

## Symposium

### Activities of the UIC/NIH Center for Botanical Dietary Supplements Research for Women's Health

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The UIC/NIH Center for Botanical Dietary Supplements Research for Women's Health has been supported by NCCAM since 1999. Several plants were selected for study based on literature reports suggesting beneficial effects to reduce the symptoms associated with menopause, i.e hot flashes. The basic philosophy of the Center is that no botanical dietary supplements should be evaluated in humans unless the botanical identity has been verified and that the test substance is chemically and biologically standardized. The most advanced of the plants being studied are Black Cohosh (*Cimicifuga racemosa*; syn: *Actaea racemosa*), Red Clover (*Trifolium pratense*) and Hops (*Humulus lupulus*). After each plant is taxonomically verified, active compounds were isolated and identified by bioassay directed fractionation.

In the case of Black Cohosh, the major active principles are triterpene glycosides (IC<sub>50</sub> ca. 50-100 mcg/ml) and a number of phenolic acids (IC<sub>50</sub> <1.0 mcg/ml) vs. serotonin receptors, mainly 5HT-7. It was found that the triterpene glycosides passed through CACO-2 cells, but the phenolic acids did not pass through CACO-2 cells in vitro. However, in a Phase I study in humans, the less active triterpene glycosides were found in blood and urine, but not the more active phenolic acids. However, most recently, we have some evidence that cimipronidine, a novel and basic compound is present in the plant that may react with the phenolic acids to form a complex that would result in absorption of the highly active phenolic acids. Work on understanding this potential phenomenon is in progress and will be reported. Both Black Cohosh and Red Clover preparations are currently involved in a four arm Phase 2 clinical study at the highest doses determined in a Phase 1 study that was found to be safe. The other two arms are placebo and a positive control, Prempro. Women will take the preparations for twelve months with the usual tests being conducted routinely, especially monitoring of liver enzymes. As of November, 2006, all subjects have entered in the trial, with about half of them finished with the 12 month treatment. We have seen no evidence of liver toxicity or other major adverse effects to date and data analysis will be started in November of 2007. Problems associated with recruitment and results to date will be discussed. Analysis of published and unpublished studies alleging that Black Cohosh may be hepatotoxic will be presented.

With regard to our work with Hops, we are working with a product that is approved as a food additive in Europe (added to beer) and has been characterized completely. The major compound in Hops with estrogenic activity is 8-prenylnaringenin (8PN) with several related compounds that are metabolized to 8PN. Since 8PN is one of the most potent estrogenic plant-derived compounds known, we are now conducting experiments in vitro and in vivo with 8PN and a standardized Hops extract to determine their pharmacokinetic and safety profiles and plan to initiate a Phase 1 clinical study. Results to date will be presented.