Special Seven: Key Botanicals in Integrative Oncology

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Disclosures

- **Compensated occasional industry-sponsored webinars and educational presentations:**
  - NutraBioceuticals, Gaia, NFH, Nordic Naturals
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  - Kyowa Hakko, Essential Formulas, Integrative Therapeutics

Outline of Topics

- I will highlight 7 herbs that are indispensable in my integrative oncology practice
- For each herb, I will start with a case vignette, review key oncology-relevant indications, seminal research studies, pharmacy, and safety considerations
- Herbs to be reviewed are:
  - Curcuma longa
  - Cordyceps spp.
  - Scutellaria baicalensis
  - Lavendula officinalis
  - Althea officinalis & Ulmus fulva
  - Silybum marianum
  - Withania somnifera

Between 50,000 – 80,000

This is the number of plants used medicinally worldwide.

Chen, SL., Yu, H., Luo, HM. *et al.* Conservation and sustainable use of medicinal plants: problems, progress, and prospects. *Chin Med* **11**, 37 (2016).

I will be discussing 7!

Patient Vignette: Turmeric

- 70y man with metastatic colorectal cancer receiving chemotherapy
- Fatigue
- Unrelated long-standing mild low back pain

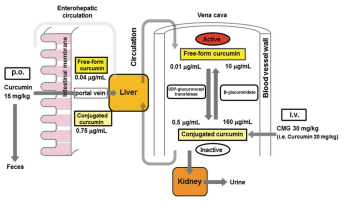
Curcumin

- Curcumin is the major bioactive component from the rhizome of turmeric (Curcuma longa)
  - 0.58% - 3.4% of dry weight of dried turmeric root
  - Also present, at lesser concentrations, are demethoxycurcumin and bisdemethoxycurcumin
- Curcumin is associated with anti-inflammatory, antioxidant, hypoglycemic, wound healing, antimicrobial, and antitumor activities.
- Curcumin itself has very poor bioavailability with only minute amounts reaching peripheral circulation after ingestion.

Luca S, Crit Rev Food Sci Nutr. 2019;60(4):626
Tsuda T, Food and Function. 2018;9:705

The Dynamic State of Curcumin Conjugation

- Main state of curcumin the body is as curcumin glucuronide.
- While this form facilitates elimination, curcumin glucuronide can also be deconjugated in circulation and intracellularly via B-glucuronidase, increasing tissue concentrations of free-form curcumin
- Free-form curcumin is unstable and most unconjugated curcumin will degrade into bicylopentadione, vanillin and ferulic acid.
- Furthermore, sites of inflammation increase deconjugation because B-glucuronidase is released at sites of inflammation
- Inflammation also increases oxidation (degradation) of curcumin to its degradation products



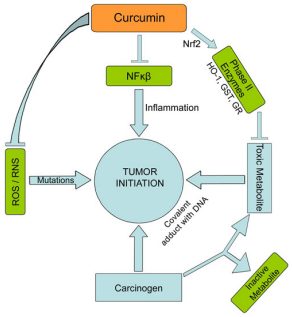
Tsuda T, Food and Function. 2018;9:705
Schneider C, J Agric Food Chem. 2015;63(35): 7606

Bioactivity of Curcumin Metabolites vs. Curcumin

- Curcumin metabolites, namely tetrahydrocurcumin (THC) and hexahydrocurcumin (HHC) are more stable than curcumin and possess significant antioxidant and anti-peroxidation activities
  - THC and octahydrocurcumin (OHC) have more potent free radical scavenging activities than curcumin
  - THC activates glutathione peroxidase and glutathione S-transferase more effectively than curcumin
- Curcumin metabolites possess anti-inflammatory activities (inhibition of 5-LOX, PGE_2 and NF-kB) but less so than curcumin.
- Curcumin has the strongest antiproliferative actions, however THC and HHC have stronger anti-angiogenic and pro-apoptotic effects
  - Curcumin conjugates (curcumin glucuronide and curcumin sulfate), while weaker than curcumin, inhibit cell proliferation and inhibit inflammatory PGE_2
- THC has more potent hypoglycemic actions than curcumin.
- HHC has stronger anti-platelet aggregation and vasorelaxant effects than curcumin

Tsuda T, Food and Function. 2018;9:705

Curcumin and inflammation

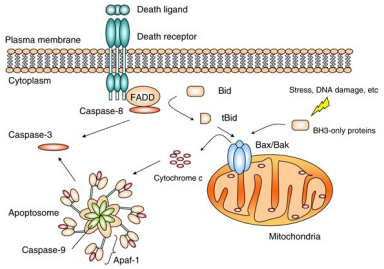


- Directly quenches reactive oxygen species (1)
- Inhibits NFkB activation (1)
- Promotes Nrf2 activation (1)
- Curcumin is a PPAR-γ agonist, leading to anti-inflammatory and anti-angiogenic effects (2)
- Activates Vitamin D receptor, leading to increased transcription of anti-inflammatory genes (3)

1. Surh YJ, Kundu JK, Na HK, Lee JS. J Nutr. 2005 Dec;135(12 Suppl):2993S-3001S
2. Allegri P, et al. Clinical Ophthalmology. 2010;4:1-6
3. Bartik L, J Nutr Biochem. 2010; 21:1153

Reduced Risk of Cancer via Enhancement of Cellular Apoptosis

- Apoptosis is the mechanism of programmed cell death typically in response to oxidative stress and is an essential component of cancer prevention.
  - A hallmark of cancer is the evasion of apoptosis by cancer cells
- Amorphous curcumin (as Curcumin-Galactomannoside, CGM, complex) has been show in-vitro to selectively upregulate pro-apoptotic mitochondrial protein, Bax (instrinsic apoptosis) and to activate apoptotic enzyme caspase-8 (extrinsic apoptosis) in malignant cells.
- Additionally, CGM downregulates anti-apoptotic Bcl-2 and the inactive form of caspase-8.



Ratheesh M, et al. Asian Pac J Cancer Prev. 2021;22(6):1713
Tomeh MA, Int J Mol ci. 2019; 20(5):1033

Curcuma longa: anti-inflammation during chemotherapy

- An 8-week randomized, double-blind, placebo-controlled eight-week trial of 98 adults with solid tumors (primarily breast, colorectal, and gastric) assessed the impact of curcumin on systemic inflammation.
- Intervention was 300mg phytosomal curcumin (Meriva; Indena SpA; Milan, Italy) three times daily, providing 180 mg curcuminoids daily.
- Chemotherapy regimens that were commonly used for these cancers were:
  - docetaxel, cisplatin-5, fluorouracil (5-FU) (gastric cancer and breast cancer)
  - topotecan-cyclophosphamide-etoposide (breast cancer)
  - cyclophosphamide-methotrexate-5-FU (breast cancer)
  - 5-FU-based regimens (colorectal cancer)
- Results: Curcumin supplementation resulted in significantly greater improvements in quality of life (QoL) compared with placebo (P<0.001).
- Additionally, various biomarkers of systemic inflammation reduced significantly in the curcumin group, including tumor necrosis factor-alpha (TNF-α), transforming growth factor-beta (TGF-β), high-sensitivity C-reactive protein (hs-CRP), and calcitonin gene-related peptide (CGRP).

Panahi Y, Phytother Res. 2014;28(10):1461

Curcuma longa: Reduced chemotherapy-induced peripheral neuropathy

- Capecitabine (Xeloda®) is associated with a 40% to 50% incidence of hand-foot syndrome (HFS), a form of peripheral neuropathy.
- In a 6-week pilot study of 40 patients (80% were female and 52% had breast cancer) receiving capecitabine, 4g of turmeric (95% curcumin extract), taken as two capsules 12 hours apart, was associated with a reduced incidence of all grades of HFS.
- The incidence of grade 2 or higher HFS (more severe) was only 10% after the first and second cycles of capecitabine as compared to observed rates of 29% to 38% in placebo groups reported in other trials.
- While these data are encouraging, this study is limited by its small size and the lack of a control group.

Scontre V, J Dietary Suppl. 2018;15(5):606

Curcumin: Safety during Chemotherapy

- IIa open-labelled RCT of 28 patients with metastatic colorectal cancer receiving folinic acid/5-fluorouracil/oxaliplatin (FOLFOX) chemotherapy once every 2 weeks with or without 2g oral curcumin daily
  - Curcumin C3, Sabinsa Corp. containing 80% curcumin and 20% demethoxycurcumin and bisdemethoxycurcumin daily.
  - Duration: up to 12 cycles of chemotherapy, or patient progression, unacceptable toxicity, death or withdrawal.
- No differences in adverse events
- In the ITT analysis, there was no statistically significant difference in overall survival or in progression free survival.
  - There was a non-statistically significant trend towards longer OS and PFS in the curcumin group.

Howells L, J Nutr. 2019;149&7):1133

Modified Curcumin

Note that comparisons of the bioavailability of different forms is difficult due to differences in subjects, curcumin dosages, and blood sampling time points.

- Clinically studied dosages range from 300mg to 8g daily.
  - Liquid extract (1:1 45% EtOH or higher): 5-14 m/day
  - Powdered herb: 4g (heaped teaspoon) mixed with water (can add 1 tsp lethicin to improve absorption); 4g – 8g/day
  - 1st Generation Modification:
    - 95% curcuminoid extract with piperine; 2x AUC all curcuminoids: 500mg curcuminoids with 5mg piperine; 1000mg – 2000mg/day
    - 25:1 herb:extract; 86% total curcuminoids complexed with essential oils of turmeric; 7x AUC): 800mg – 1600mg/day
  - 2nd Generation Modification:
    - Water-dispersible colloidal suspension with 30% curcuminoids with 24x AUC): 300mg – 600mg/day
    - Submicron colloidal suspension in gum ghatti 30% curcuminoids; 27x AUC): 600mg -1200mg/day
    - Curcuminoid phytosome – complexed with lecithin; 30x AUC curcuminoids: 1500mg – 3000mg/day
  - 3rd Generation Modification:
    - Amorphous complex of curcuminoids with galactose and mannose polysaccharides; 25x – 39x AUC free curcuminoids): 320mg – 640mg/day [100mg curcuminoids/320mg CGM]
    - Amorphous powder of curcuminoids mixed with starch, ground in distilled water and freeze-dried for stability; 3.7x higher bioavailability than 2nd generation submicron colloidal suspension): 225mg - 450mg/day [90mg curcuminoids/225mg Amorphous curcumin extract]

A good resource: Hegde M, ACS Omega. 2023;8:10713

Curcumin: safety

- Turmeric has Generally Recognized as Safe (GRAS) status in the United States in doses as high as 10-12g in healthy individuals (1)
- One case report of iron deficiency anemia with 3g turmeric extract daily (turmeric reduces iron absorption by 20-90%).(2)
  - Monitor Hgb with long-term use.
- A handful of case reports (~21) of hepatotoxicity from long-term use have been reported. A review of these cases concluded that this toxicity was like due to: added adjuvants that inhibit detoxification enzymes, adulteration with synthetic curcumin or contamination with heavy metals, dyes, mycotoxins, NSAIDs, polyaromatic hydrocarbons or pyrrole alkaloids (3) or due to piperine (4)
  - In 2022, the global curcumin market was $242M (over 5 million curcumin supplements)
- Turmeric is high in oxalates therefore is contraindicated in patients with kidney disease, and those on a low oxalate diet, however, curcumin does not have oxalates. (5)
- Daily supplementation of amorphous curcumin at 1000mg daily for 90 days did not cause any adverse effects or alter any parameters of hepatic, renal, or hematological function. (6)

1. Lao CD, et al. BMC Complement Altern Med, 2006;6:10
2. Smith T and B Ashar. Cureus. 2019;11(1):e3858
3. Stati G, Front Pharmacol. 2021;12:780330
4. Halegoua-DeMarzio D, Am J Med. 2023;136(2):200
5. Panholi V, et al. Toxicol Rep. 2021;8:1255

Curcumin CYP activity

- Turmeric inhibits CYP3A4 and CYP2C9 in vitro.
- However, a human pharmacokinetic study found that 4g curcuminoids with 24mg piperine twice daily failed to cause changes in plasma levels, clearance, elimination half-life or metabolite levels of various CYP3A4 and CYP2C9 probe drugs.(1)
- Whole turmeric root (≥ 3g) is a weak CYP2D6 inhibitor (2)
  - Weak inhibitors do not alter drug metabolism in a clinically relevant manner, i.e. has no effect boundary
- Curcumin (3.6g) is a mild CYP2D6 inducer (3)
  - This could thereby potentially reduce drug efficacy, however, unlikely to a clinically significant degree. e.g. Tamoxifen 7.7% reduction in AUC.
- The phytosomal, or liposomal, form of curcumin minimizes the risk of herb-drug interactions, as compared to turmeric/curcumin products containing piperine (an alkaloid derived from black pepper [*Piper nigrum*, Piperaceae]) (4)

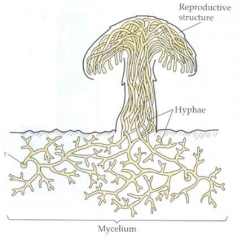
1. Volak LP, et al. Br J Clin Pharmacol. 2013 Feb;75(2):450-62
2. Al-Jenoobi F, Eur J Drug Metab Pharmacokinet. 2015;40(1): 61
3. Hussaarts K, Cancers (Basel). 2019;11(3):403
4. Mach CM, Anticanxer Res. 2010;30(3):811

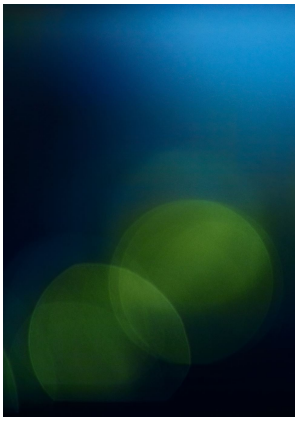
Patient Vignette: Cordyceps

- An elder woman with renal cell carcinoma is receiving cisplatinum chemotherapy
- She has developed signs of renal insufficiency
- Moderate neutropenia
- Fatigue
- Hx of chronic asthma

First a bit about Fungi

- Mushrooms form interconnected networks
- Mushrooms (fruiting bodies) are connected to one another in long filaments, hyphae.
- The hyphae spread through a substrate and form a net, or mycelium.
- Extracts are made from fruiting bodies or mycelia, or both





Mushroom dosage forms: polysaccharide extracts

Contain:

- Polysaccharides with protein (proteoglycans)
  - These are found as beta-glucans.
    - Beta glucans glucose polymers linked together by 1→ 3 linear B-glycosidic chain, in other words, protein-bound polysaccharides beta-linked by sugar (glucose, galactose, xylose or mannose) molecules
- Triterpenes (Reishi), Phenols (Chaga), Purine nucleosides and adenosine (Cordyceps)

Extracts are either:

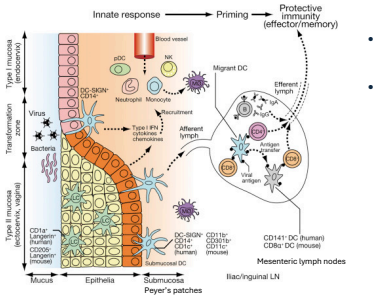
- Hot aqueous – yields high polysaccharides but low triterpenes
  - Ground mushroom cooked in hot water for several hours, fluid is evaporated, and residual is dried.
- Ethanolic – more triterpenes and fewer polysaccharides
- Combined (aqueous followed by ethanolic) to give higher yield of both (especially important for Reishi)

Powell M. Medicinal Mushrooms: A Clinical Guide (Mycology Press, 2010)
Chilton J. Science and Cultivation of Edible Fungi. Int. Soc Mushroom Science, eds. Baars & Sonnenberg, 2016

Given that polysaccharides are essentially non-digestable, how do mushrooms have immunogenic effects?

The apparent paradox of the high bioactivity of mushrooms given the low bioavailability of beta-glucans can be explained by the fact that the **bioactivity is derived from interaction with Gut-Associated Lymphatic Tissue (GALT) and from other metabolites that are formed from gut microbiota biotransformation**

Polysaccharide Digestion

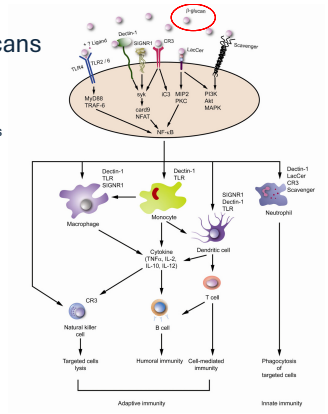


- Fermented by intestinal microbial flora into bioactive short-chained fatty acids (acetate, propionate, butyrate), and/or,
- Bind to specific receptors of immune cells, and/or,
- Rapidly internalized by enterocytes (M cells), enter GALT Peyer's patches where they are taken up by dendritic cells. Remain in Langerhans dendritic cells (mucosal dendritic cells) for days.
  - Dendritic cells sample the polysaccharides to present them to specific T lymphocytes in Peyer's Patches and in mesenteric lymph nodes
  - Dendritic cells are the most potent white blood cells to rapidly activate naïve CD4+ T and CD8+ T lymphocytes

Gao B, J Ethnopharmacol. 2018;224:465
De Jesus M, PLoS One. 2014;9(3):e91002
Kissenpfennig A, Mol Cell Biol. 2005;25(1):88

Direct Immune Activation by β-Glucans

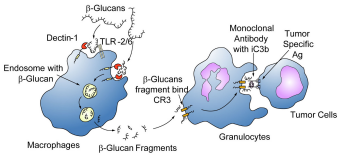
- The innate immune system identifies infectious agents or compounds by means of Toll-like pattern-recognition receptors (TLRs).
- These TLRs recognize pathogen-specific macromolecules called pathogen-associated molecular patterns (PAMPs).
- Polysaccharides, esp. B-glucan, cannot penetrate cells due to their large molecular mass, so the first step in the modulation of cellular activity is binding to macrophage, dendritic and NK cell TLRs.
  - Glucans are fungal PAMPs for the innate immune system
- Mushroom polysaccharides stimulate a predominately Th1 (cytotoxic) response via increased production of Th1 cytokines (IL-2, IL-12, IFN-Y)
- Th2 (humoral, or antibody dependent) is generally suppressed, or activated to a lesser extent, under influence of mushroom polysaccharides



Chan GC–F, Chan WK, Sze D M-Y. J Hemat Oncol. 2009;2:25.
Lull C. et al. Mediators of Inflammation. 2005(2):63-80.

Complement-dependent Anti-tumor Immunity by β-glucans

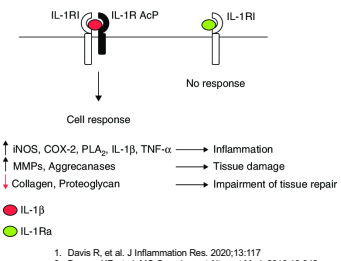
- Dendritic cells in GALT as well as macrophages engulf beta-glucans via TLR2/6 receptors and travel to spleen, lymph nodes and bone marrow.
- In bone marrow and endothelial reticular system, macrophages degrade B-glucans into smaller soluble B-1,3-glucan fragments.
- These fragments are released and taken up by circulating innate immune cells (neutrophils, NK cells, monocytes and dendritic cells) via complement receptor-3 (CR3).
  - These innate immune cells are then primed to phagocytize cells which express iC3b (iC3b opsonized target cells, such as tumor cells and infected cells).
  - Additionally, CR3 binding increases the expression of anti-inflammatory cytokines (TGF-B2, IL-10), thereby controlling the immunoinflammatory response.



Chan GC–F, Chan WK, Sze D M-Y. J Hemat Oncol. 2009;2:25
Albeituni S, Anticancer Agents Med. Chem. 2013;13(5):689

Immunoregulatory Actions

- **Mycelium/fruiting body mushrooms extracts[1,2]:** activate innate immunity and increase interferon production, while also exerting anti-inflammatory actions, specifically by increasing IL-1Ra – which inhibits the inflammatory effects of IL-1b
  - Mushrooms include: Agaricus, Cordyceps, Enokitake, Amadou, Agaikon, Reishi, Maitake, Lion's Mane, Chaga, Shiitake, Mesima, Birch Polypore, Pearl Oyster, Split Gill Polypore, Turkey Tail



1. Davis R, et al. J Inflammation Res. 2020;13:117
2. Benson KF, et al. MC Complement Alternat Med. 2019;19:342

Cordyceps

- Beta glucans
- Purine nucleosides (cordycepin)
- Adenosine compounds (3'-deoxyadenosine, 2'-deoxyadenosine, d-mannitol)

- Immunomodulatory
- Anti-inflammatory
- Antioxidant
- Pro-differentiation
- Anti-proliferative
- Energy-enhancing

- Wild fungus found in Tibet above 10,000 feet.
- Wild fungus is parasitic and colonizes larvae of moths so that their body is filled with mycelium such that the fungus is comprised of both the fungus and parasite.
- Wild cordyceps is very rare.
- Market cordyceps is produced from a mycelial strain (Paecilomyces hepialid) isolated from wild cordyceps and then fermented.

Cordyceps: Innate Immune Enhancement

8-week RDBPCT of 80 healthy adults

- Randomized to 1.68g of Cordyceps extract or placebo
- Cordyceps resulted in 39% increase in Natural Killer (NK) cell cytotoxic activity compared to placebo. (P<0.019)
- No changes in serum inflammatory cytokines suggesting the lack of an inflammatory effect.

4-week RCT of 80 healthy men

- 1.5g – 3.g (50% alcohol extracts)
- The Cordyceps group showed a statistically significant greater increase in NK cells (P = .0010), lymphocytes (P ≤ .0001), and Th1 cytokines IL-2 (P = .0096) and IFN-γ (P = .0126), compared with placebo
- No adverse effects noted

Jung SJ, et al. BMC Complemen Altern Med. 2019;19(1):1-8
Kang H, et al. J Med Food. 2015;18(10):1164

Cordyceps: Immunomodulation

- Retrospective study of 67 kidney transplant recipients.
- All recipients received anti-rejection drugs (tacrolimus plus prednisone or mycophenolate mofetil plus cyclosporine A)
  - 25 also received a dry powder preparation of Cordyceps sinensis mycelia
- No differences in survival rate, occurrence of reject reactions or renal function recovery
- However, **Cordyceps group had lower LFTs, lower infection rates and higher T-lymphocyte counts** (P<0.01).

Abstract only, article in Chinese:
Ding CG, et al. Zhongguo Xhong Xi Yi Jie He Za Zhi. 2009;29(11):975.

Cordyceps: Adaptogen

- 120week DBRCT of 20 healthy adults ages 50-75yo
- Randomized to 333mg cordyceps extract (Cs-4) three times daily or placebo
- Cordyceps increased exercise performance:
  - 10.5% increase in metabolic threshold (measured by muscle activity threshold prior to lactic acid accumulation)
  - 8.5% increase in ventilatory capacity (measured by ventilation threshold above which H+ stimulates ventilation)
  - No changes seen in placebo
  - No changes in VO2max in either group
- These changes correlate with the ability to perform a higher level of exercise without fatigue

Chen S, et al. J Altern Complement Med. 2010;16(5):585.

Cordyceps: Pulmonary Anti-inflammation

- A 2-month randomized controlled trial of 60 adult patients with moderate chronic asthma
- Inhaled corticosteroids and beta-agonists as needed +/- Cordyceps supplementation
- Cordyceps group had **reduced serum markers of airway inflammation**, including lower IgE, sICAM-1, IL-4 and MMP-9 (P<0.05 or P<0.01)

Wang N-Q, et al. Zhongguo Zhong Yao Za Zhi. 2007;32(15):1566.

Cordyceps: Dosing

- 500mg -2g three times daily
- Mycelium extract

Cordyceps Affinities & Energetics

Cordyceps is an energizing immunomodulator

Cardiovascular: Anti-inflammatory cardiotonic

Endocrine: Anti-inflammatory; post-infection fatigue

Renal: Renal tonic

Pulmonary: Lung tonic and respiratory anti-inflammatory

Neurologic: Improves stress response; adaptogenic

Warm (activates, increases internal digestive heat, expands and stimulates); sweet

Patient Vignette: Chinese skullcap

- 8y boy with childhood acute lymphoblastic leukemia
- Receiving maintenance chemotherapy (3rd phase of treatment) to reduce risk of recurrence
  - Chemotherapy is daily 6-mercaptopurine, weekly oral methotrexate intravenous vincristine with prednisone every 6 weeks
- Insomnia
- Frequent colds

Chinese Skullcap

- **Scutellaria laterifolia** and **Scutellaria baicalensis**
- **Common names:** Chinese skullcap
- **Family**: Labiatae
- **Parts used:** S. laterifolia – Herba; S. baicalensis - radix
- **Constituents:**
  - **S. laterifolia:** Flavonoid glycoside: scutellarin, scutellarien and others; Iridoids - catalpol; Volatile oil; Waxes; Tannins
  - **S. baicalensis:** Flavonoids: baicalin, baicalein, wogonside, wogonin
- **Medicinal actions:**
  - **S. laterifolia -** Sedative, nervine relaxant, antispasmodic, nervine tonic
  - **S. baicalensis** – Anti-tumor, Anti-inflammatory, antibacterial, anti-hypertensive, anti-allergy, sedative

Scutellaria baicalensis: indications

- Suppresses inflammatory cytokine production (TNF-a, NF-kB, IL-1)
- Activates GABA-A receptors and is useful in reducing anxiety and providing related sedation
- TCM: Anti-febrile and detoxification; useful during acute infections
- Increases NREM and REM sleep during darkness, and increases wakefulness during light periods

Chang HH, et al. J Ethnopharmacology. 2011;135:359-68.

Scutellaria baicalensis: anti-ALL

- Scutellaria baicalensis root extract inhibits acute B-lymphoblastic leukemia cells, attributable in large measure to baicalin (1)
  - Arrests cell cycle, induces apoptosis via caspase activation.
  - 72% of bone marrow-derived blasts from patients with acute B-lymphoblastic leukemia are sensitive to the apoptotic effects of baicalin and S. baicalensis extract
- In leukocytes obtained from children with acute leukemia, Scutellaria baicalensis extract, concentrated to baicalin, resulted in: (2)
  - increased production of IFNγ by peripheral blood leukocyte
  - increased nonspecific antiviral immunity
  - Also, S. baicalensis induced apoptosis of B-lymphocyte cell lines (without affecting healthy lymphocytes)

1. Orzechowska B, Int Immunopharmacol. 2020; 79:106114
2. Orzechowska B, Int Immunopharmacol. 2014;23(2):558

Scutellaria baicalensis: Hepatocellular carcinoma

- Meta-analysis of 7 clinical and 17 preclinical *in vivo* studies along with 31 *in vitro* studies were included
  - TCM preparations with Scutellaria baicalensis as the leading herb combined with transcatheter arterial chemoembolization or standard chemotherapy treatment
- Scutellaria baicalensis significantly improved tumor objective response rate (Risk ratio (RR) = 1.57, 95% confidence interval: [1.30, 1.90], $p < 0.00001$).
- In-vivo and in-vitro studies showed slowed tumor growth with exposure to S. baicalensis extract, baicalein, baicalin, and wogonin
  - Increased apoptosis

Ma M-Y, Ann Medicine. 2024;55(2):2247004

Scutellaria: Synergistic with Chemotherapeutics

- Cisplatin: enhanced cell death, autophagy, reduced drug resistance
- 5-FU: enhanced cell death, reduced drug resistance
- Paclitaxel: enhanced apoptosis
- Gemcitabine: enhanced apoptosis
- Methotrexate: enhanced distribution and tissue exposure of methotrexate in the body

Xhou X, Biomed Pharmacother. 2021;138:111445

S. baicalensis: pharmacy

- Powdered root: sig 3-9 gm/day
- Standardized extract: 90% baicalin: 500mg daily
- Tincture
  - Fresh or dried (1:5); sig 2-4 ml TID
    - weekly max. = 80 ml of 1:5
  - Fresh 1:2; sig 30 drops TID –QID
    - Weekly max = 30 ml of 1:2 tincture
- Safety: phase I, RDB, single dose trial of baicalein (100-2800mg) in 72 healthy adults:
  - Median t ½ life of 0.5-3h for baicalein and baicalin
  - No SAEs, only 11 mild adverse events – all resolved.
  - No signs of hepatotoxicity or renal toxicity (1)
- Interactions (in-vivo):
  - Strongly inhibits CYP2C9 and mildly increases CYP2E1.
  - No significant change was observed for CYP3A4. (2)

1. Li M, J Ethnopharmacol. 2014;156:210
2. Xhou X, Biomed Pharmacother. 2021;138:111445

Patient Vignette: Lavender

- 54y woman with ER+/PR+/Her2n- stage II breast cancer
- Completed partial mastectomy, chemotherapy and radiation
- Now taking Tamoxifen
- Experiencing hot flashes with panic
- Also, underlying anxiety

Lavender officinalis

- Contains volatile oil, primary active constituents of which are linalool and linalyl acetate – considered responsible for the anxiolytic effects
- Potentiates $GABA_A$ receptors, inhibits glutamate binding in brain
- Over 400 RCTs on lavender and anxiety
- Review included 15 RCTs, involving 1565 participants
  - 8 trials investigated the effects of lavender inhalation, with 4 reporting a significant positive effect for at least one anxiety measure
  - 3 trials assessed oral lavender
- Of these trials, 7 reported a significant positive effect for at least one anxiety measure.
- Effective studied dose = 20-80mg per day; also use topically, as tea, as aromatherapy

Perry R. et al. Phytomedicine. 2012;19(8-9):825-35.

Lavender: Clinical Indications

- Anxiety
- Mild depression
- Insomnia
- Bacterial and Fungal infections
- Topically for acne and inflammation
- Dyspepsia, colic
- Tension h/a, migraine h/a
- Spasmodic dysmenorrhea

Lavender

- 10-week DBRPCT: 221 adults with subclinical anxiety were randomized to oral extract of lavender angustifolia oil WS 1265 (Silexan®) or placebo
  - 80mg lavender extract
- Anxiety **decreased significantly more** in the Lavender group over placebo ($p<0.01$), **there was a greater number of responders** in the lavender group **(76.9 vs. 49.1%, P<0.001), and higher percentage of remission (60.6 vs. 42.6%, P=0.009).**
- Lavender extract also improved the quality and duration of sleep, as well as general mental and physical health.
- There was no sedative effect and the lavender extract was well-tolerated.

Kasper S, et al. Int Clin Psychopharmacol. 2010;25(5):277.

Lavender

- An oral lavender preparation (Silexan®, WS 1265) was compared to low-dose lorazepam (Ativan®) for the treatment of GAD.
- Multicenter, DBRCT, Jadad score of 4
- N = 77 adults (2/3 were female) with GAD (HAM-A > 18)
- Lavender extract compared to lorazepam x 6 weeks
- Primary outcome measure: HAM-A score
- The mean of the HAM-A total score decreased from 25+/-4 points at baseline in both groups and to a similar extent in both groups:
  - by 11.3+/-6.7 points (45%) in the lavender group; response rate of **52.5%**
  - by 11.6+/-6.6 points (46%) in the lorazepam group; response rate of **40.5%**
- At study end, **40% of lavender group vs. 27% of conventional group** were in remission (HAMA <10)
- **Unlike lorazepam, lavender has no potential for drug abuse or sedative effects.**

Woelk H and S. Schlafke. Phytomedicine. 2010;17(2):94-9.

Lavender aromatherapy: Insomnia & Fatigue in Multiple Sclerosis

- Insomnia and associated fatigue affects 1/3 to 2/3 of all MS patients.
- 63 patients with MS diagnosed at least 1 year previously and with fatigue and insomnia were randomized to either control or treatment with lavender aromatherapy.
  - Treatment: three drops of lavender essential oil were applied to two cotton pads and placed 15-20cm from the pillow each night 30 min before bedtime x 30 nights.
- The lavender aromatherapy improved sleep quality (measured by PSQI score with mean improvement of 3 points, p<0.001).
  - There was no improvement in the control group

Kavuran E and Yurttas A. Niger J Clin Pract. 2024; 27(5):635

Lavender officinalis: Dosing

2 teaspoons (10 grams) infusion with 1 cup (250 ml) of boiling water for fifteen minutes. Three cups (750 ml) can be consumed each day.

1:5 dry herb tincture: 1/2–3/4 teaspoon (2–4 ml) of tincture can be taken BID or TID

1:2 dry herb tincture: 15-30mL per week

Standardized oil extract: 80 – 160mg daily

Lavender: Safety

- There is concern that lipophilic estrogenic components of lavender could accumulate in adipose tissue and, upon continuous exposure, potentially act as endocrine disruptors.
  - There are several case reports which describe prepubertal gynecomastia in boys in association with topical lavender use (1)
  - A case report series published in 2019 found three prepubertal girls with premature thelarche (prepubertal breast development) and one boy with gynecomastia from continuous topical exposure to lavender essential oils and lavender fragranced products over several months to years (2)
    - In all cases, breast development resolved after discontinuance of the lavender products without recurrence.
- However, in all of these case reports, the lavender was not well characterized. **The products in these case studies were later chemically analyzed and found to have synthetic endocrine-disrupting chemicals while lacking lavender essential oil**, instead having 'lavender extract' or 'lavender fragrance'. (3)
- In a **systematic review**, which included the 2019 Ramsey publication, it was concluded that **there is little to no evidence that lavender acts as an endocrine disruptor in children nor that it has significant estrogenic effects**. (4)
- Additionally, **inhalation of lavender essential oil did not increase salivary estrogen concentrations in perimenopausal women** (5)
  - This is supported by an in-vivo study that found no estrogen receptor activation or proliferation effects from lavender essential oil on breast cancer cells (MCF-7) (6)

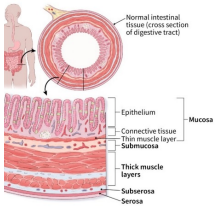
1. Diaz A, J Pediatr Endocrinol Metab. 2016;29(1):103
2. Ramsey J, J Clin Endocrinol Metab. 2019;104(11):5393
3. Giroux J-M and Orjubin M. J Clin Endocrinol Metab. 2020;105(7):e2677
4. Hawkins J, Complement Ther Med. 2020;49:102288
5. Shinohara K, Neuro Endocrinol Lett. 2017;37(8):567
6. Simoes B, Ther Adv Med Oncol. 2018;10:1758835918766189

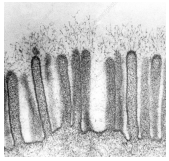
Patient Vignette: Marshmallow root & Slippery elm bark

- 40y woman receiving radiation therapy for metastatic ovarian cancer
- Hx of bowel obstructions after initial pelvic surgery
- Currently experiencing constipation

Components of the intestinal mucosal layer

- Intestinal mucosa is comprised of the epithelium, lamina propria and muscularis mucosae layers
- Central to the intestinal lumen and a part of the mucosa is a layer of mucus
- Mucus is a gel-like layer comprised of mucins
  - 90% water
  - Mucins = large glycosylated proteins:
    - Transmembrane mucins cover enterocytes and form the glycocalyx which protect the epithelium and provide a surface for attachment of commensal bacteria
    - Gel-forming mucins (mostly MUC2) are secreted by Goblet cells and form protective net-like layers over epithelial surfaces

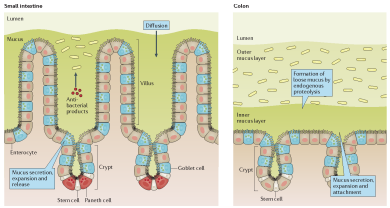




Johansson M and Hansson G, Nat Rev Immunol. 2016;16(10):639
Eutamene H, et al. Exp Rev Gastroent Hepatol. 2018;12(1):83

Intestinal mucus

- Mucus = Gel-like layers loosely adherent to the epithelium
  - Is a complex colloid comprised of hydrophilic mucins (branched glycoproteins)
    - Contain antibacterial peptides and proteins that kill or trap bacteria
    - More than 20 subtypes in humans; major mucin in the intestines is mucin-2 (MUC-2)
- Mucus hydrates and protects the epithelium



- **Small intestine**: single layer of mucus produced by Goblet cells
  - Loosely attached to epithelium, easily penetrable due to the presence of mucus pores which allow for nutrient uptake
  - Contains antibacterial modulators to repel pathogenic bacteria including defensins, lysozymes and peptides secreted by Paneth cells
  - Fluids and motor activity move the mucus and trapped bacteria to the colon
- **Large intestine**: mucus consists of two layers (esp. in distal colon)
  - adherent, mostly sterile inner mucus layer produced by Goblet cells
  - loosely adherent outer mucus layer which contains colonic microbiota. These commensal bacteria secrete mucinases and proteinases that degrade the outer mucus contributing to its irregular and less adherent consistency
- Mucus layer is thinner on right side of colon and thickens distally

Herath M, et al. Front Cell Infect Microbiol. 2020;10:249
Eutamene H, et al. Exp Rev Gastroent Hepatol. 2018;12(1):83

Demulcents

- Deficiencies in the intestinal barrier caused by neuroendocrine mediators, immune activation, infections, acute toxicants and inflammants, ingested toxins, etc. lead to altered intestinal barrier and increased intestinal permeability
- Mucoprotectants, which provide a protective film over the intestinal mucosa, are one way to reduce intestinal permeability and improve the function of the intestinal barrier.
- Demulcents are botanicals with high concentration of mucopolysaccharides which provide mucoprotection

Table 1. Factors and mechanisms underlying an increase in intestinal permeability [3,25].

Factors that can affect intestinal barrier function
• Proinflammatory cytokines [26]
• Pathogenic bacteria [24,27]
• cAMP [28]
• Gliadin peptides [29]
• Proteases [22,23]
• Hormones [30]
• Ethanol [31]
• Cellular stress (e.g. heat) [32]
• Psychological and physical stress [33]
• Genetic factors [34]
Mechanisms by which intestinal permeability is altered
• Altered expression/localization, or abnormal regulation, of tight junctions [35,36]
• Altered microbial flora affect the signaling that maintains or impairs barrier function [24,27,37–39]
• Active inflammation or increased pro-inflammatory cytokines [26]
• Increased epithelial cell shedding [40,41]

Eutamene H, et al. Exp Rev Gastroent Hepatol. 2018;12(1):83

Ulmus fulva (Slippery elm) bark

- Slippery elm powder derived from the tree bark has a high concentration of mucopolysaccharides
- These undigestable mucopolysaccharides are mucoprotectants
- These mucopolysaccharides are hydrophilic mucoprotectants, provide substrate for commensal bacteria, and bulk and lubricate the stool.
- No clinical studies to date demonstrating the mucoprotection ⊗

Ulmus fulva (slippery elm) and Microbiome

- Slippery elm is known to contain a high content of polysaccharides, including linear chains of alternating D-galacturonic acid and L-rhamnose residues with α-linkages containing galactose and 3-O-methyl galactose[1]
- In vitro anaerobic cultivation of human fecal inoculums from 12 healthy vegetarian donors with Triphala, slippery elm, or Licorice resulted in **increased microbial diversity**.[2]
  - Slippery elm resulted in 299 unique bacterial species belonging to 131 genera
  - Inoculation with Triphala and Glycyrrhiza glabra produced similar results
- Predominant bacterial species differed by herb:
  - Triphala (*Emblica officinalis*, *Terminalia bellerica*, and *Terminalia chebula*) induced large increases in the relative abundance of Dorea, Sutterella, Phascolarctobacterium, Lactobacillus, and Butyrivibrio (range=116–580-fold).
  - Slippery elm yielded similar outcomes also with large increases for Dorea, Sutterella, and Phascolarctobacterium (range=169–298-fold)
  - Licorice produced comparable increases for *Pseudomonas, Acinetobacter, Victivallis, Acidaminococcus, Phascolarctobacterium, and Sutterella.*

1. Hough L, et al. Nature. 1950;165:134
2. Peterson CT, et al. JACM, 2018;24(7):656

Slippery Elm dosing

- Ulmus often works the best if dosed frequently.
- Gruel: Mix 1 Tablespoon powder to 4 ounces cold water (cold water best extracts the mucilage). Let sit for at least 10 minutes. Add to hot cereal or 1 cup hot water. Add cinnamon and/or honey. Eat or drink in two to three divided doses.
  - Children: use Young's Rule = add 12 to the child's age and then divide the child's age by this summed number. The result is the fraction of the adult dose to use.
- Decoction: Mix 1 part powder to 8 parts water (mix the powder with small amount cold water first to ensure the extraction of the mucilage). Boil gently for 15 minutes and let cool; sig 1/2 cup TID
- Decoction: Mix 1 tsp. bark into 1 cup cold water. Let sit for 4-12 hours, strain; sig 1/2 cup BID-QID.
- Theoretically, slippery elm could slow the absorption of oral drugs taken concurrently. Slippery elm is safe for children and the oral use is safe for pregnant women.

Althea officinalis (marshmallow)

- Root and leaves contain Mucilage: hydrophilic polysaccharides
  - Physically contribute to outer mucin layer in intestines
- Also contain flavonoids, polyphenols, vitamins, terpenes, tannins
- No clinical studies ⊗

Sharifi-Rad , Phytother Res. 2020;34(3):546.

Marshmallow dosing

- Infusion: 2-4 g/cup cold water, infuse overnight; 1 cup TID [1 tsp. = 1.4 g]
- Children under age 8y: 1g/cup; 1 cup daily
- Tincture: 1:5 25% EtOH; sig 1-4 ml TID; weekly max. dose is 100 ml
- Children 2- 8y: 1ml BID
- Well-tolerated; safe in children
- No known interactions; could interfere with absorption of oral drugs

Marshmallow Root Latte

- 6 ounces marshmallow root tea
- 6 ounces oat milk (a demulcent!)
- 1/2 -1 teaspoon maple syrup
- Pinch nutmeg

- Prepare marshmallow root tea day prior. Combine 1 teaspoon marshmallow root powder and 12 ounces water in Mason jar, refrigerate overnight.
  Combine all ingredients in small saucepan, bring to gentle simmer. Pour into mug and enjoy

Clinical vignette: Milk thistle

- 75y man with colorectal cancer, metastatic to liver receiving FOLFIRI chemotherapy
  - Elevated liver enzymes prior to chemotherapy
- Milk thistle standardized extract, 420 mg extract (80% silymarin) once daily (in the evening)
- Also consider:
  - Active hexose correlated compound (Shiitake mushroom extract): 1.5g twice daily
  - Probiotic (Lactobacillus/Bifidobacter) 50B

Silybum marianum: Description

- Also known as St. Mary's thistle
- Member of Asteraceae (Daisy) family
- Seeds (fruits) contain:
  - Flavolignans: 1.5 - 3%
    - Silymarin: silybin (70%), silydianin, silychristin
  - Oil (oleic acid, palmitic acid)
  - Sterols (cholesterol, campesterol, stigmasterol, sitosterol)
  - Mucilage
- Milk thistle has been used for centuries to protect liver from toxins and to treat hepatic damage

Silymarin: main biologically active constituent

- Part flavonoid (taxifolin) and part lignan, joined through oxidative coupling
- Seven flavonoids:
  - silybin (70%) consisting of two diastereomers silybin A, silybin B
  - isosilybin (5%) (as isosilybin A and isosilybin B)
  - silychristin (20%) (with isosilychristin)
  - silydianin (10%)
- Extracted silymarin is 70-80% silymarin flavonoids and 20-35% fatty acids.
  - Most biologically active flavononlignan is silybin.

Wadhwa K, Molecules. 2022;27(16):5327
AbouZid S. Silymarin Flavonolignans. Studies in Natural Products Chemistry. 2013
Jaggi A, Singh N. Adv Exp Med Biology. 2016;929:25

Medicinal Actions

- Antioxidant
- Anti-inflammatory
- Hepatoprotective
- Bitter
- Cholagogue
- Nephroprotective
- Pro-apoptotic
- Galactagogue: (safe during breast feeding)
- Anti-viral
- Photoprotectant (topical)

Hepato-protective

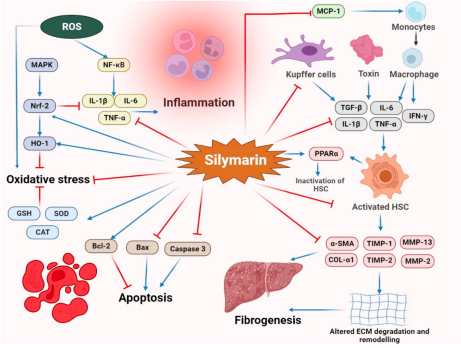


Figure 3. Various hepatoprotective modes of action of silymarin.

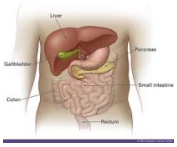
Wadhwa K, Molecules. 2022;27(16):5327

Hepatoprotective: Mechanisms of Action

- Decreases intracellular production and release of transaminases (AST, ALT, GGT, ALK)
- Improve hepatocellular membrane integrity
- Increases Nrf-2 non-enzymatic antioxidant response system and downregulates NFkB
- Increases enzymatic antioxidants (glutathione, Se transferase)
- Reduces pro-inflammatory inflammatory cytokines by mpeding NLRP3 inflammasome activation and the release of inflammatory cytokines (TNF-a, IL-6, IL-1B, IL-12B,TGFb etc)
- Pro-apoptotic and anti-apoptotic (counters the oxidative stress induces inflammatory stimulation of caspases)
- Reduces hepatic fibrosis by reducing hepatic stellate cells and Kupffer cells thereby reducing their translation into myofibroblasts
  - Myofibroblasts normally exude extracellular matrix proteins contributing to inflammation
- Reduce collagen and procollagen required in fibrosis and increases MMP-2, thereby preventing fibrosis
- Blocks and inactives oxidative hepatotoxins
- Triggers hepatic regeneration by increasing RNA and RNA polymerase I synthesis thus repairing damaged liver cells

Wadhwa K, Molecules. 2022;27(16):5327

Silymarin: Liver Enzymes



- Systematic review of 29 RCTs (n=3,846)
- Participants had a variety of underlying conditions
- Silymarin dosages ranged from 140mg to 420mg for varying durations
- 65.5% of the studies reported reduced liver enzyme (ALP, ALT, AST) levels, 20.7% exhibited no significant change, and 13.8% observed elevated liver enzymes.
  - Of note the 13.8% studies that observed increased liver enzymes utilized low doses
  - Doses associated with liver enzyme reduction were 200-400mg silymarin daily.

Martinez E, Cureus. 2023;15(10):e47608

Milk thistle: Hepatoprotection from toxicants

- A controlled clinical trial was conducted with 49 workers with a 5 – 20 year exposure to toluene and/or xylene vapors and with elevated AST and ALT, and/or abnormal hematological values including low platelet count, leukocytosis, or relative lymphocytosis
- Thirty workers were treated with oral Legalon® (140mg milk thistle standardized extract) TID x 30 days and compared to 19 workers without any intervention.
- The milk thistle was associated with improved AST, ALT, platelet counts.
- There was a nonsignificant trend of improvement for leukocytosis and relative lymphocytosis.

Szilard S, Acta Med Hung. 1988;45(2):249

Anti-cancer

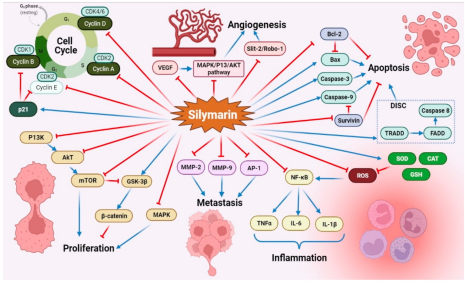


Figure 5. Anti-cancer mechanisms of silymarin.

Wadhwa K, Molecules. 2022;27(16):5327

Anti-cancer: Mechanisms of Action

- Causes cancer cell cycle arrest at G1/S-phase
- Preserves apoptosis proteins
- Inhibits survival and growth kinase pathways (MAPK, ERK1/2, JNK 1/2)
- Downregulates inflammatory transcription factors
- Reduces invasiveness, metastasis and angiogenesis

Wadhwa K, Molecules. 2022;27(16):5327

Milk thistle: Chemotherapy toleration, pediatrics

- RDBCT pilot study, 50 children with acute lymphoblastic leukemia (ALL) and hepatic toxicity were randomized to receive 5mg/kg standardized milk thistle extract or placebo
- No significant differences in the frequency of side effects, incidence, and severity of toxicities or infections were observed between groups.
- However, at day 56, the milk thistle extract group had a significantly lower AST (P = .05) and a trend toward a significantly lower ALT (P = .07).

Ladas E, Cancer. 2010;116(2):506

Milk Thistle: Chemotherapy-Induced Hepatotoxicity

- Randomized, triple-blind, placebo-controlled trial of 30 patients with non-metastatic breast cancer and with at least grade 2 liver injury based on ultrasound
- Patients were randomized during the 4th and final cycle of dose-dense Adriamycin/Cytoxan prior to paclitaxel
- Over 1 month, the women received either the intervention of 140mg of silymarin three times daily or the control of milk thistle without silymarin.
- After one month of supplementation, there was a non-significant trend in reduction in fatty liver; however, there were no significant differences in severity by FibroScan or liver function tests.

Moezian G, J Oncol Pharm Pract. 2022;28(4):827

Milk Thistle: Chemotherapy-Induced Hepatotoxicity

- Pilot study of 70 patients with metastatic colorectal cancer receiving first-line FOLFIRI chemotherapy (5-fluorouracil/leucovorin/irinotecan) with bevacizumab.
- Oral dosing of 150mg of milk thistle extract three times daily for 1 week resulted in less diarrhea (5.7% v 14.6%, p= 0.002) and less nausea (27% v 40.2%, p=0.005) compared to controls
- There was no difference in liver toxicity; however, this trial was likely of insufficient duration to assess this.

Chang TK, Oncol Res. 2021;28(7):801

Milk thistle: Radiotherapy-induced mucositis

- Pilot DBRPCT of 27 patients with head and neck cancer receiving radiotherapy.
- Intervention: Oral silymarin, 420mg in 3 divided doses starting on day 1 of radiotherapy and continuing to the end of radiotherapy in 6 weeks
  - Cisplatin was administered by infusion every 21 days x 3 cycles
- Although mucositis scores increased in both groups, the mucositis was delayed in the silymarin group and the scores were significantly lower in silymarin group ($p<0.05$)

Elyasi S, Phytotherapy Res. 2016;30(11):1879

Topical Milk thistle: Capecitabine-induced Hand-Foot Syndrome

- RDBPCT of 40 patients with GI cancer and receiving capecitabine chemotherapy.
- Randomized to silymarin gel 1% applied to palms and soles twice daily starting with chemotherapy x 9 weeks or placebo.
- Median HFS scores were significantly lower in the silymarin group by 9 weeks ($p<0.05$) although the HFS scores did increase in both groups.
  - Silymarin group took longer to develop HFS and developed less severe HFS.

Elyasi S, Phytotherapy Res. 2017;31(9):1323.

Pharmacy

- 30:1 seed extract standardized to 80% silymarin
  - 140mg – 450mg TID or 420mg – 1350mg once daily
  - Children: 140mg daily
- 12-15g seed (providing 200-400mg silymarin)
- Poor bioavailability due to low aqueous solubility
  - This is overcome with silymarin nanoparticles and phytosomes (phosphatidylcholine complex)

Wadhwa K, Molecules. 2022;27(16):5327

Contraindications & Drug/Herb Interactions

- Well-tolerated.
- Considered safe during pregnancy and breast-feeding
- May inhibit drug efflux pumps thereby reducing resistance to antibiotics and oral chemotherapy resistance
  - Therefore, milk thistle is ideally suited during antibiotic therapy, especially with hepatotoxic antibiotics
- In-vivo studies have found silymarin flavonoids to inhibit cyp3A4 and cyp2C9, however, these effects have not been demonstrated in humans and are considered to not be clinically relevant (1)
- Silymarin (140mg TID x 14d) has been shown increase AUC of losartan in individuals with CYP2C9*1/*1 genotype (2)

1. Loguercio C, World J Gastroenterol. 2011;17(18):2288
2. Han Y, Eur J Clin Pharmacol. 2009;65(6):585

Patient Vignette: Ashwagandha

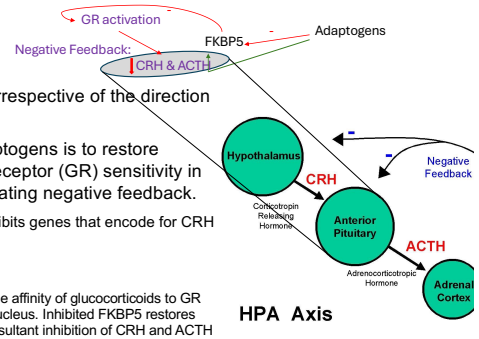
- Middle-aged executive who has recently completed treatment for sarcoma
- No evidence of disease, however, significant anxiety with each post-treatment scan
- Also, experiencing high stress from work, residual treatment fatigue and mild treatment-related anemia

Ashwagandha

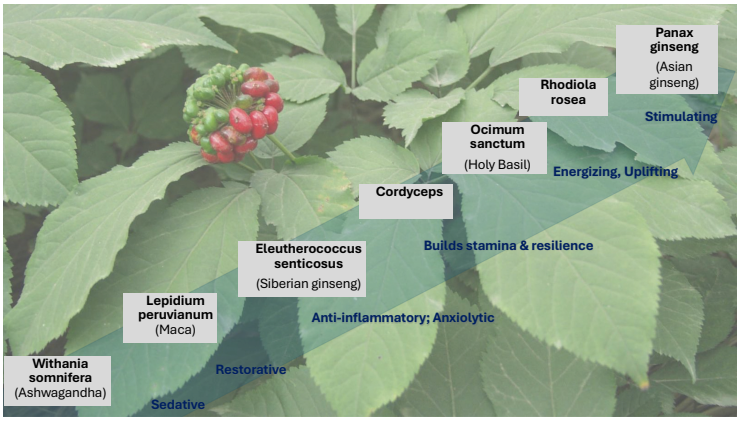
- Withania somnifera
- Solanaceae
- **Part used**: Root
- **Constituents:** Alkaloids: isopelietierine, anaferine; Steroidal lactones: withanolides, withaferins; Saponins; Iron
- **Medicinal actions:** Hypotensive, bradycardic, spasmolytic, anti-tumor, immunomodulating, anti-inflammatory, adaptogenic, sedative.
  - Withania is adaptogenic and tonic, stimulating weight gain, increased cell counts and reducing inflammation

Adaptogens

- 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.
- Adaptogens:
  - 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;56(5):567-72
Zannas AS, Neuropsychopharmacology. 2016;41:261-74
Verjee S, Planta Med. 2018;84(9-10):696.



Ashwagandha: Mechanism of Action

- It is best suited to individuals who are debilitated and who suffer from nervous exhaustion and anemia.
- Withania is helpful in convalescence after acute illness or stress, impotence, chronic disease with inflammation and bony degeneration, as a general tonic and adaptogen.
- Withania exerts a sedative effect and thereby rests and restores the health of the nervous system and person overall.
- High doses of the alkaloids have demonstrated prolonged hypotensive, bradycardic, respiratory stimulant and cerebral depressant effects by binding to and stimulating GABA-A receptors.
- The alkaloids are spasmolytic to smooth muscles systemically and exert an overall sedative action.

Malhotra CL, et al, Ind J Med Res, 49, 1962:448.
Malhotra CL, et al, Ind J Physiol Pharmacol, 9, 1965:9.

Not recommended during
- Pregnancy (may have abortifacient effects)
- Lactation (unknown safety)
- Children: safety established for anxiety and ADHD; recommend > 10y

Withania somnifera (Ashwagandha): stress

- 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.
- 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
- 39 patients with ICD-10 classified anxiety disorders were randomized to receive an ethanolic extract of *Withania somnifera* or placebo x 6 weeks. 88% of ashwagandha subjects showed reduction in anxiety compared to 50% of the placebo subjects. Ashwagandha was well-tolerated.
  - Andrade C, 2000. PMID: 21407960

Ashwagandha: Anxiety and stress

- Systemic review of ashwagandha for anxiety and stress.
- Of 62 screened, 5 human trials met inclusion criteria.
- 3 studies compared several dosage levels with placebos for anxiety and, of these, 2 showed significant benefit of ashwagandha over placebo and the 3rd showed a trend towards benefit.
- One study compared naturopathic care with ashwagandha versus psychotherapy for anxiety. Anxiety scores decreased by 56.5% in naturopathic/ashwagandha group and by 30.5% in psychotherapy group. ($p<0.0001$)
- The 5th study measured changes in Perceived Stress Scale scores in ashwagandha group versus placebo and there was 44% reduction in stress scores in ashwagandha group and a 5.5% reduction in placebo group ($p<0.0001$).

Pratte MA, et al. J Altern Complement Med. 2014;20(12):901-8.

Ashwagandha: Fatigue

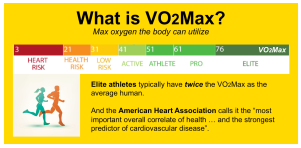
- Two-arm, parallel 12-week RDBPCT
- 120 overweight adults (40-75y of age)
- Intervention = standardized ashwagandha root extract, Witholytin®
  - 200mg standardized to 1.5% withanolides
  - Dose was 200mg twice daily
- Stress scores reduced by 39.5%, however, this was not different than placebo
- There was a statistically significant reduction in fatigue in the ashwagandha group compared to placebo ($p=0.016$)

Smith S, J Psychopharmacol. 2023;37(11): 1091

Ashwagandha: Endurance effects

- Ashwagandha improves cardiorespiratory endurance.
- 12-week DBPCT of 50 adults (male and female)
- Ashwagandha resulted in greater oxygen consumption at peak physical exertion (+5.67 increased VO2max) compared to placebo (+1.86 increased VO2max). ($P<0.0001$)
  - Ashwagandha was KSM-66 [full-spectrum root extract], 300mg (1 capsule) twice daily
  - VO2 max = a person's ability to take in, transport, and utilize oxygen and is probably the best assessment of endurance capabilities.
- Ashwagandha improved all measured aspects of QoL (physical health, psychological health, social health) at 12 weeks compared to placebo ($P<0.05$)

Choudhary B, Ayu. 2015;36(1):63.



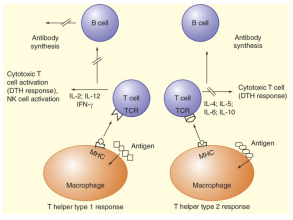
Ashwagandha: Insomnia

- 8-week parallel RDBPCT of 80 adults; 40 healthy and 40 with delayed onset and poor sleep quality insomnia randomized to placebo or 300mg ashwagandha standardized extract (KSM-66®) capsule twice daily
  - KSM-66 is a 15:1 extract standardized to withanolides >5%
- In both healthy and insomnia subjects, there was a significant improvement in the sleep parameters in the Ashwagandha root extract supplemented group.
- The improvement was found more significant in insomnia subjects than healthy subjects.
- Significant improvement in sleep onset latency ($p < 0.013$), HAM-A outcomes ($p < 0.05$), mental alertness ($p 0.01$), and sleep quality ($p < 0.05$) of the insomnia patients.
  - Sleep onset latency ($p < 0.0001$) and sleep efficiency ($p < 0.0001$) were the most improved parameters, followed by total sleep time ($p < 0.002$) and wake time after sleep onset ($p < 0.040$).

Langade D, J Ethnopharmacol. 2021;264:113276

Ashwagandha: Immune Effects

- Immunomodulator:
  - Enhances NK cell proliferation and activity[1, 4]
  - Increases Th1 cell-mediated immunity by increasing IFNγ, IL-2 while decreasing associated inflammation by lowering TNFa[2, 3, 4]
  - Prevents IκB degradation thereby decreasing NF-κB nuclear translocation and NF-κB binding to DNA transcription sites of various inflammatory cytokines[1]
  - Withania extracts also attenuates immunoinflammation by increasing IL-10 secretion (immunosuppressive)[5]
  - Protects against immunosuppression (increases WBC and PLTs) in cyclophosphamide-induces immunosuppression[6]



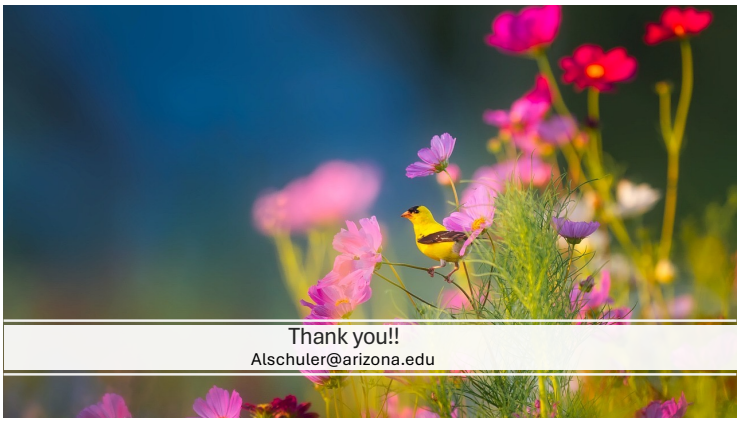
1. Malik, F, et al. Eur J Cancer. 2009;45(8):1494.
2. Kaur P, et al. Biomed Pharmacother. 2017;95:1815.
3. Malik, F, et al. Life Sci. 2007;80(16):1525.
4. Mikolai J, J Altern Complement Med. 2009;15(4):423.
5. Khan MA, et al. Antiinflamm Antiallergy Agents Med Chem. 2019;18(1):55
6. Agarawal R, et al. J Ethnopharmacol. 1999;67(1):27.

Ashwagandha: Dosing

- 3-6 g/day of dried root
- 1:5 tincture --- 12-25 ml/day; 1:2 tincture—6-12 ml/day
- 450 – 900mg standardized extract to at least 2.5% withanolides
- Note: Clinical effects are usually not seen for at least 1 month. In India, ashwagandha is given with pungent, heating herbs (ginger, pepper) to increase its tonic effects.
- **Toxicity:** Mild and occasional reports of h/a, nausea. Use with caution in hyperthyroidism as may increase thyroxin levels
- **Interactions**:
- - Additive effects with: hypoglycemic drugs, antihypertensive drugs, benzodiazepines, CNS depressants
- - May counteract immunosuppressants

In Summary: 7 (8 really) indispensable herbs in integrative oncology

Curcuma longa:	anti-inflammatory; improves chemotherapy tolerance
Cordyceps spp.:	energizing; improves anti-tumor innate and cytotoxic immunity, reduces inflammation
Scutellaria baicalensis:	anti-tumor, anti-inflammatory, synergistic with chemotherapy
Lavendula officinalis:	reliable anxiolytic, not estrogenic
Althea officinalis & Ulmus fulva:	demulcent; reduces intestinal inflammation during chemotherapy and radiation
Silybum marianum:	antihepatotoxic, antitumor, improves chemotherapy toleration
Withania somnifera:	adaptogen; reduces stress, anxiety and fatigue



Thank you!!

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