

## Evidence-based alternative medicine and health treatment for HIV/AIDS patients

Sompop Prathanurug, Ph.D.  
Associate Professor  
Department of Pharmaceutical Botany  
Faculty of Pharmacy, Mahidol University

## What is CAM?

**CAM** is a group of diverse medical and health care systems, practices, and products that are not presently considered to be part of conventional medicine.



## Are complementary medicine and alternative medicine different from each other?

- Complementary medicine is used together with conventional medicine.
- Alternative medicine is used in place of conventional medicine.

## What are the major types of complementary and alternative medicine?

- Whole Medical Systems
  - built upon complete systems of theory and practice.
  - Homeopathic medicine
  - Traditional Chinese Medicine
  - Ayurveda



## What are the major types of complementary and alternative medicine?

- Mind-Body Medicine
  - to enhance the mind's capacity to affect bodily function and symptoms.
  - Meditation
- Biologically Based Practices
  - use substances found in nature,
  - herbs, foods, vitamins, dietary supplements



## What are the major types of complementary and alternative medicine?

- Manipulative and body-based practices
  - massage, chiropractic
- Energy Medicine
  - involve the use of energy fields.
  - Bioelectromagnetic-based therapies
  - Qi gong



## The purposes of this session are to:

- Review CAM used in HIV-infected patients
- Review the situation of the development of naturally derived Anti-HIV agents
- Assess beneficial effects and risks of CAM in HIV-infected patients
- Discuss risks and benefits associated with the use of CAM by HIV-infected patients

## CAM used in HIV-infected patients: Thailand

- The frequency of use of CAM by HIV-positive patients in Thailand, 2000.
- An interview survey
- 160 HIV-seropositive patients attending Out-Patient Division, King Chulalongkorn Memorial Hospital.
- 95% used CAM
  - Mor-Pra (84%)
  - Chee-Wa-Jit (67%)
  - Ya Mor (55%)
  - Ya Tiab (53%)
  - Vitamin (51%)

## CAM used in HIV-infected patients: Thailand

- Most patients used more than one CAM.
- The most common source of information on CAM was friends.
- Patients who saw CAM providers made a median of 4 visits to them per year, compared with 12 visits per year to their primary care physician and nurse practitioner.
- CAM is frequently used by HIV-positive patients in Thailand and their physicians need to be aware of this possibility.

Complementary Therapies in Medicine, 2003, 11: 39-41.

## CAM used in HIV-infected patients: US

- Cross-sectional survey of U.S. national probability sample of HIV-infected patients (2,466 adults) in care from December 1996 to July 1997.
- 52.5 % had recently used at least one type of CAM.
- 25.5 % used CAM with the potential for adverse effects
- 26.2 % had not discussed such use with their health care provider.
- 2.5 % of patients substituted CAM for conventional HIV therapy.

JAIDS 2003, 33: 157-65.

## CAM used in HIV-infected patients: EU

- This case-control study compared the characteristics of HIV-infected ever and never CAM users in seven European countries (Italy, Belgium, France, Germany, Greece, Spain, United Kingdom).
- CAM use was more common among females than males and in more educated subjects.
- CAM use was less common among subjects taking highly active antiretroviral therapy (HAART), but was more common in outpatients who reported HAART-related side effects.
- The most commonly used CAMs were dietary supplement, massage, yoga, and phytotherapy.

Complementary Therapies in Medicine, 2006, 14: 193-9.

## CAM used in HIV-infected patients: Canada

- A survey of HIV positive people on antiretroviral therapy and CAM use in British Columbia, Canada, 2002
- cross-sectional study, 682 participants
- 47% of patients had used CAM.
- vitamins/minerals (81%)
- meditation/yoga (36%)
- massage (31%)
- marijuana (30%)
- dietary supplements (24%)
- herbal medicines (19%)

Complementary Therapies in Clinical Practice, 2006,12: 242-8

## CAM used in HIV-infected patients: A systematic review

- A systematic review of randomized clinical trials assessing the effectiveness of complementary therapies for HIV and HIV-related symptoms.
- Comprehensive literature searches were performed of seven electronic databases.
- The trials were published between 1989 and 2003.
- 30 trials met our predefined inclusion/exclusion criteria.

## CAM used in HIV-infected patients: A systematic review

- 18 trials were of stress management
- 5 of Natural Health Products
- 4 of massage/therapeutic touch
- 1 of acupuncture
- 2 of homeopathy

## CAM used in HIV-infected patients: A systematic review

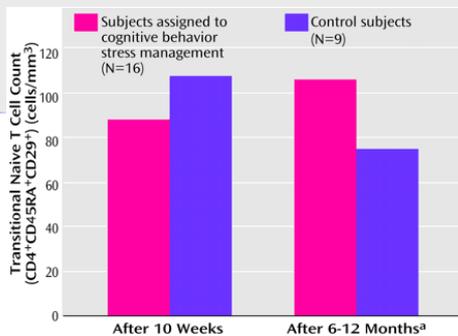
- Most trials were small and of limited methodological rigour.
- The results suggest that stress management may prove to be an effective way to increase the quality of life.
- For all other treatments, data are insufficient for demonstrating effectiveness.
- The effectiveness of CAM therapies has not been established.

Int J STD & AIDS 2005; 16: 395-402.

## CAM : Stress management

- Patient characteristics: Twenty-five male patients, mean age  $37 \pm 7.5$
- Intervention: a 10-week stress management versus wait-listed control.
- Outcomes measured: CD4(+), CD45RA(+), CD29(+) cells.
- Results: Men receiving stress management had significantly higher immune marker levels after six to 12 months follow-up.

Am J Psychiatry 2002; 159: 143-5.

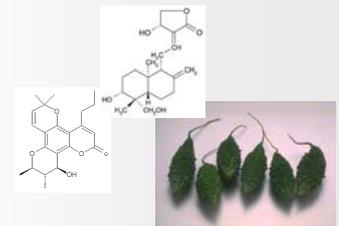


Transitional Naive T Cell Counts for HIV-Positive Men Immediately After Cognitive Behavior Stress Management and at 6-12-Month Follow-Up and for HIV-Positive Men in a Control Condition at Comparable Time Points

<sup>a</sup>Significant difference between groups according to ANCOVA controlling for 10-week cell count ( $p < 0.03$ )

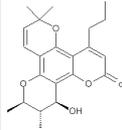
Am J Psychiatry 2002; 159: 143-5.

## Naturally derived Anti-HIV agents



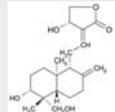
## Naturally derived Anti-HIV agents: (+)-calanolide A

- Pyranocoumarin
- *Calophyllum lanigerum* var. *austrocariaceum* (Clusiaceae)
- Non-nucleoside reverse transcriptase inhibitors (NNRTI)
- A favorable safety profile in both animal and human subjects
- Phase-II clinical study
- Anti-TB *in vitro*



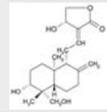
## Naturally derived Anti-HIV agents: andrographolide

- Diterpene lactone
- *Andrographis paniculata* (Acanthaceae)
- A phase I dose-escalating clinical trial
- 13 HIV positive patients and five HIV uninfected, healthy volunteers.
- The planned regimen was 5 mg/kg bodyweight for 3 weeks, escalating to 10 mg/kg bodyweight for 3 weeks, and to 20 mg/kg bodyweight for a final 3 weeks.



## Naturally derived Anti-HIV agents: andrographolide

- A significant rise in the mean CD4+ of HIV subjects occurred after administration of 10 mg/kg andrographolide
- No statistically significant changes in mean plasma HIV-1 RNA levels throughout the trial
- Andrographolide may inhibit HIV-induced cell cycle dysregulation rather than interrupting viral replication directly.
- An anaphylactic reaction in one patient was reported.



Calabrese *et al.* *Phytother Res* 2000;14:333-8.

## Naturally derived Anti-HIV agents : MRK29

- *Momordica charantia*
- Protein from ripe fruit and seed: MRK29 (28.6 kD)
- Inhibit reverse transcriptase
- Increase 3-fold TNF activity



Jiratchariyakul *et al* *Planta Med* 2001;67:350-3.

## Naturally derived Anti-HIV agents : Systematic review

- To assess beneficial effects and risks of herbal medicines in patients with HIV infection and AIDS.
- Selection criteria: Randomized clinical trials on herbal medicines compared with no intervention, placebo, or antiretroviral drugs in patients with HIV infection, HIV-related disease, or AIDS.

## Naturally derived Anti-HIV agents : Systematic review

- Nine randomized placebo-controlled trials involving 499 individuals with HIV infection and AIDS met the inclusion criteria.
- Methodological quality of trials was assessed as adequate in five full publications and unclear in other trials.
- Eight different herbal medicines were tested.

## Naturally derived Anti-HIV agents : Systematic review

- IGM-1 improved health-related QOL in 30 symptomatic HIV-infected patients
- An herbal formulation of 35 Chinese herbs did not affect CD4 cell counts, viral load, AIDS events, symptoms, psychosocial measure, or quality of life.
- SPV30 showed no effects in new AIDS-defining events, CD4 cell counts, or viral load.
- Combined treatment of SH and antiretroviral agents showed increased antiviral benefit compared with antiretrovirals alone.
- SP-303 appeared to reduce stool weight and abnormal stool frequency in 51 patients with AIDS and diarrhoea.

## Naturally derived Anti-HIV agents : Systematic review

- Qiankunng appeared not to affect HIV-1 RNA levels.
- Curcumin ineffective in reducing viral load or improving CD4 cell counts.
- Capsaicin ineffective in relieving pain associated with HIV-related peripheral neuropathy.
- The occurrence of adverse effects was higher in the 35 Chinese herbs preparation than in placebo (79% versus 38%,  $p = 0.003$ )
- Qiankunng was associated with stomach discomfort and diarrhoea.

## Naturally derived Anti-HIV agents : Systematic review

- There is insufficient evidence to support the use of herbal medicines in HIV-infected individuals and AIDS patients. Potential beneficial effects need to be confirmed in large, rigorous trials.

Lui *et al.* Cochrane Database of Systematic Reviews 2005, Issue 3. Art. No.: CD003937.

## Naturally derived Anti-HIV agents : SH

- A randomized double blind placebo controlled trial
- to determine the efficacy and safety of combined-herbs (SH) given with zidovudine (ZDV) and zalcitabine (ddC)
- HIV-infected Thai patients (N=60)
- 3 hospitals in northern Thailand
- 2002 to 2003.
- ZDV 200mg + ddC 0.75mg + SH 2.5g three times/day
- ZDV 200mg + ddC 0.75mg + placebo 2.5g three times/day
- 24 weeks.

Sangkilporn *et al.* Southeast Asian J Trop Med Public Health 2005;36:704-8.

## Naturally derived Anti-HIV agents : SH

- *Glycyrrhiza glaba*
- *Morus alba*
- *Cathamus tinctorius*
- Capillaris (*Artemisia capillaris*)
- Astragalus (*Astragalus membranaceus*)

## Naturally derived Anti-HIV agents : SH

- HIV RNA at week 4 and thereafter was significantly decreased from the baseline value in both groups.
- The decline in HIV RNA in the SH group was significantly more than that in the placebo group.
- The CD4 cells in the SH group at week 12 and thereafter were significantly increased from the baseline value.
- It is concluded that an addition of SH herbs to two nucleoside reverse transcriptase inhibitors has greater antiviral activity than antiretrovirals only.

## Herb-Drug Interaction

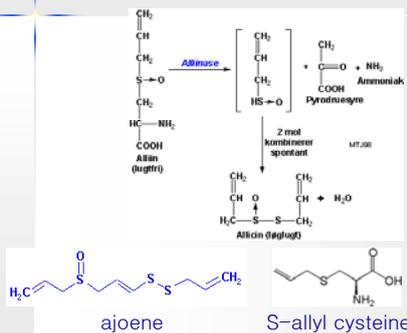


## Herb-Drug Interaction: Garlic

- *Allium sativum*
- Sulfur compounds
- Alliin is not present in garlic in its natural state.
- When garlic is chopped or otherwise damaged, the enzyme alliinase converts alliin into alliin.
- alliin is unstable
- Other active compounds: ajoene diallyl disulfide, S-allyl cysteine



## Herb-Drug Interaction: Garlic

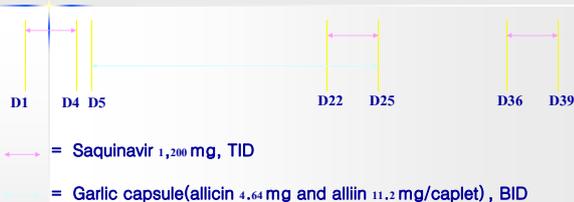


## Herb-Drug Interaction: Garlic

- Ten HIV-infected patients
- A 12 week experimental study taking 5 grams daily of an aged garlic extract for 6 weeks followed by 10 grams daily for another 6 weeks.
- Seven patients were able to complete the garlic regimen with significant improvement of immune parameters.
- Ajoene, an active compound in oil-macerated garlic, suppresses HIV-1 replication *in vitro*.



## Herb-Drug Interaction: Garlic



Piscitelli S, et al. Clin Infect Dis 2002; 34:234-8.

## Herb-Drug Interaction: Garlic

- Saquinavir
  - AUC decreased 51 %
  - $C_8$  decreased 49 %
  - $C_{max}$  decreased 54 %
- After 10-day washout, AUC, trough, and  $C_{max}$  returned to only 60-70 % of baseline values.



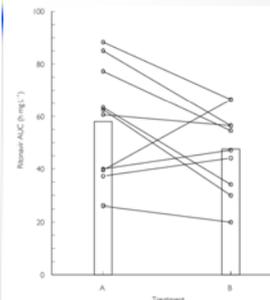
## Herb-Drug Interaction: Garlic

- Effect of short-term administration of garlic supplements on single-dose ritonavir pharmacokinetics in healthy volunteers
- Ten healthy volunteers (five male, five female)
- a crossover design to receive 400 mg of a single dose of ritonavir within 10 min after eating breakfast either alone or with 10 mg of Natural Source Odourless Garlic.
- They received a total of eight doses of garlic extract (2 × 5 mg capsules) taken twice daily for 4 days.
- Ritonavir and the seventh garlic dose were administered simultaneously.



Gallicano K. *et al.* Br J Clin Pharmacol 2003; 55:199-202.

## Herb-Drug Interaction: Garlic



Individual AUC<sub>(0,∞)</sub> values for ritonavir after treatment with a 400-mg single dose of drug alone (A) and with garlic after the seventh dose of garlic (B). (Vertical bars represent mean AUC values for ten participants).



## Herb-Drug Interaction: Garlic

- Acute dosing of the garlic capsules over 4 days did not significantly alter the single-dose pharmacokinetics of ritonavir in healthy volunteers.
- Given the complex effects of both ritonavir and garlic on drug metabolism, the results should not be extrapolated to steady-state conditions, where the possibility of an interaction still needs to be evaluated.
- The garlic product used in the experiment containing allicin less than 1 µg/g).



Gallicano K. *et al.* Br J Clin Pharmacol 2003; 55:199-202.

## Acute heart transplant rejection due to St. John's wort



- St. John's wort (*Hypericum perforatum*)
- antidepressant
- St. John's wort & cyclosporin

(Lancet, Feb. 2000)

## Herb-Drug Interaction: St. John's Wort

An inducer of CYP3A4 in cytochrome P-450 enzyme system



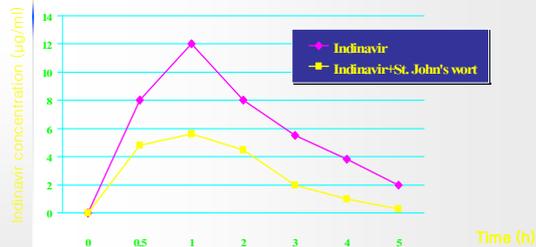
Increase the metabolism of protease inhibitors, non-sedating antihistamines, Calcium channel blockers, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, benzodiazepines, estrogens, macrolide antibiotics, cyclosporin, carbamazepine, ketoconazole, and cortisone

## Indinavir concentrations and St. John's wort

- An open-label study in 8 healthy volunteers
- First, measured the amount in the body of Indinavir when taken alone.
- Next, the participants were given only St. John's wort for 2 weeks.
- Finally, Indinavir and St. John's wort were given together.

Lancet 2000;355:547-8.

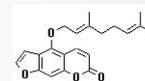
## Indinavir concentrations and St. John's wort



Mean concentration–time of Indinavir alone and with concomitant St. John's wort

## Herb–Drug Interaction: Grapefruit Juice

- *Citrus x paradisi*
- A hybrid of *Citrus maxima* and Sweet Orange (*Citrus sinensis*)
- bergamottin and derivatives inhibit CYP<sub>3A4</sub> in vitro and healthy volunteers.



## Herb–Drug Interaction: Grapefruit Juice

- elevate serum concentration of protease inhibitors
- doubles the oral bioavailability of Saquinavir.
- increased adverse effects



## KEY POINTS:

- Most of HIV–infected patients used CAM.
- Health care professionals must be knowledgeable about CAM to assist patients in making informed choices regarding their use.
- The risks and benefits of all therapies, including CAM options, should be considered by patients and health care providers prior to the start of treatment.
- When treatment failures and adverse effects of therapy are seen, the possible influence of CAM needs to be considered.

## Suggestions regarding patient–Health care providers communication with CAM

- Perform a complete drug history.
- Collect and record data concerning CAM use.
- Listen to your patients and support them in a nonjudgmental fashion.
- Keep abreast of the latest information.

## Where to find additional information

<http://medplant.mahidol.ac.th> :

Medicinal plant information center  
Faculty of Pharmacy, Mahidol University

<http://nccam.nih.gov>

National Center for Complementary and Alternative Medicine,  
National Institutes of Health, USA

<http://www.quackwatch.com>  
Quackwatch