

HIV & Herbal Therapies

Jennifer Cocohoba, Pharm.D.

Assistant Clinical Professor

UCSF School of Pharmacy

National HIV/AIDS Clinicians' Consultation Service

11/22/2004

“Herbs” in CAM

- Biologically based therapies (BBT)
- Herbs
 - Echinacea
 - St. John’s Wort
- Dietary Supplements
 - Chromium piccolinate
 - L-carnitine
- Vitamins
 - Vitamin E, Vitamin C

How many HIV+ patients use it?

- AMCOA study (1995-1997)¹
 - N = 1675; 63% use CAM + ARVs
- Duggan et. Al. (2001)²
 - N =19; 50% used herbs
 - 7% used CAM ALONE; 64% MD's unaware
- Hsiao et. al. (1996-1997)³
 - N = 2466; 53% CAM; 3% substitute CAM
 - Patients with a negative attitude towards ARVs were more likely to use CAM
- Fairfield et. al. (1998)⁴
 - N = 180 (telephone survey)
 - 67.8% used herbs, vitamins, dietary supps
 - 45% visited a separate CAM provider & saw CAM provider MORE than regular provider
 - Yearly average expense = \$938 (all CAM)

What products are patients using?

- AMCOA study
 - Vitamin C (63%)
 - MVI w/minerals (54%)
 - Vitamin E (53%)
 - Garlic (53%)
- Southwell et al (Top 10)⁵
 - Echinacea
 - Ginseng
 - Gingko
 - St. John's Wort
 - Goldenseal
 - Garlic
 - Saw Palmetto
 - Chinese herbs
 - Milk thistle

Reasons

- Why do HIV(+) patients say they use BBT?
 - **To cure HIV**
 - **For adverse effects**
 - To delay onset of symptoms
 - “Its [extremely] helpful”
 - Feel more in control of their health and disease
 - Because they don’t believe in ARVs
 - “Its natural”

Objectives

- Review 10 common herbs used by HIV+ individuals
 - Indications
 - Dosing
 - Side Effects
 - Interactions
- Discuss patient talking points around herbal therapies
- Identify 2 references for herbal medication information

Herbs with potential to treat HIV

POTENTIAL RT INHIBITORS

- Andrographis paniculata
- Anogeissus acuminata
- Buchenavia capitata
- Callophylum inophyllum
- Callophylum langerium
- Camellia sinensis
- **Cephaelis ipecacuanha**
- Curcuma aeruginosa
- Detarium caryophyllum
- Euodia roxburghiana
- Euphorbia watanabe
- Fagara xanthoxyloides
- Gelonium multiflorum
- Helicteras isora
- Jacobinia suberecta
- Lepidobotrys staudtii
- Macaranga sinensis
- Mallotus japonicum
- Maprounea africana
- Morus spp
- Myrica rubra
- Phyllanthus emblica
- Plumeria rubra
- Psidium guajava
- Punica granatum
- Q. myrsinaefolia
- Rumex cyprius
- Sindora sumatrana
- Swertia frachetiana
- Terminalia bellerica
- T.chebula
- Terminalia horrida
- Trichosanthes kirilowii

Herbs with potential to treat HIV

POTENTIAL P.I.'s

- Andrographis paniculata
- Areca catechu
- Curcuma aeruginosa
- Eugenia jambolona
- Helicteras isora
- S.indica
- Sindora sumatrana
- Terminalia arjuna

MECHANISM UNKNOWN

- A. indica
- Bersama abyssinica
- Chassalia parvifolia
- Combretum paniculatum
- Conospermum incurvum
- Gossypium spp.
- Homoalanthus nutans
- Maesa lanceolata
- Polomorphe peltata
- Rauwolfia serpentina
- Symphonia glabulifera
- Ximenia americana
- Xylophia spp.

Herbs with potential to treat HIV

TARGET OTHER STEPS

- Yarrow
- Anistrocladus abbreviatus
- Canivalia ensiformis
- Castanospermium australe
- C.longa
- Dodonaea angustifolia
- Eugenia caryophyllata
- Euphorbia kansui
- Galanthus nivalus
- **G.glabra**
- ★ G.radix
- ★ Hippeastrum hybrid
- ★ Hypericum perforatum
- ★ Listera Ovata
- ★ Loranthus parasiticus
- ★ Momordica chrantium
- ★ Omphalea diandra
- ★ Papaver somniferum
- ★ Phytolacca americana
- ★ Schumanniophyton
- ★ Syzygium claviflorum
- ★ Urtica dioica

Echinacea (*Echinacea Purpurea*)

INDICATION(S)

- HIV: immune system stimulation
- Prevention of colds/URIs, antiviral, antiseptic, vasodilator

TYPICAL DOSE

- 6-9mL/day of fresh extract. 900mg/day of pallida root tincture. Powdered form doses vary...2-8 wks

SIDE EFFECTS

- Allergic reactions, fever, N/V (rare)

POTENTIAL INTERACTIONS/NOTES

- Controversial for use in HIV/AIDS, may worsen autoimmune diseases, may alter fertilization, ...

Astragalus (*Astragalus membranaceus*)

INDICATION(S)

- HIV: immune system stimulation
- Other: colds, URIs, diabetes, antiinflammatory, antioxidant, antiviral (hep B), vasodilator, liver protector, diuretic

TYPICAL DOSE

- 1-30grams orally per day of powdered root. Doses > 28 g/day may offer no extra benefit or cause immune suppression.

SIDE EFFECTS

- Fairly non-toxic, gas, bloating, lowered blood pressure.

POTENTIAL INTERACTIONS/NOTES

- None known. Controversial for use in HIV/AIDS.

Immune stimulants

- Theory
 - ↑ T-cell activation
 - stimulate TNF-alpha
- Concerns/Controversy
 - If T-cells stimulated, will they be functional?
 - If more T-cells produced, does this increase the vector for virus (give virus more T-cells to invade)
- Level of evidence
 - Clinical studies lacking re: ↑ numbers or activation

Goldenseal root (*Hydrastis canadensis*)

INDICATION(S)

- HIV: infections, reverse transcriptase inhibitor
- Other: gastritis, anorexia, ulcers, internal bleeding disorders

TYPICAL DOSE

- 0.5 – 1gram PO TID of the rhizome and/or root

SIDE EFFECTS

- GI upset, constipation, nervousness. Spasms, delirium (long term)

POTENTIAL INTERACTIONS/NOTES

- No more than 500mg berberine constituent (8-100g of root)
- Recommend short term use to minimize side effects
- Acid-inhibiting drugs, decrease B vitamin absorption, blood pressure medications (↑BP), cause additive sedation, inhibit anticoagulant effects of heparin

Ginger (*Zingiber officinale*)

INDICATION(S)

- HIV: nausea, vomiting, dyspepsia, flatulence
- Other: antioxidant, anti-lipid agent, antiplatelet, motion sickness

TYPICAL DOSE

- 250mg- 1gram of powdered ginger rhizome/root 2hrs – 30mins prior to needed effects

SIDE EFFECTS

- (Generally well tolerated) GI upset, flatulence, bloating (rare)

POTENTIAL INTERACTIONS

- Use less than 5 grams/day to minimize side effects
- Acid inhibitors, anticoagulants, barbituates (additive), diabetes meds (additive), hypertensives (↑/↓ BP),

Milk thistle (*Silybum marianum*)

INDICATION(S)

- HIV: Digestion aid, mild liver toxicity, hepatitis
- Others: cancer, hangover, anorexia, malaria, menstrual stimulation

TYPICAL DOSE

- 200-400mg/day divided doses (BID-TID) of seeds and above-ground parts of the plant

SIDE EFFECTS

- Diarrhea, GI upset/heartburn, allergy

POTENTIAL INTERACTIONS

- Not for patients allergic to daisies (asteracea family)
- Use one with 70-80% standardized silymarin
- None with HIV meds. Theoretical intx with meds metabolized by CYP2C9 (amitriptyline, valium, etc)

Milk Thistle Interaction?

- Sequential crossover trial in 10 healthy subjects⁸
 - Indinavir 800mg Q8H until steady state (4th dose)
 - Milk thistle 160mg TID days 3-15
 - Combination therapy days 16-18
- Results
 - AUC 20.7 h/mg*L vs 19.4 h/mg*L
 - Cmin 0.340 mg/L vs 0.232 mg/L
- Conclusion: No interaction! Same results in a previous study⁹....

St John's wort (*Hypericum Perforatum*)

INDICATION(S)

- HIV and Others: Depression, anti HIV activity¹¹

TYPICAL DOSE

- 900mg/day (usually divided TID) of 0.3% standardized hypericin

SIDE EFFECTS

- Photosensitivity, GI upset, dizziness, confusion, sedation, dry mouth, vivid dreams, restlessness

POTENTIAL INTERACTIONS/NOTES

- Safe up to 8 weeks
- Does not help HIV¹²
- PIs, NNRTIs, 5HT agonists/antidepressants, amitriptyline (↓), anything metabolized by CYP3A4, CYP2C9, p-GP

St. John's wort and Indinavir

- Open label prospective study in 8 healthy volunteers¹³
 - IDV 800mg Q8H until steady state (blood samples)
 - Day 3 - washout with SJW 300mg TID (x 14 days)
 - Day 16 re-start IDV until steady state again
- Results
 - IDV AUC (-57%, p=0.0008)
 - C5 hours (-49% to -99%, p=0.027)
 - Cmax and tmax not significantly altered
- Conclusions: Concomitant administration of SJW with IDV results in significant ↓ in IDV concentrations
- Caveats: more convincing due to numbers...

St. John's Wort – ARV Interactions

- St. John's Wort and Nevirapine
 - Case series of 5 pts w/NVP levels done Q3mos
 - NONMEM analysis (population pharmacokinetics)
 - Oral clearance ↑ 35%
- St. John's Wort and p-glycoprotein¹⁴
 - 22 healthy volunteers on placebo vs. SJW x16d
 - Baseline p-GP expression compared to 16 & 32 days post treatment
 - P-GP expression increased 4.2 fold in SJW group

Ginkgo biloba

INDICATION(S)

- HIV: AIDS dementia, impotence, venous insufficiency, RT inhibitor
- Other: stress, anxiety, short term memory, antitussive, gastrointestinal

TYPICAL DOSE

- 120-240mg/day divided B-TID (std 24% flavones 6% terpenes)

SIDE EFFECTS

- GI upset, headache, nausea, diarrhea. Seizures, death (high doses)

POTENTIAL INTERACTIONS/NOTES

- If using raw seeds use < 8-10 per day.
- antiepileptics (may ↑ seizures), anticoagulants, antiplatelet agents, MAOIs (additive), thiazide diuretics (↑ BP), fertility agents

Kava kava (*piper methysticum*)

INDICATION(S)

- HIV and Others: Stress, anxiety, insomnia

TYPICAL DOSE

- 300mg TID (standardized to 70% kavalactones) from the rhizome, root and/or stem

SIDE EFFECTS

- GI upset, sedation, ataxia, mydriasis, hyporeflexia, possible hepatotoxicity in large doses

POTENTIAL INTERACTIONS

- If using, use short term (< 6 months) and draw LFTs
- Additive liver toxicity, sedatives (additive), levodopa (antagonistic)

Melatonin (*N*-acetyl-5-methoxytryptamine)

INDICATION(S)

- HIV: sleep and possible anti-HIV effects
- Others: insomnia, jetlag, alzheimers disease, depression

TYPICAL DOSE

- 0.3mg PO QD titrated up to 0.75mg PO QD, 1-2 hrs prior to needed effects (bedtime)

SIDE EFFECTS

- Drowsiness, dysthymia, headache, itching

POTENTIAL INTERACTIONS/NOTES

- Hormone from pineal gland– not an herb
- CNS depressants, immunosuppressive agents (may stimulate immune system), verapamil (↓ melatonin levels)

Garlic (*allium sativum*)

INDICATION(S)

- HIV: Anti-HIV activity, hyperlipidemia
- Other: Hypertension, atherosclerosis, H.pylori, cancer, antifungal

TYPICAL DOSE

- 600-900mg divided TID. Raw garlic contains active ingredient (alliin broken down to → allicin)

SIDE EFFECTS

- Breath odor, heartburn, flatulence, N/V/D

POTENTIAL INTERACTIONS

- Anticoagulants, antiplatelet agents, diabetes medications (additive), fish oils

Garlic-Saquinavir interaction

- Open-label prospective study in 9 healthy volunteers¹⁶
 - Days 1-4 saquinavir (Fortovase) 1200mg TID with meals
 - Day 5-23 washout with garlic capsules (only) BID
 - Day 23 –25 re-started SAQ + garlic BID
 - Days 26-35 washout with garlic (again)
 - Days 36-39 restart saquinavir + garlic BID
 - Blood samples on days 4, 25, and 39
- Results
 - Saquinavir AUC during the 8-h dosing interval -51%
 - Cmin during the 8-h dosing interval -49%
 - Cmax decreased by 54%
 - After the 10-day washout period, the AUC, trough, and Cmax values returned to 60%-70% of their values at baseline
- Conclusions: Don't use garlic if SAQ is your sole PI...

Garlic-Ritonavir interaction

- Randomized crossover trial in 10 healthy volunteers¹⁷
 - Garlic or placebo given 5mg BID x 6 doses
 - 400mg single dose ritonavir + garlic/pbo on 7th dose
 - One additional dose of garlic
- Results
 - Nonsignificant ↓ in RTV-AUC 17%
 - Nonsignificant ↓ in RTV-Cmax 1%
- Conclusion
 - Acutely, no interaction observed
 - Can not r/o interaction because not steady state

Evaluating a product

- Read labels very carefully
 - Types of herbs or supplements
 - Lists amount of individual ingredients it contains
 - Claims of efficacy out of line?
 - Reputable company?
 - Contact information for company?
 - Lot number or expiration date?
 - Product look intact?
- Background information
 - Trials vs. case series, vs. individual reports
 - Information source reputable
 - How old is information? More updated info available?

Other points to consider

- Single vs combo herbs
 - From drugstore, pt may get single herb, easier to ID
 - Herbalists give in combo – know all herbs – modify if necessary
- Talking with patients is key
 - Know all their meds
 - Determine health goals
 - Discuss “BEST”: beliefs, evidence, safety, taking it
- Communicate with other providers, assign responsibility
 - Herbalist, CAM provider, etc
 - PCP may want to monitor for side effects & communicate efficacy
- Too many herbs, vitamins, dietary supplements for 1 talk...

Herbal resources



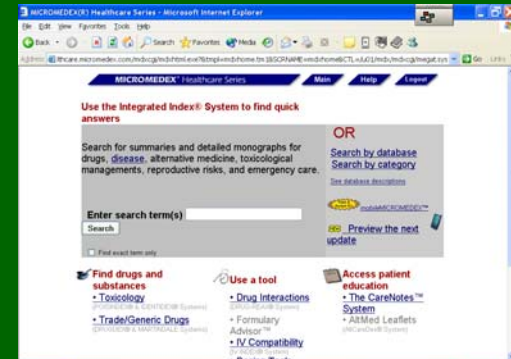
The Complete German Commission E Monographs: Therapeutic guide to herbal medicines



Tyler's Honest Herbal



Natural Medicines Comprehensive Database (www.naturaldatabase.com)



Micromedex: ALTMEDEX

Herbal Drug Interactions

- HIVinsite: www.hivinsite.com
 - Database of antiretroviral interactions
 - Limited in scope, but referenced and free
- Micromedex: www.naturaldatabase.org
 - Again, limited in scope, but referenced and \$\$
- Natural Database: www.naturaldatabase.com
 - Referenced and includes theoretical interactions but you must look up every herb & pay \$\$

Dietary Supplement Resources

Int'l Bibliographic Info on Dietary Supps Database

NIH Office of Dietary Supplements & Nat'l Agricultural Library,
Food and Nutrition Information Center

<http://ods.od.nih.gov/databases/ibids.html>

Description: IBIDS comprehensive bibliographic database to help health care providers, researchers, and consumers find credible, scientific literature on dietary supplements. Visitors may search for either consumer-oriented or professional level (peer-reviewed research) documents, or both. Currently, the database contains dietary supplements citations/abstracts from MEDLINE, AGRICOLA, and AGRIS databases dating from 1986 to the present.

Conclusion

- HIV positive patients may take a variety of BBT to treat HIV and its related symptoms. Important to understand therapy goals of patient.
- Many indications for each product --- clarify which indication your patient is taking it for.
- Very little information about efficacy or specific safety of herbal therapies and dietary supplements.
- Broad information about general side effects available. Consider concomitant disease states and what might need to initially be monitored. Discuss openly with patients.

References

1. Standish LJ, Greene KB, Bain S, Reeves C, Sanders F, Wines RB, Turet P, Kim JG, Calabrese C. Alternative medicine use in HIV-positive men and women: demographics, utilization patterns, and health status. *AIDS Care*. 2001;13:197-208
2. Duggan J, Peterson WS, Schutz M, Khuder S, Charkraborty J. Use of complementary and alternative therapies in HIV-infected patients. *AIDS Patient Care and STDs*. 2001; 15:159-167
3. Hsiao AF, Wong MD, Kanouse DE, Collins RL, Liu H, Andersen RM, Gifford AL, McCutchan A, Bozzette SA, Shapiro MF, Wenger NS, HCSUS Consortium. Complementary and alternative medicine use and substitution for conventional therapy by HIV-infected patients. *JAIDS* 2003 Jun 1; 33(2):157-65
4. Fairfield KM, Eisenberg DM, Davis RB, Libman H, Phillips RS. Patterns of use, expenditures, and perceived efficacy of complementary and alternative therapies for HIV-infected patients. *Ach Int Med* 1998 Nov 9;158(20):2257-64
5. Southwell H, Valdez H, Gripshover B, McComsey G, Salata R, Davidson R, Lederman M. Use of alternative therapy among HIV-infected patients at an urban tertiary center. 8th Conference on Retroviruses and Opportunistic Infections. Abstract #497

References, continued

6. No authors listed. Are echinacea and HIV not a good mix? *Treatmentupdate*. 1999 Feb;11(1):3.
7. Gudima SO, Memelova LV, Borodulin VB, Pokholok DK, Mednikov BM, Tolkachev ON, Kochetkov SN. Kinetic analysis of interaction of human immunodeficiency virus reverse transcriptase with alkaloids. *Mol Biol (Mosk)*. 1994 Nov-Dec; 28(6): 1308-14.
8. DiCenzo R et al. Concentrations of milk thistle and indinavir in healthy subjects. *Pharmacotherapy* 2003; 23(7):866-870
9. Piscitelli SC et al. Effect of milk thistle on the pharmacokinetics of indinavir in healthy volunteers. *Pharmacotherapy* 2002 May;22(5):551-6.
11. Taher MM, Lammering GM, Hershey CM, Valerie KC. Mood-enhancing antidepressant St. John's wort inhibits the activation of human immunodeficiency virus gene expression by ultraviolet light. *IUBMB Life*. 2002 Dec; 54(6): 357-64.
12. Gulick RM, McAuliffe V, Holden-Wiltse J, et al. Phase I studies of hypericin, the active compound in St. John's Wort, as an antiretroviral agent in HIV-infected adults. *AIDS Clinical Trials Group Protocols 150 and 258*. [Ann Intern Med](#) 1999;130:510-4.
13. Piscitelli S. et al. Indinavir concentrations and St. John's wort (letter). *The Lancet* 2000, Feb 12;355: 547-548
14. Hennessy M, et al. St. John's wort increases expression of P-glycoprotein: implications for drug interactions. *Br. J Clin Pharmacol* 2002; 53:75-82
15. Lissoni P, Vigore L, Rescaldani R, Rovelli F, Brivio F, Giani L, Barni S, Tancini G, Ardizzoia A, Vigano MG. Neuroimmunotherapy with low-dose subcutaneous interleukin-2 plus melatonin in AIDS patients with CD4 cell number below 200/mm³: a biological phase-II study. *J Biol Regul Homeost Agents*. 1995 Oct-Dec; 9(4): 155-8

References, continued

16. Piscitelli S. et al. The effect of garlic supplements on the pharmacokinetics of saquinavir. *Clin Infect Dis.* 2002; 34:234-238
17. Gallicano K, Foster B, Choudhri S. Effect of short-term administration of garlic supplements on single-dose ritonavir pharmacokinetics in healthy volunteers. *Br J Clin Pharmacol.* 2003 Feb; 55(2): 199-202.