Menopause Classification

- **Premature Menopause**
  - About 8% Women (US) stops having period before age 40
  - Same symptoms as Menopause
- **Peri-menopause**
  - Average women go through this phase age 45~49
  - Wildly fluctuating Estrogen Level
  - Same symptoms as Menopause
- **Menopause**
  - Estradiol level<50 pg/mL; FSH>50 mIU/mg; no period for >1 yr*
  - Average age for onset of menopause is 52 in US
  - Symptoms last 2~8 years, many more than 5 years
- **Surgical Menopause**
  - After Hysterectomy/Bilateral surgery

* ***Definition:*** Dr. Joel Harglove, MD, Chairman, Vanderbilt Menopause Center, Nashville, TN

New Product Innovation: FeminaPlus®

- **Femina Plus® has 3 herbal extracts**
  - *Phlomis umbrosa*: Shanzhiside methyl ester
  - *Cynanchum wilfordii*: Cinnamic acid (wilfosides)
  - *Angelica gigas* Nakai: decursin / nodakenin

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 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**
- **US FDA's full Acknowledgement as New Dietary Ingredient**
- **Health Canada's Approval**

Clinical study II (Non-Asian) – Protocol

Randomized Double-blind, Placebo-controlled study (CA, USA)	
Test material	Femina Plus
Dosing period	3 months (2009-2010)
Method	Double-blind
Evaluation style	Long Term Safety Evaluation
Patients (n=61)	32 subjects in placebo group & 29 active group
Inclusion Criteria	Age>42 years old & Diagnosis of menopausal syndromes (average age=53)

Clinical Study II - Efficacy

- **Report** (Kupperman Menopause Index & scores of vaginal dryness)
  – Stearling IRB

- The mean KMI scores were significantly reduced in FeminaPlus group from 29.45±7.39 at baseline to 13.62±7.61 at week 6 after and to 11.31±5.78 at week 12 while those were from 29.16±6.55 at baseline to 23.31±8.96 at week 6 after and to 23.66±7.98 at week 12 in the placebo group. The improvement was statistically significant in comparison with the two groups ($p<0.01$, t-test).

Results

Kupperman Menopause Index and Vaginal Dryness (Difficulties in Sexual Intercourse) Improved Significantly

Vaginal Dryness (Difficulties in Sexual Intercourse)

KMI

Somatic

- Hot flush/ Night sweat
- Paresthesia
- Insomnia
- Vertigo
- Fatigue
- Muscular skeletal pain

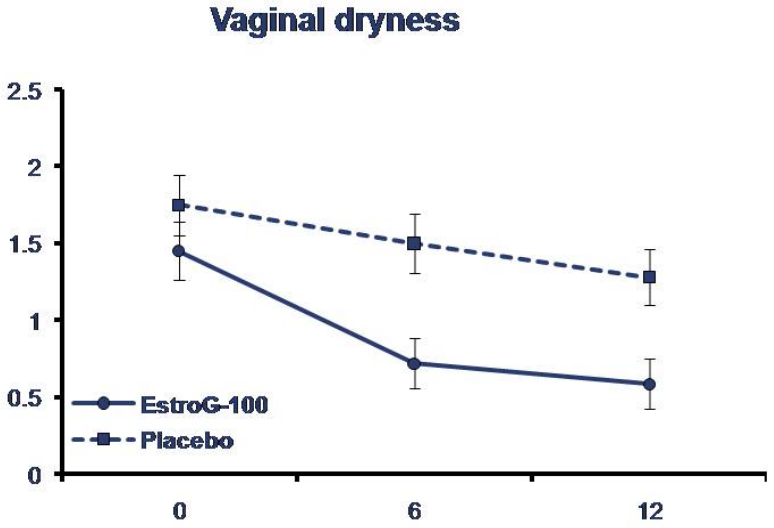
Psychological

- Nervousness
- Melancholia
- Formication

Femina Plus® was confirmed to improve both somatic and physiological symptoms with statistical significance.

Vaginal Dryness (Difficulties in Sexual Intercourse)

	FGF-271 Mean±SD	Placebo Mean±SD
Week0 (Baseline)	1.45±1.02	1.75±1.11
Week6	0.72±0.88	1.50±1.11
Change from baseline	-0.72±0.84 ** †† ##	-0.25±0.57 #
Week12	0.59±0.87	1.28±1.02
Change from baseline	-0.86±0.88 * ##	-0.47±0.72 ##
		p=0.0536

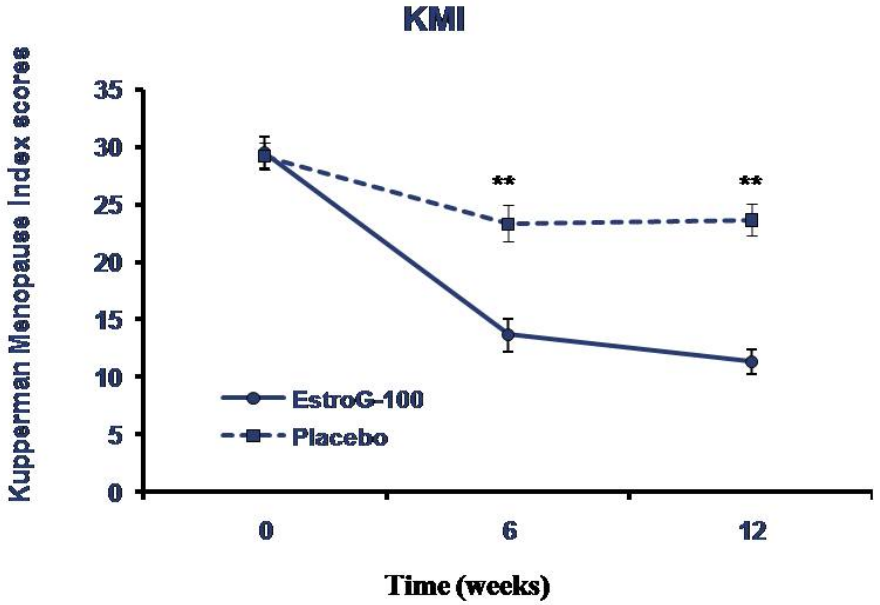


*; *p*-<0.05 compared between groups, **; p<0.01 compared between groups by t –test
††; p<0.01 compared between groups by Wilcoxon rank sum test
#; *p*-<0.05 compared to baseline, ##; p<0.01 compared to baseline by paired t-test

Vaginal Dryness Improved
Unlike Black cohosh and Isoflavone

Kupperman Index

	FGF271 Mean±SD	Placebo Mean±SD
Week 0 (Baseline)	29.45±7.39	29.16±6.55
Week 6	13.62±7.61	23.31±8.96
Change from baseline	-15.83±9.10 **††##	-5.84±6.15##
Week 12	11.31±5.78	23.66±7.68
Change from baseline	-18.14±8.46 **††##	-5.50±5.34##



**; p<0.01 compared between groups by t –test
††; p<0.01 compared between groups by Wilcoxon rank sum test
##; p<0.01 compared to baseline by paired t-test

Kupperman Index for Moderate to Severe Menopausal Symptoms Improved

2nd Clinical- Symptoms Analysis

Symptom	Femina Plus (n=29)			Placebo (n=32)		
	Week 0	Week 6	Week 12	Week 0	Week 6	Week 12
Vasomotor	2.24±0.69	1.03±0.82$^{**\dagger\dagger\#\#}$	0.79±0.73$^{**\dagger\dagger\#\#}$	2.22±0.66	1.78±0.75$^{\#\#}$	2.06±0.76
Paresthesia	1.31±0.85	0.59±0.78$^{*\dagger\#\#}$	0.55±0.74$^{*\dagger\#\#}$	1.41±0.91	1.13±0.94$^{\#}$	1.09±0.96$^{\#\#}$
Insomnia	2.28±0.84	1.28±0.96$^{**\dagger\#\#}$	0.97±0.82$^{**\dagger\dagger\#\#}$	2.03±0.86	1.63±1.01$^{\#}$	1.63±0.87$^{\#}$
Nervousness	1.72±0.88	0.76±0.69$^{**\dagger\dagger\#\#}$	0.66±0.67$^{**\dagger\dagger\#\#}$	1.56±0.84	1.22±0.83	1.34±0.75
Melancholia	1.93±0.88	1.03±0.68$^{**\dagger\dagger\#\#}$	0.83±0.71$^{**\dagger\dagger\#\#}$	1.59±0.95	1.31±0.93	1.31±0.74
Dizziness	0.97±0.82	0.21±0.49$^{**\dagger\dagger\#\#}$	0.21±0.41$^{**\dagger\dagger\#\#}$	0.75±0.72	0.72±0.77	0.59±0.80
Fatigue	2.21±0.77	0.90±0.77$^{**\dagger\dagger\#\#}$	0.72±0.70$^{**\dagger\dagger\#\#}$	2.00±0.88	1.69±0.90$^{\#}$	1.59±0.80$^{\#}$
Arthritic Pain	1.59±1.02	0.79±0.94$^{**\dagger\#\#}$	0.55±0.78$^{*\dagger\#\#}$	1.84±0.95	1.63±0.83	1.47±0.88
Headache	1.34±1.04	0.69±0.76$^{\#\#}$	0.66±0.77$^{\#\#}$	1.53±0.95	1.13±0.91$^{\#}$	0.84±0.72$^{\#\#}$
Palpitation	1.00±0.96	0.48±0.69$^{\#}$	0.55±0.63$^{\#}$	1.31±0.93	0.91±0.82$^{\#\#}$	0.75±0.84$^{\#\#}$
Formication	0.83±0.85	0.14±0.44$^{*\ \#\#}$	0.28±0.45$^{\#\#}$	1.25±1.05	0.88±1.01$^{\#\#}$	0.72±0.96$^{\#\#}$

*; *p*-<0.05 compared between groups, **; p<0.01 compared between groups by t –test †; *p*-<0.05 compared between groups, ††; p<0.01 compared between groups by Wilcoxon rank sum test, $^{\#}$; *p*-<0.05 compared to baseline, $^{\#\#}$; p<0.01 compared to baseline by paired t-test

Black Cohosh & Isoflavone (Soy)

- **Black Cohosh**
  - First developed in Germany, it has been prescription medication in EU
  - Numerous clinical studies showed strong as well as mixed efficacy, until recently, it is claimed to cause liver damage (Natural Products Insider, July 30, 2007) and last 360-subject NIH sponsored clinical trial showed no efficacy (Natural Products Insider, Jan. 15, 2007)

- **Isoflavone (Genistein)**
  - Mixed Reviews on Efficacy: Asian diets are rich in isoflavone (miso soup, tofu, soy bean paste, bean sprouts), but symptoms manifest at the same rate as in Western countries
  - The key compound, Genistein, has been shown to bind to estrogen receptors alpha & beta and thus may be carcinogenic (National Toxicology Program TR 545, NIH)

Truth of Isoflavone

Effective Dose

As Isoflavone Aglycones, the Symptoms Improved w/ Daily Intake of 70 ~ 100mg, but…

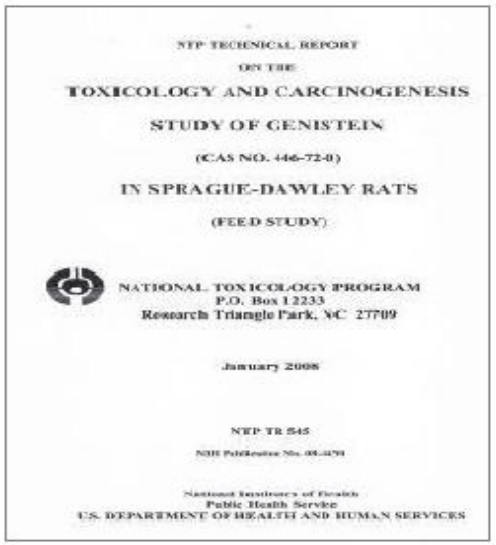
Limitation of Dose

Upper Limit of the Daily Intake of Isoflavone Aglycone is 30mg.
– Food Safety Commission (Japanese Government)

Clinical Research on Isoflavones

Daily Intake	Researcher	Research Result	Published
Soy Isoflavone 34 mg	Washburn	No effect	1999
Soy Isoflavone 36 mg	Penotti	No effect	2003
Soy Isoflavone 60 mg	Duffy	No effect	2003
Genistein 54 mg (Isoflavone 77mg)	Crisafulli	Significant Improve	2004
Genistein & Daidzein 70mg (Isoflavone 79mg)	Fauer	Significant Improve	2002
Isoflavone 100 mg	Han	Significant Improve	2002

Is Isoflavone Carcinogenic?!!



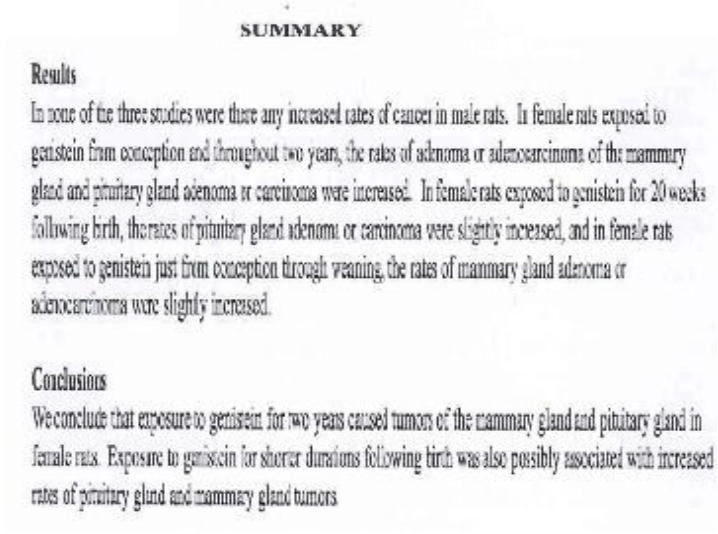
NTP TECHNICAL REPORT
ON THE
TOXICOLOGY AND CARCINOGENESIS
STUDY OF GENISTEIN
(CAS NO. 446-72-0)
IN SPRAGUE-DAWLEY RATS
(FEED STUDY)

NATIONAL TOXICOLOGY PROGRAM
P.O. Box 12233
Research Triangle Park, NC 27709

January 2008

NTP TR 545

Public Health Service
U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES



SUMMARY

Results

In none of the three studies were there any increased rates of cancer in male rats. In female rats exposed to genistein from conception and throughout two years, the rates of adenoma or adenocarcinoma of the mammary gland and pituitary gland adenoma or carcinoma were increased. In female rats exposed to genistein for 20 weeks following birth, the rates of pituitary gland adenoma or carcinoma were slightly increased, and in female rats exposed to genistein just from conception through weaning, the rates of mammary gland adenoma or adenocarcinoma were slightly increased.

Conclusions

We conclude that exposure to genistein for two years caused tumors of the mammary gland and pituitary gland in female rats. Exposure to genistein for shorter durations following birth was also possibly associated with increased rates of pituitary gland and mammary gland tumors.

Genistein (a major isoflavone aglycone) May Cause Cancers

(NIH & FDA – National Toxicology Program, Genistein Final , Jan, 2008)

- ✓ **Exposure to Genistein for 2 years caused mammary gland / pituitary gland adenoma in female rats.**
- ✓ **Exposure to Genistein for shorter duration following birth was also possibly associated with increased rates of pituitary gland and mammary gland tumors.**

Genistein The Risks of Causing Cancer: 3 out of 4 Post Menopausal Cases of Intake of the Isoflavone – AFSSA (French Food Commission)

Why Is GenisteinToxic?

- **Cancer Causing Risks**

  - Isoflavone could be toxic because its high level of hormone-like action.
  - It could be Hormone Dependent Cancer Causing Material due to its High Binding Affinity to Estrogen Receptor α, and β

	Relative Binding Affinity	
	α	β
Estradiol	100	100
Coumestrol	20	140
Genistein	4	87

- **Isoflavone from Sources other than Soybean**

  - Chinese Scholar Tree (*Sophora japonica)*: Isoflavone Contents 5 to 6 times Higher than Soybean
  - Red Clover has also Higher Isoflavone Contents than Soybean