain potential downfalls & how to self-monitor
- Convince patient to follow progress by “objective goals” (along with you)
- Agree on timeline for re-evaluation of use

# Alternative Medicines
## Internet Sites

- **Office of Dietary Supplements**
  www.ods.od.nih.gov
- **National Center for Complementary & Integrative Health**
  www.nccih.nih.gov
- **NCI Office of Cancer Complementary & Alternative Medicine**
  www.cam.cancer.gov
- Center for Food Safety & Applied Nutrition (CFSAN) (Policies & Guidance & Labeling)
  www.fda.gov/about-fda/center-food-safety-and-applied-nutrition-cfsan/cfsan-foia-electronic-reading-room
- Research Council for Complementary Medicine
  www.rccm.org.uk
- Consumer Labs (Independent Qualitative Analysis)
  www.consumerlabs.com
- American Botanical Council
  www.abc.herbalgram.org

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# Alternative Medicines
## Journals

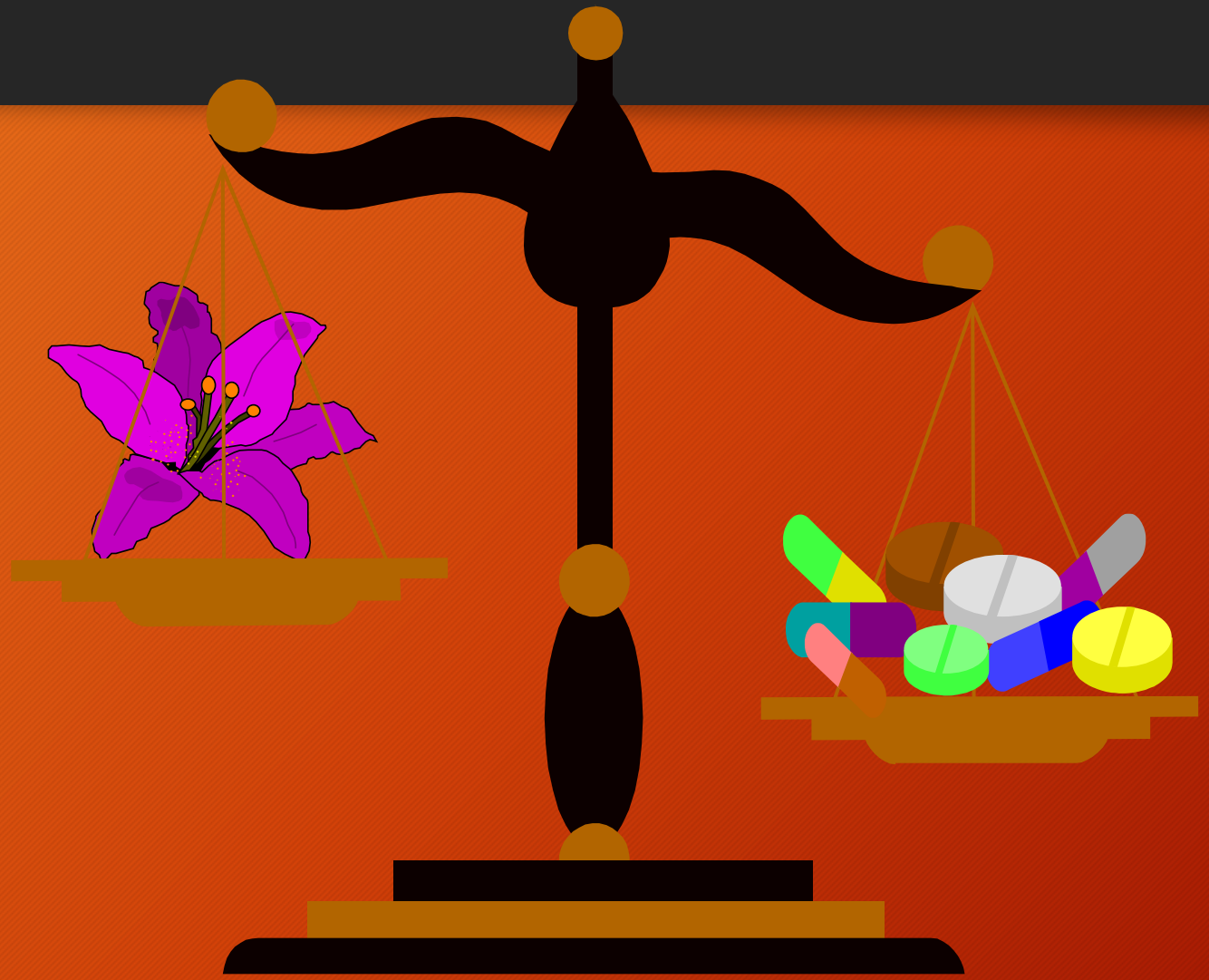
- Alternative Therapies in Clinical Practice
- Alternative Therapies in Health & Medicine
- Complementary Therapies in Medicine
- European Journal of Herbal Medicine
- Journal of Alternative and Complementary Medicine
- Focus on Alternative and Complementary Medicine
- HerbalGram

“All substances are poisons . . .
there is none which is not a poison.
The right dose differentiates a poison from a remedy.”

**Philippus Aureolus Thephrastus Bombastus von Hohenheim-Paracelsus**

**(PHYSICIAN-ALCHEMIST 1493-1541)**

# QUESTIONS / COMMENTS ?



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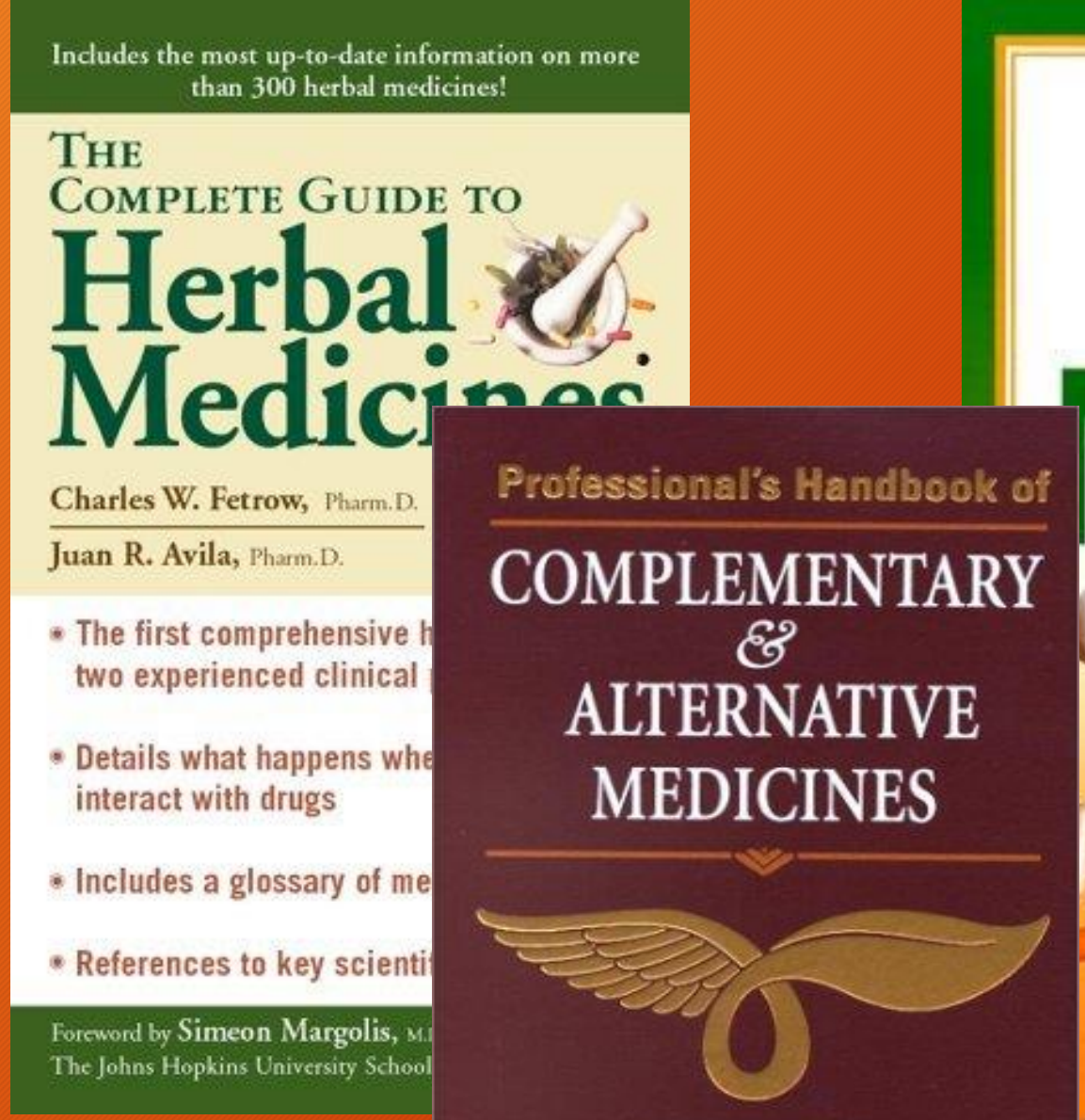





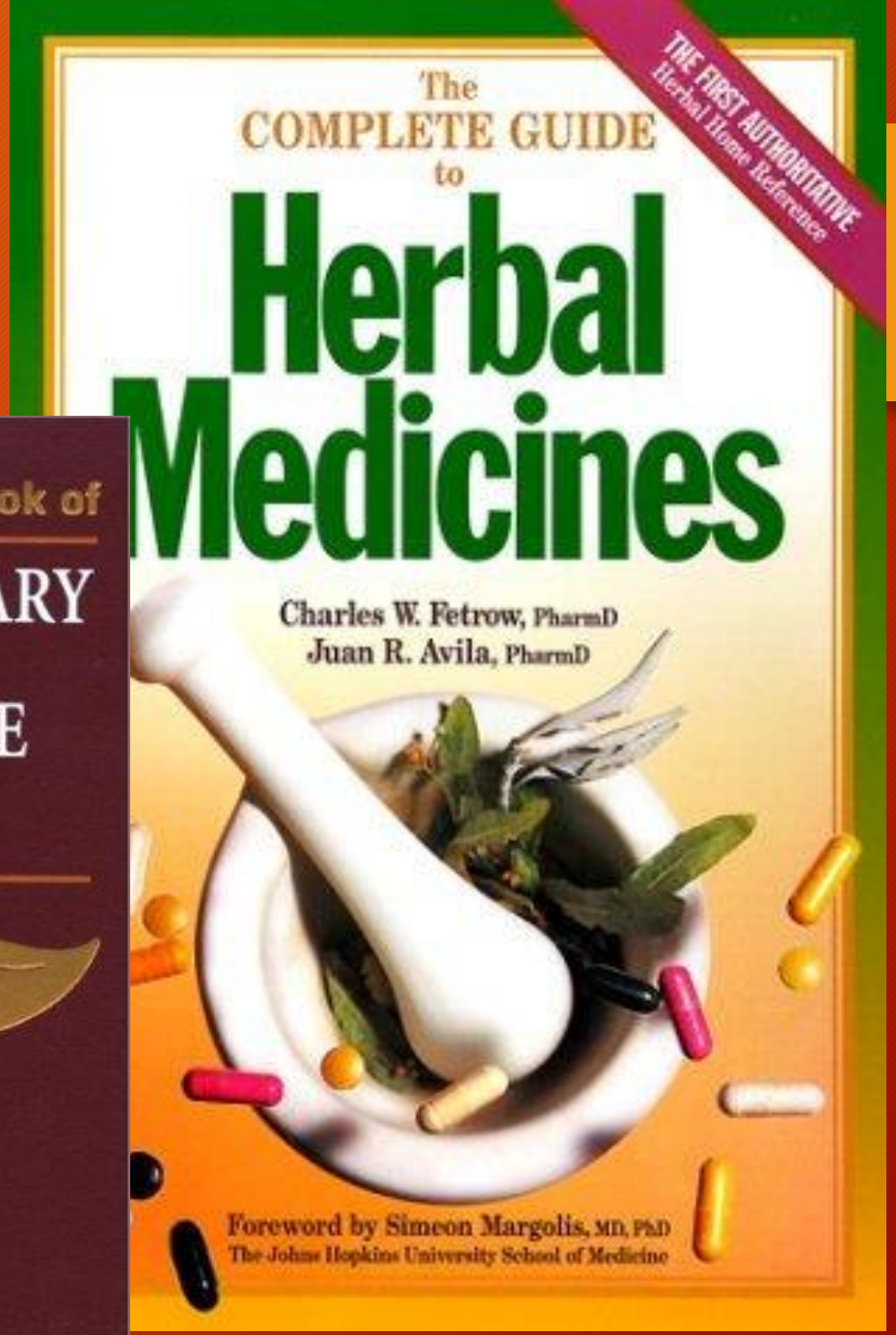


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