Milk Thistle

✿ Botany
- Silybum marianum
- Asteraceae family (daisy, thistles, artichoke)

✿ History
- long used to treat “liver problems

✿ Chemistry
- fruits/seeds contain flavonolignans
- silymarin=crude mixture of flavonolignans; actually is mixture of several e.g. silybinin
- Seeds generally used
Milk Thistle

**Pharmacology**
- silymarin has strong antioxidant properties
- has ability to block toxin entry through membranes
- stimulates liver regeneration; undergoes enterohepatic circulation
- increases glutathione
- stimulates ribosomal RNA polymerase
- has anti-carcinogenic activities in vitro and in animals

**Uses**
- liver cirrhosis
- hepatitis A,B,C
- liver toxin poisoning (e.g. amanita mushroom)

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**Viral Hepatitis (A or B)**

in several studies patients “normalized” hepatic function tests faster in the milk thistle group compared to placebo; shorter hospital stay

**Hepatitis C** – unknown efficacy; Tanamley et al. (Dig Liver Dis. 2004 Nov;36(11):752-9) were not able to show improvement compared to a multivitamin control at 1 yr (n=141).

**Toxin and Drug Inducted Hepatitis**

both animal and some small patient studies show protective effect of milk thistle or silymarin

**Alcohol Related Liver Disease**

some improvement in liver function tests compared to placebo in limited studies
- cirrhosis: Pares et al. J. Hepatol 28:615-621, 1998; no effect on survival or clinical course of alcoholics; n=200; 2yr study
- cirrhosis: (Ferenci et al. J. Hepatol 9:105-113, 1989 showed 58% 4yr survival in treated vs 39% placebo (p=0.036); 4 yr study
- Lucena et al. (Int J Clin Pharmacol 2002;40:2-8) showed increase in glutathione and decreased liver peroxidation in patients with alcoholic cirrhosis but no change in routine liver tests in treated compared to placebo. N=60

A meta-analysis (Am J Med 2002;113:506-15) concluded no strong benefit but more studies needed; animal studies indicate considerable promise for beneficial activities
Serum alanine aminotransferase activity

Mortality from liver disease
Milk Thistle

• Cautions
  • Nothing special

• Interactions
  • None of significance reported as yet. Recently shown to not affect indinavir pharmacokinetics

• Products
  • flavonolignans are not water soluble
  • extract used
  • extracts containing at least 70% silymarin are best
  • A lipid complex of silibin has high bioavailability

Milk Thistle

Summary

- Efficacy: of unproven help for liver injury due to hepatitis and drugs and alcohol.
- Safety: good
- Drug interactions: None of significance reported as yet. Recently shown to not affect indinavir pharmacokinetics
- Product selection: extract containing 80% silymarin is best
- Dose: 200mg TID
- Questions remaining include
  - *Does milk thistle really not work for its hepatitis C and for alcoholic liver disease?*
Evening Primrose Oil

Botany
Oenothera sp., a wildflower/weed on the East USA coast
The seed is pressed to yield an oil

History
Many native American uses for the plant
Recent years have focused on the uses of the seed oil

Chemistry
• Seed contains about 14% oil of which half is gamma linolenic acid (GLA); this is a omega –6 essential fatty acid;
  
  • note: omega –3 fatty acids are present in fish oils and flaxseed oils and have different uses (e.g. lower cholesterol and risk of cancer
  
  • GLA is a precursor to prostaglandin E1 which modulates inflammation
  
  • Other rich sources of GLA are borage seed oil (20%GLA) and black current oil (15% GLA)
Pharmacology of GLA

• GLA is precursor to several prostaglandins and leukotrienes that influence pain and inflammation

• The idea is to “flood the system” with precursor to enhance synthesis.

• Linoleic acid is an essential amino acid widespread in our diet

• GLA is formed from linoleic acid and is not found in common foods

Uses of GLA and Evening Primrose Oil

• Cyclic mastalgia

• PMS

• Diabetic neuropathy

• Eczema

• Arthritis and many other uses

\[
\begin{align*}
\text{H}_3\text{C}(\text{CH}_2)_4 & \quad \text{(CH}_2)_4\text{COOH} \\
\gamma\text{-Linolenic Acid}
\end{align*}
\]

6,9,12 octadecatrienoic acid

Linoleic is 9,12 octa decadienoic acid-plentiful in diet
Evidence

• The evidence is surprisingly weak for most uses

• Several placebo controlled trials in the 1980s showing improvement in breast pain associated with menses; a recent study showed no effect (Am J Obstet Gynecol. 2002 Nov;187(5):1389-94).

• No strong evidence to show improvement of other symptoms of PMS or post menopausal symptoms

• Eczema use has been not effective in recent studies

• Use in diabetic neuropathy and rheumatoid arthritis looks promising based on a small number of older controlled studies

• More evidence is needed to support use of EPO in Raynauds syndrome, ADD, osteoporosis and obesity, hyperlipidemias

Safety

No special concerns at present

Dose: 2-6g of EPO/d or even higher
Evening Primrose Oil

**Summary**
- Efficacy: uneven evidence for most uses; best for diabetic neuropathy, cyclic breast pain, and possibly rheumatoid arthritis
- Safety: good
- Drug interactions: none noted so far but increased blood clotting time has been noted. Caution with warfarin.
- Product selection: Efamol is the best studied; has 1g/capsule
- Dose: 2-6g/d
- Questions remaining include
  - *Does EPO really work for its many suggested uses?*

Valerian

**Botany**
- Valeriana officinalis, garden heliotrope
- roots and rhizomes used
  - powder
  - tincture

**History**
- roots long used as tranquilizer and sedative
Valerian

**Chemistry**
- 0.1%-0.3% volatile oil in roots
- contains sesquiterpenes e.g. valerenic acid
- contains valepotriates
- contains baldrinal and other decomposition products

**Pharmacology**
- volatile oil is sedative in animals
- valepotriates have tranquilizer activity
- water extract is sedative and has neither!
- ? Active components
- in vitro-
  - aqueous extracts causes release of GABA (similar to benzodiazepines)
  - inhibit GABA breakdown
- mechanism unknown, active components unknown!

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![Chemical structures of Valerian compounds](image)
Fig. 2.16. Effect of 4 week’s treatment with an ethanol valerian extract (600 mg/day) compared with a placebo. The results were assessed by the Görtelmeyer sleep questionnaire (SF-B) and statistically evaluated. A significant difference between valerian and placebo is seen only after a 4-week course of treatment (Vorbach et al., 1996).

Fig. 2. Differences in sleep stages: NREM 1, NREM 2, REM, and slow-wave sleep (SWS) between baseline and long-term treatment under placebo and valerian.

Donath et al. Pharmacopsychiatry 2000;33:47-53. N=16; valerian for 14d; crossover study
Valerian

**Precautions**
- drowsiness, avoid alcohol
- restlessness, nausea
- worry over valepotriate epoxide (liver damage) but commercial products have little
- not pregnancy, not infants, not nursing
- limit use to 2 weeks (?? ??), withdrawal signs have been reported but these reports are suspect
- acute overdose (20x) gave only mild effects

**Dose**
- 400mg – 600mg of an extract at hs
- 2-3g of powder to make tea
- 1-3ml of tincture

**Products**
- valerenic acid as marker

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Fig. 2. Mean Sleep quality (SQ) at baseline and after 2, 4 and 6 weeks of treatment (PP analysis).

Valerian

Summary

- Efficacy: long historical use; limited number of controlled studies but all show some efficacy. Acute use may be ineffective.
- Safety: good but be careful as with any sedative
- Drug interactions: none noted so far
- Product selection: Alluna, Sedonium are excellent brands
- Dose: about 600mg of a root extract at HS
- Questions remaining include
  - *How effective is this for occasional use?*
  - *How effective is this for chronic insomnia?*

Grape Seed Extract

Botany

- Seeds from Vitis vinifera

History

- Relatively recent use as an antioxidant

Chemistry

- seeds contain proanthocyanidins (OPC)
- OPC s are oligomeric or polymeric flavonoid like polyphenolic compounds
- OPC s have strong antioxidant and free radical scavanging activities
- OPC s are also high in pine bark (pycnogenol)
Pharmacology

- In vitro will prevent destruction of elastin, collagen and hyaluronic acid
- In animal models will reduce capillary permeability and decrease swelling and inflammation
- Action due to the ability of OPC s to block free radical damage and otherwise protect against oxidative damage
Uses

- Treatment of varicose veins
- Reduce swelling due to surgery or injury
- Treat and prevent macular degeneration
- To reduce the risk for cancer and heart disease
- Treat diabetic retinopathy and neuropathy
- Other

Evidence

- Varicose veins
  - Reasonable evidence based on placebo controlled trials. Trials published in French and Italian thus not readily evaluated by all
  - Reduce pain and swelling due to injury/surgery
    - Three controlled studies (in French)
- Vision - one study
- Heart Disease – some evidence for potential

Other – limited evidence from animal or in vitro studies; may lower cholesterol in combination with chromium
LDL oxidation; N=15 with CAD; grape juice x14d; Stein et al 1999;100:1050-1055.

Flow mediated vasodilation; N=15 with CAD; grape juice x14d; Stein et al 1999;100:1050-1055.
Safety

Considered nontoxic

Interactions

OPCs have antiplatelet adhesion properties so that an anticoagulant effect could be noted at higher doses; avoid concurrent use with warfarin and other anticoagulants

Products

Grape seed extract products contain 100mg of extract per capsule. Dose: 100mg TID
Grape Seed Extract

Summary
- Efficacy: probably effective for peripheral venous insufficiency. May help vision and macular degeneration. Other uses need more work.
- Safety: good
- Drug interactions: careful with anticoagulants
- Product selection: ? Most are not standardized to OPCs
- Dose: 100mg TID
- Questions remaining include
  - Will grape seed extract help in vascular diseases other than varicose veins? What about coronary disease?

Bilberry
- Botany- extract of the fruit of the “European Blueberry” which has a white inside. Vaccinium myrtillus. Common blueberries are other Vaccinium sp.
- History-used by English pilots in WWII to improve night vision
- Chemistry-contains anthocyanosides (glycosides of anthocyanidins); these like OPCs (see grape seed extract) are powerful antioxidants
- Pharmacology- antioxidant and free radical scavanging activities with maybe special action in the eye
- Use-poor night vision, cataracts, macular degeneration, diabetic retinopathy
• Evidence -
  • conflicting small studies. More work needs to be done; recent study by the US Navy showed no benefit in night vision (Muth et al. Alter Med Rev 2000;5:164-173) in a small placebo controlled study (n=13) in men with normal vision
  • Retinopathy. Diabetic and hypertensive retinopathy improvement in 2 small studies.

• Safety-OK  Interactions- none

• Products - look for extracts standardized to 25% anthocyanosides; 100mg qd or BID

• Summary - safe but unproven product for vision problems

*Anthocyanidin structure*
Green Tea

Botany-Camillia sinensis leaves
black tea—fully fermented leaves; 40 mg caffeine/cup
green tea—steamed, nonfermented leaves; 20 mg/cup
oolong tea—partially fermented
white tea—steamed leaf buds; 15 mg/cup

Chemistry—the hot water extract of the leaves contains OPCs and other antioxidant/free radical scavenging compounds (see grape seed extract); green and white tea has mainly catechins, black tea has theaflavins.

Pharmacology—protective activity against experimental cancers in animals and some epidemiological evidence for protective effects for stomach, colon, pancreatic cancers and lower cardiovascular disease risk.

Uses—probably need multiple cups/d; tablets of the dried extract are commercially available but do they have the same effect?

Archiv Intern Med 2003;163:1448-1453  n=240  12 weeks used theaflavin enriched green tea extract in capsule form
Green Tea

Evidence-increased consumption correlates to decreased risk of several cancers and possibly heart disease in studies on Japanese; extracts may lower cholesterol but evidence is weak

Cautions-caffeine! Although the amount is less than in a cup of coffee; contains vitamin K so be careful with warfarin

Products-? Green tea or black? Capsules or tea?

Questions-how much? Does black tea have the same effect? How much benefit?

June 30, 2005, FDA denied health claim for Green Tea

1. "Two studies do not show that drinking green tea reduces the risk of breast cancer in women, but one weaker, more limited study suggests that drinking green tea may reduce this risk. Based on these studies, FDA concludes that it is highly unlikely that green tea reduces the risk of breast cancer."

2. "One weak and limited study does not show that drinking green tea reduces the risk of prostate cancer, but another weak and limited study suggests that drinking green tea may reduce this risk. Based on these studies, FDA concludes that it is highly unlikely that green tea reduces the risk of prostate cancer."