

Science of Femina Plus®



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

3 herbal extracts were chosen:

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 in Korea Food Codex and in China
 - 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 as New Dietary Ingredient**
(FDA Docket No. 1995-S-0039 Report 668)
- **Health Canada's Approval** (Product License Issuance - NPN 80026169)

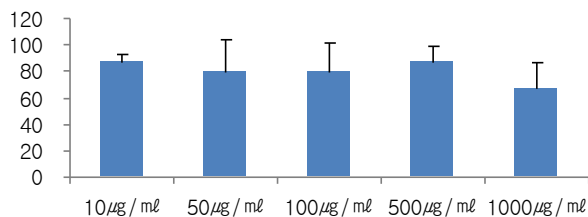
MCF-7 cell & ER Binding Affinity

Femina Plus[®] is Safe!

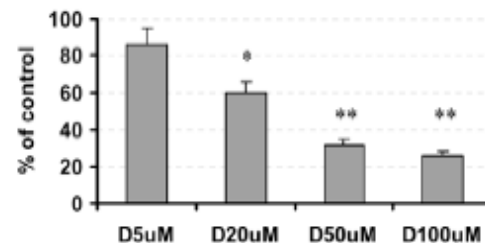
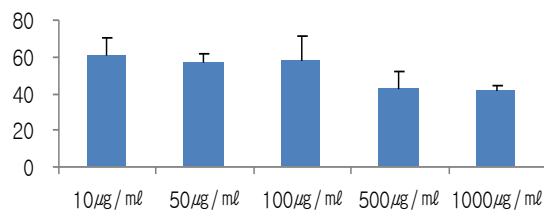


MCF-7 proliferation inhibition

Cynanchum wilfordii extract

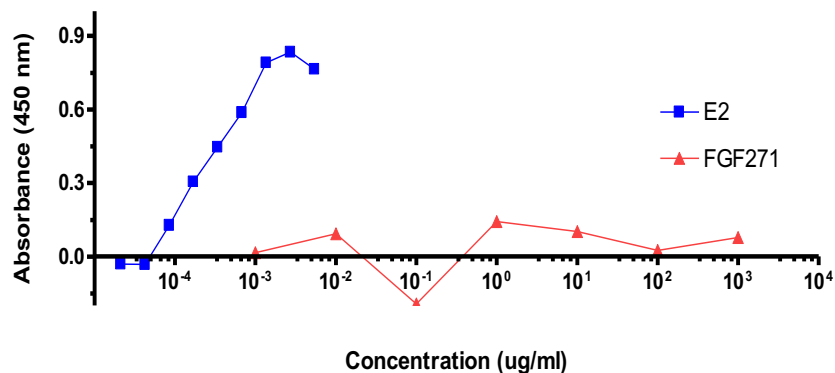


Phlomis umbrosa extract

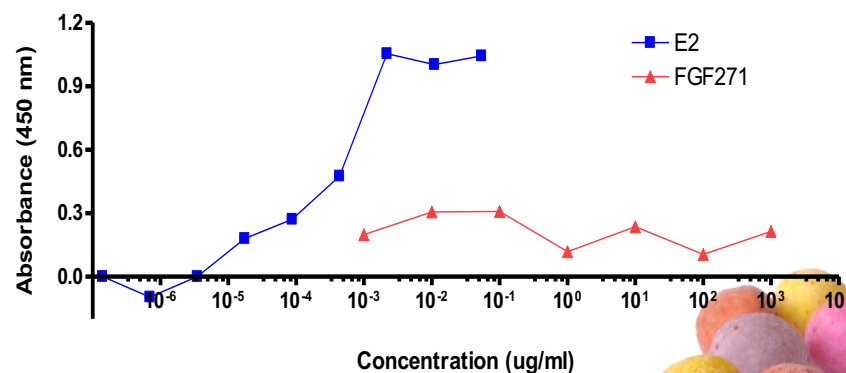


Estrogen receptor binding affinity test

Affinity of EstroG to ER alpha



Affinity of EstroG to ER beta



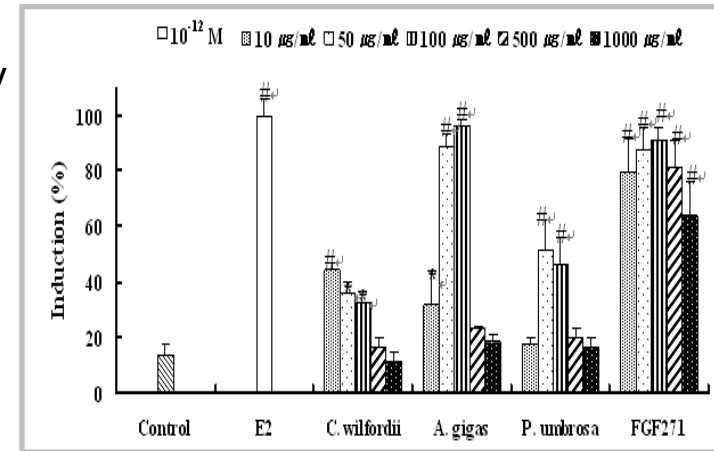
EnBio Estrogen Receptor / Coactivator, Ligand Assay System



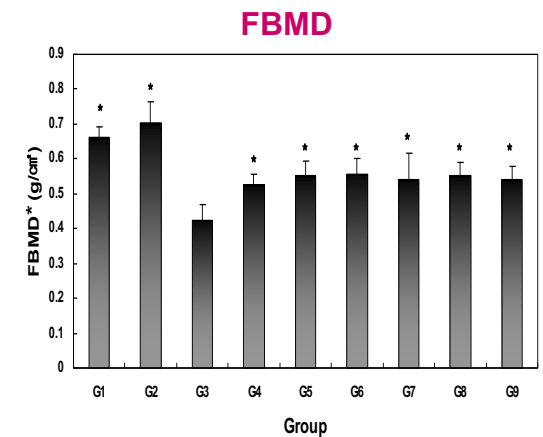
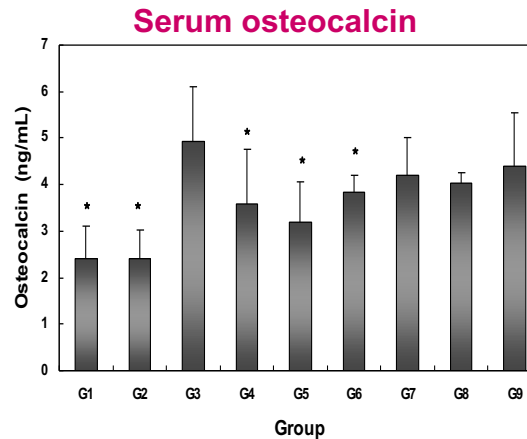
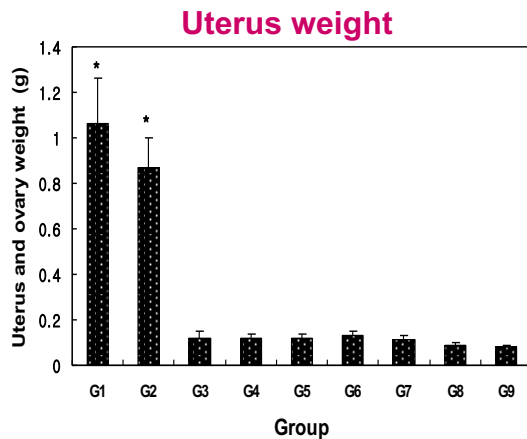
Estrogenicity



- **E-screen test:** Screen herbal extracts for Estrogenicity
- **Synergetic Effects of 3 Constituent herbal extracts confirmed**
- Lee *et 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**



Clinical study I (Asian) - Protocol



Randomized Double-blind Placebo-controlled study

(Samsung Cheil Hospital, Seoul, Korea)

Test material

EstroG-200

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 $0.746 \pm 0.10 \rightarrow 0.763 \pm 0.13$ ($P < 0.05$)
Serum hGH Level Significant improvement	After 12 months $0.25 \pm 0.21 \rightarrow 0.92 \pm 0.97$ (ng/mL) ($P < 0.05$)
Serum Osteocalcin Level Significant improvement	After 12 months $6.02 \pm 2.74 \rightarrow 5.66 \pm 3.01$ (ng/mL) ($P < 0.05$)
Serum Alkaline Phosphatase Level Significant improvement	After 12 months $73.35 \pm 21.02 \rightarrow 60.42 \pm 14.87$ (IU/L) ($P < 0.05$)
Serum Triglyceride Level Significant improvement	After 12 months $119.1 \pm 54.72 \rightarrow 92.16 \pm 49.94$ (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 diarrhea at 2000 mg/kg, but all recovered next day

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

- Ames (Bacterial Reverse Mutation)

- Micronucleus

- Chromosome aberration



Key Findings of Femina Plus®



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

Filed to WHO, ① <http://www.wpro.who.int/internet/files/pub/97/89.pdf>

② <http://www.wpro.who.int/internet/files/pub/97/201.pdf>

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

Binding affinity of EstroG-100 to ER alpha and beta, College of Veterinary Medicine Chungbuk National University, Kang, *et al.* 2007

- **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



Estrogenicity:

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 researches, 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



- We conducted 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 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 EstroG-100 working on 2-3 symptoms within 7-10 days.



EstroG-100® : Affects on Skin Tone



- We conducted one, unpublished study in 2011, addressing the affects of EstroG-100 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 topicals.

