Science of Femina Plus®

- **Herbal extracts screened out of 71 herbal extracts via non-reproductive tract target tissue response (E-screen test)**

  <u>3 herbal extracts were chosen:</u>

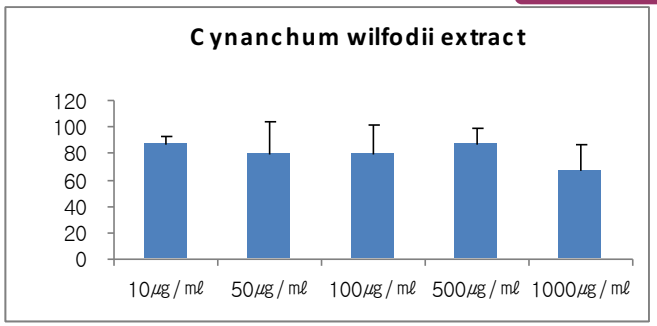
  Cynanchum wilfordii, Phlomis umbrosa,* and *Angelica gigas Nakai

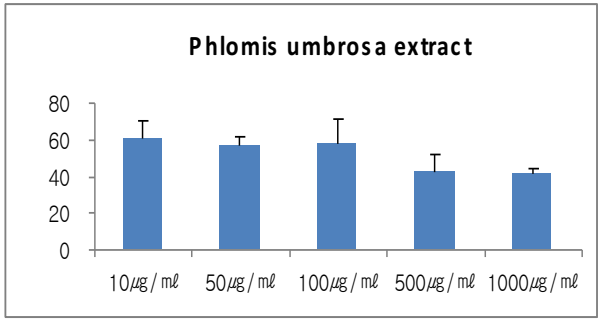
- **Proven Safety**
  - About 400 years of documented use in Korea and China as folk medicine
  - Registered as safe food ingredient
  - No increase of uterus weight in ovariectomized rat tests
  - Inhibition of proliferation of human breast cancer cell (MCF-7)
  - No binding Affinity to both Estrogen Receptor α and β, cancer-inhibitory
  - Safe: Acute & Multi-dose toxicity tests , Genetic toxicity tests

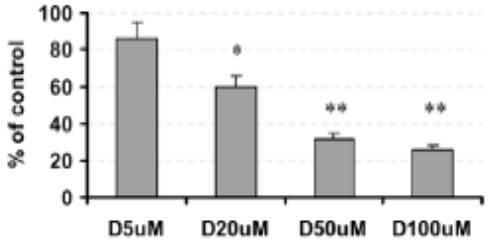
- **Proven Efficacy *in vitro, in vivo*, and 2 published human (Asian and non-Asian) clinical studies (one in Korea, one in USA)**
- **US FDA's full Acknowledgement**
- **Health Canada's full Acknowledgement**

MCF-7 cell & ER Binding Affinity proves Femina Plus® is Safe!

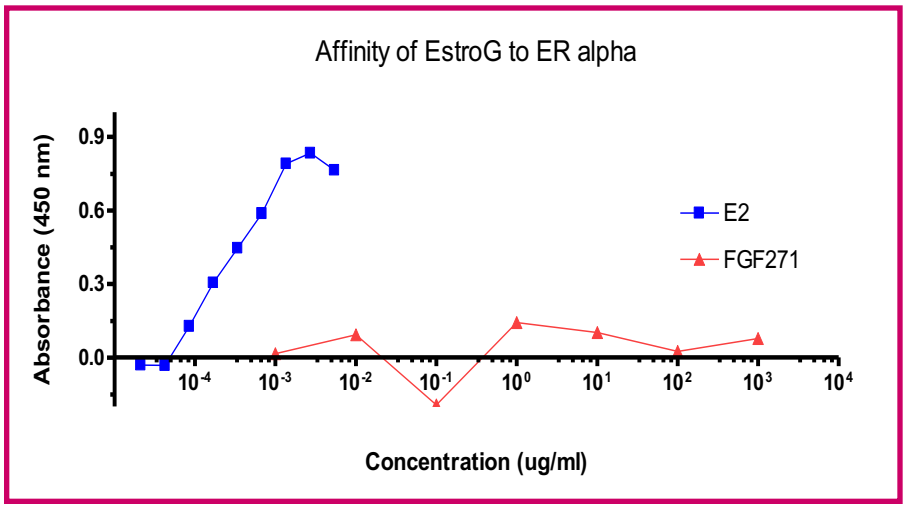
MCF-7 proliferation inhibition

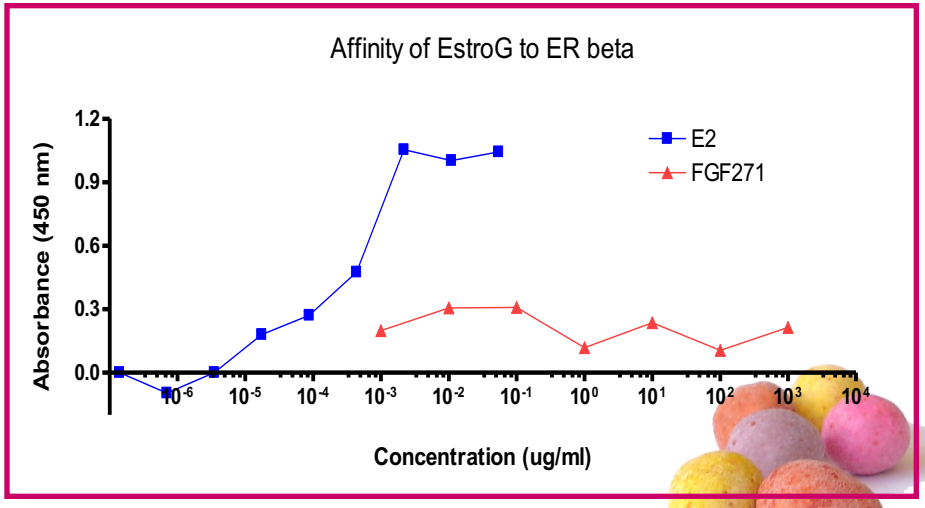






Estrogen receptor binding affinity test

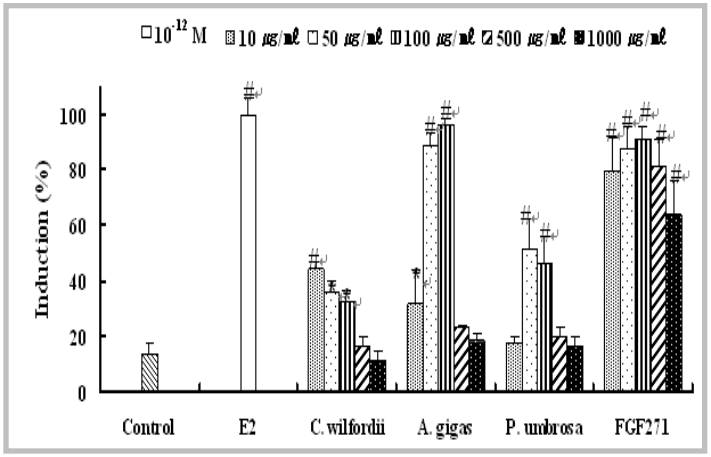




EnBio Estrogen Receptor / Coactivator, Ligand Assay System

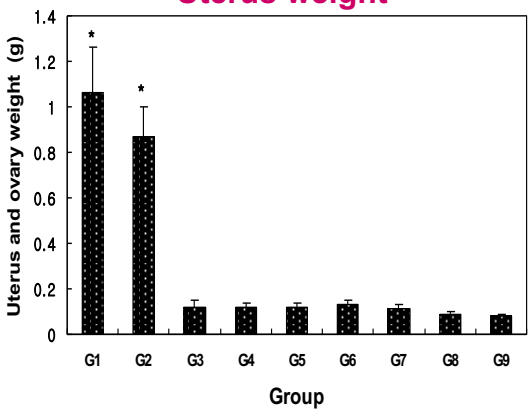
Estrogenicity

- **E-screen test:** Screen herbal extracts for Estrogenicity
- **Synergetic Effects of 3 Constituent herbal extracts confirmed**
  - Lee *at al.. Lab. Anim. Res. 24(2): 167-172 (2008)*

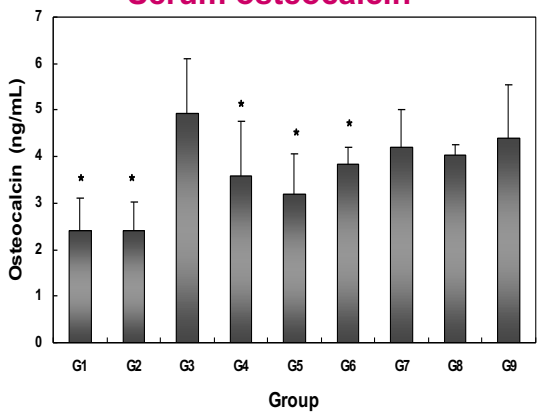


- **Significantly improved in serum osteocalcin and FBMD in OVX rat**
- **No change in weight, liver, kidney, and uterus weight in OVX rat**

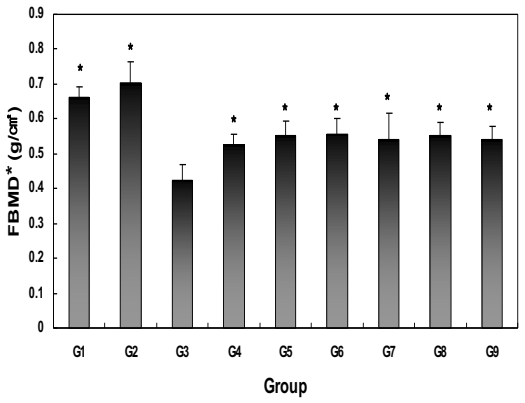
Uterus weight



Serum osteocalcin



FBMD



Clinical study I - Protocol

Randomized Double-blind Placebo-controlled study (Samsung Cheil Hospital, Seoul, Korea)	
Test material	Femina Plus
Dosing period	12 months (May 2003-April 2004)
Method	Double-blinded
Evaluation style	Long Term Safety Evaluation
Patients (n=47)	23 subjects in placebo group & 24 active group
Inclusion Criteria	Age>45 years old & Diagnosis of menopausal syndromes (average age=54)

Clinical study I - Efficacy

Climacteric Symptoms 5 times better improvement than placebo with significance	After 3 months OR=5.04 (95% C.I.=1.4-18.1) Fisher's Exact Test
Femoral Bone Mineral Density Significant improvement	After 12 months 0.746±0.10 → 0.763±0.13 (P<0.05)
Serum hGH Level Significant improvement	After 12 months 0.25±0.21 → 0.92±0.97 (ng/mL) (P<0.05)
Serum Osteocalcin Level Significant improvement	After 12 months 6.02±2.74 → 5.66±3.01 (ng/mL) (P<0.05)
Serum Alkaline Phosphatase Level Significant improvement	After 12 months 73.35±21.02 → 60.42±14.87 (IU/L) (P<0.05)
Serum Triglyceride Level Significant improvement	After 12 months 119.1±54.72 → 92.16±49.94 (mg/dL) (P<0.05)

Toxicology Study on BOTH male & female rats

- **Toxicology study on BOTH male & female rats**

  500 mg/kg, 1000 mg/kg, 2000 mg/kg single dose

  No mortality observed (MLD>2000 mg/kg)

  No body weight changes observed

  No toxicological, abnormal findings in necropsy observed

  Slight diahrria at 2000 mg/kg, but all recovered next day

- **3 Genetic Toxicity Tests – proven nontoxic**

  Ames (Bacterial Reverse Mutation)

  Micronucleus

  Chromosome abberration

Key Findings of Femina Plus®

- **Unlike Black Cohosh, it is antihepatotoxic or liver protective**

- **Unlike Soy, it proved to be not binding to Estrogen receptors alpha and beta**

  Binding affinity of Femina Plus to ER alpha and beta

- **Inhibitory effect of the proliferation of human breast cancer cell or MCF-7**

  ① College of Veterinary Medicine Chungbuk National University, Kang, *et al*. 2007

  ② Jiang C, *et al*. Decursin and decursinol angelate inhibit estrogen-stimulated and estrogen-independent growth and survival of breast cancer cells. Breast Cancer Research. 9(6): R77 (2007), 6 Nov 2007

Mechanism of Action

Estrogenecity:

In a non-reproductive tract target tissue response for e-screen assay, Femina Plus promoted ALP synergetically more than any of the individual herbal extract

Estrogen-like & anti-estrogen action:

to result in some benefits (eg, bone metabolism and menopausal symptoms) and not to influence human body to have adverse effects on endometrium and breast tissue based on the following available evidences:

- In two animal studies, Femina Plus did not increase the uterus weight of ovariectomized rats while it increased femoral bone mineral density
- It did not show any affinity to both estrogen receptor alpha and beta
- Each herbal extract of Femina Plus showed inhibitory effect of the proliferation of human breast cancer (MCF-7) cells
- In two clinical studies, it improved menopausal symptoms, bone density of femoral bone neck, bone markers without any serious side effects with no increase of body weight and BMI and without influencing level of E2 and FSH

Femina Plus® : Speed of Action

- There were two, unpublished studies in 2011, addressing speed of action, or, how quickly does Femina Plus work
- Study in cooperation with two commercial companies evaluating Femina Plus
- **Design:** Open Label study, 4 weeks, to evaluate results in Wk#1, #2, #3, #4, plus summary
- **Purpose:** to evaluate if these two companies will launch Femina Plus based on timing of action and general performance.

Feedback from FDM&C marketers- RE: customers have low tolerance for a product that does not manage menopausal symptoms fast. On average in the USA, Q&A evaluations show Femina Plus working on 2-3 symptoms within 7-10 days.

Femina Plus® : Affects-Skin Tone

- We conducted one, unpublished study in 2011, addressing the affects of Femina Plus on skin care
- Study in cooperation with one commercial company
- **Design:** Open Label study, 6 week, to evaluate results, plus summary
- **Purpose:** To evaluate if this company will launch Femina Plus based on benefits of: skin wrinkling, face blushing, skin moisture, and skin shining.
- **Results:** significant improvement, and performance towards compatibility with skin treatment topical's.