

# FEMANIN



**Capricorn**  
life sciences

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## MENOPAUSA?

*Da oggi toglie il disturbo*

- *Vampate*
- *Fragilità Ossea*
- *Difficoltà a dormire*



The advertisement features a smiling woman with short brown hair, wearing a patterned, long-sleeved top, with her arms crossed. The background is white with pink floral accents. The text is in pink and black. The Capricorn life sciences logo is located in the bottom left corner of the advertisement.

# MENOPAUSE? WHAT IS IT?



## PRE

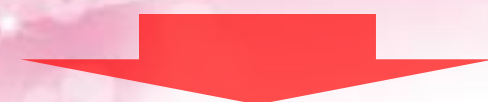
Irregular menstruation  
First flushes  
Abdominal swelling  
Irritability

## MENOPAUSE

Hot flushes  
Sleep disturbance  
Weight increase  
Mood swings  
Vaginal dryness

## POST

Osteoporosis  
Depression  
Excessive perspiration  
Urinary problems



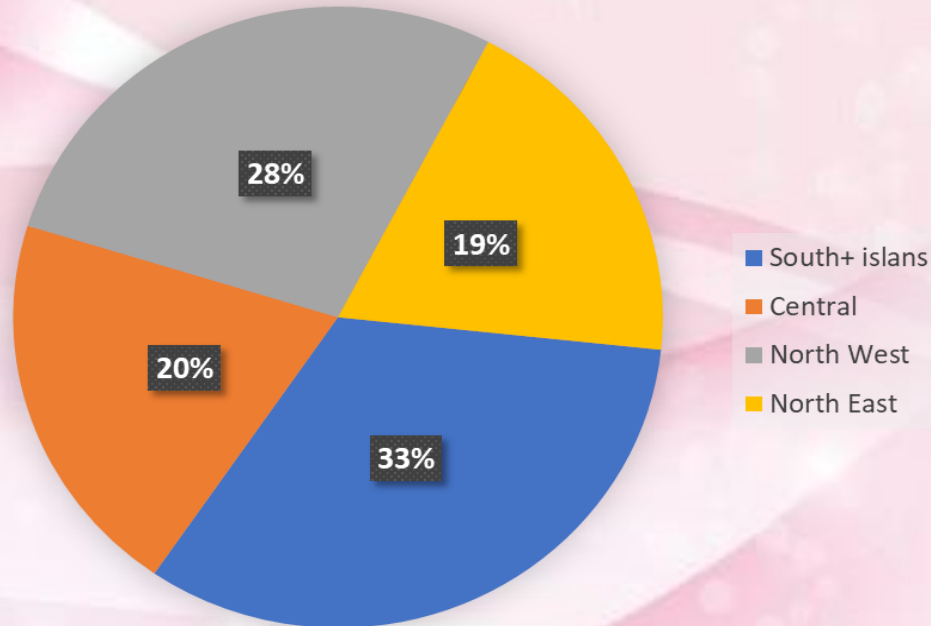
The life cycle of the phenomenon starts beforehand and continues afterwards

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## Menopause in numbers

Distribution of women experiencing the menopause by geographical area (source: ISTAT)

In Italy **13,508,270 women** are at menopause age  
The average age of the menopause in Italy is 50.8 years.



*Distribution of women experiencing the menopause by geographical area (source: ISTAT)*

Five women out of 100 enter spontaneous menopause before the age of 40 and 15 before the age of 45. Smokers enter the menopause almost one year earlier, especially women who smoke more than 20 cigarettes a day. The same applies to women who haven't had children, whereas women who have had more than four children enter the menopause later than the women with no children.

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**ITALIAN WOMEN  
AND  
THE MENOPAUSE**

A quantitative study carried out January 2011

## THE CLINICAL TRIAL

- Commissioned in October 2010
- Conducted by employing 1,017 online interviews carried out using the c.a.w.i. (computer-aided web interviewing) method on a representative sample of Italian women aged between 25 and 60 years, corresponding to 154,000 adults

## WOMEN AND THE MENOPAUSE

- A 50-year-old woman in 2010 is very different from a 50-year-old woman from 20 years previously. The 2010's woman is active and has a greater life expectancy (almost 90 years); she takes care of herself and new projects, even during menopause.
- She is apprehensive about menopause 47 but finds alternative solutions to the pharmaceutical approach (greater awareness of the side effects, fewer prescriptions by gynecologists).
- The use of supplements and other natural products is now widespread 70
- She is increasingly aware that, with menopause, she faces typical, short-term symptoms (hot flashes, sleep disturbance, and the risk of osteoporosis 64 of the interviewed sample). With effective and innovative supplements, the menopause market is subject to growing demand and ample loyalty opportunities.
- However, as things currently stand, there have yet to be any genuine innovations on the market that may boast more successful effectiveness than traditional phytoestrogens.

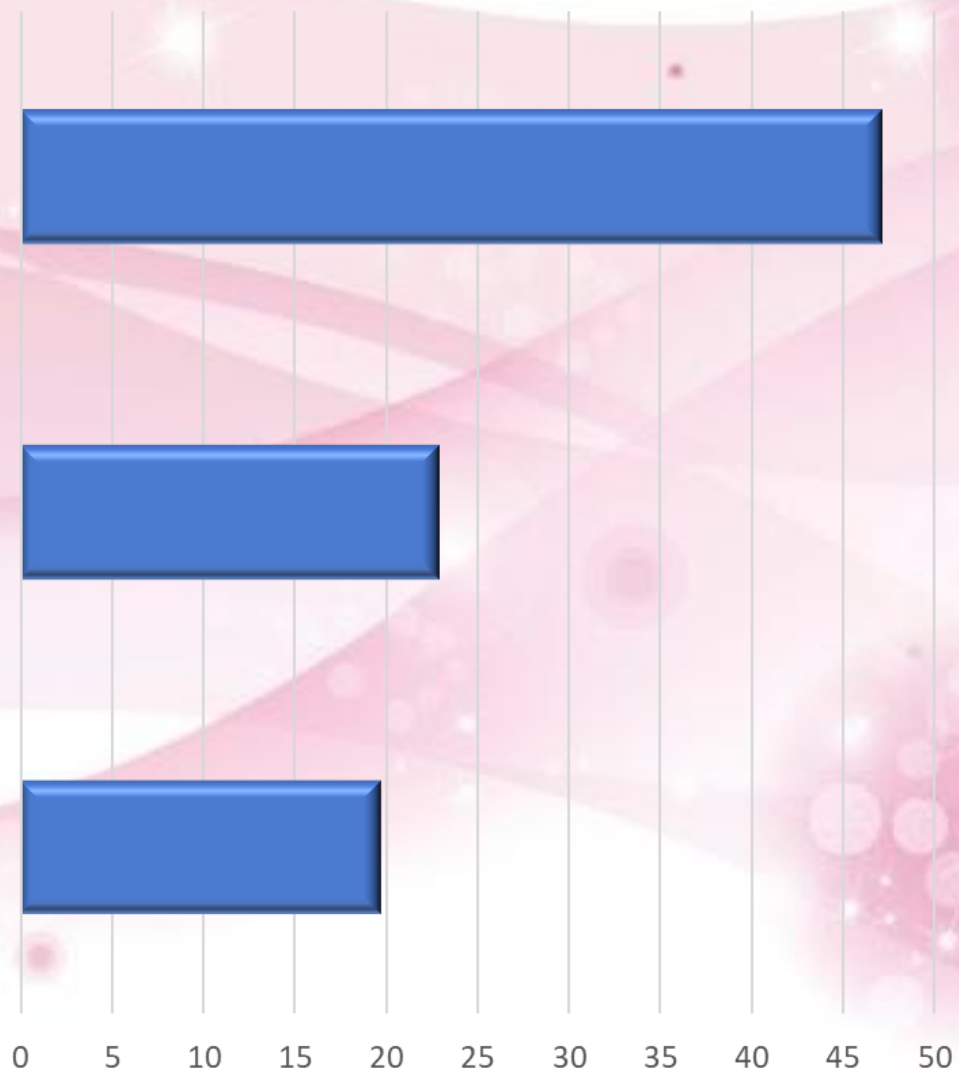
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## Products and therapies to fight menopause

Natural supplement specific for menopause based on Soy, Flax, Red Clover and Hops

Homeopathic Products

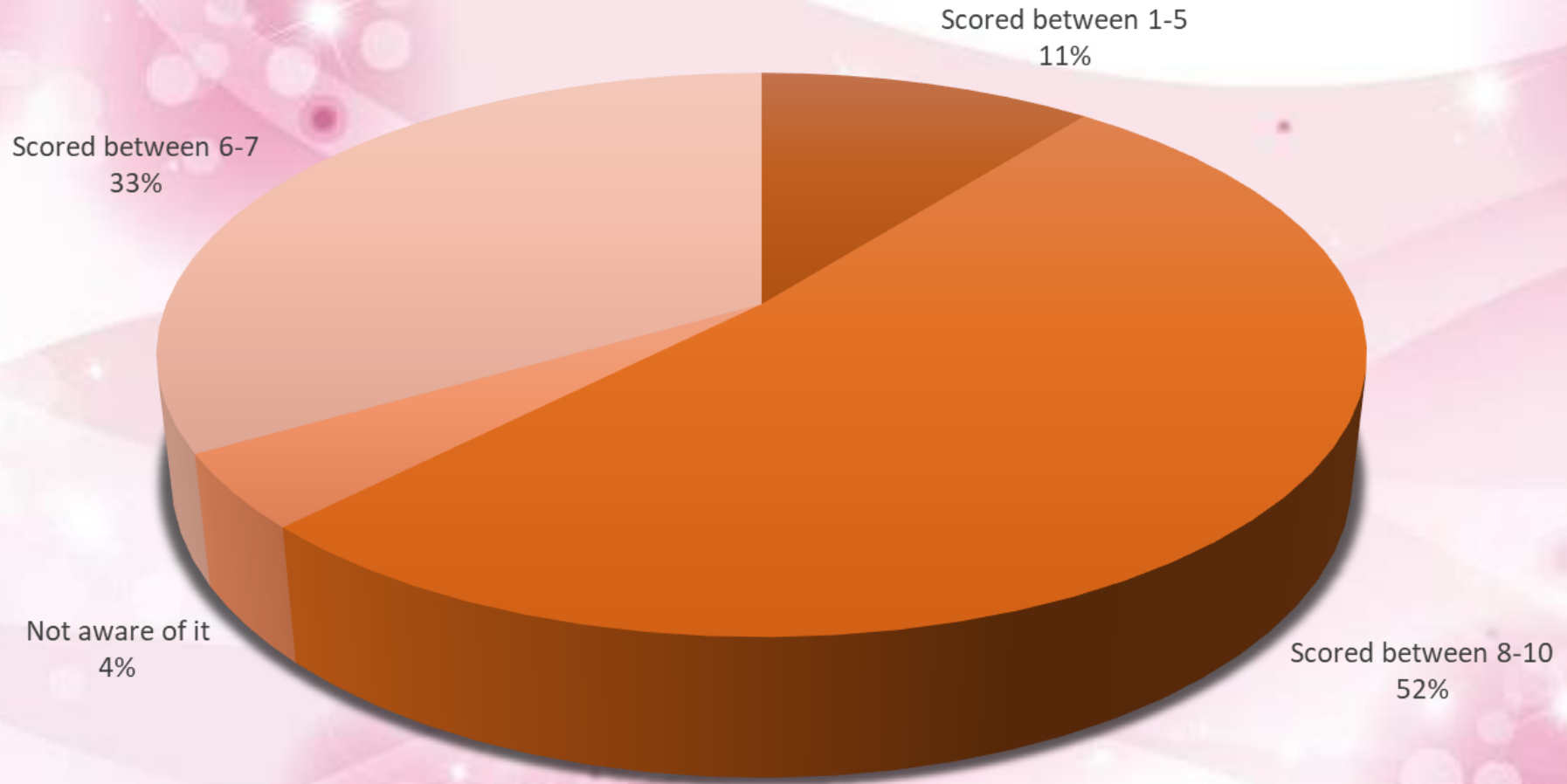
Hormon replacement Therapy



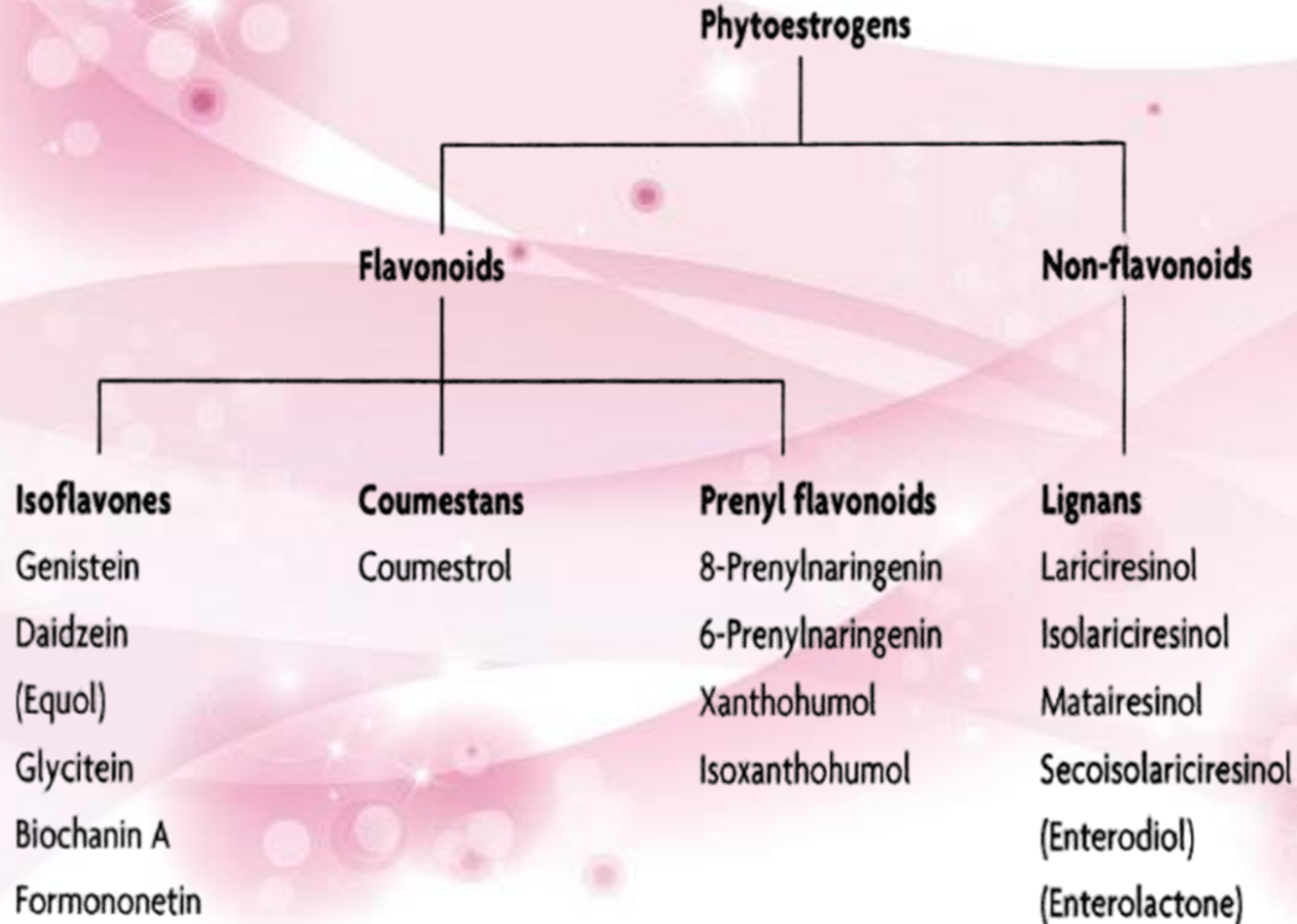


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## API Evaluation



■ Scored between 1-5   ■ Scored between 8-10   ■ Not aware of it   ■ Scored between 6-7



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# ISOFLAVONES

The main ones are:

- Genistien
- Daidzein
- Gliciteina
- Biocanin A
- Formononetin

Genistein, daidzein and glicitein are found in soy

Biocanin A and formononetin are found in clovers and and in alfalfa sprouts

Isoflavones are also found in Fabaceae (lentils, beans, peas, chickpeas) and in whole grains (wheat, rice, barley, rye and oats)

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# PHYTOESTROGENS

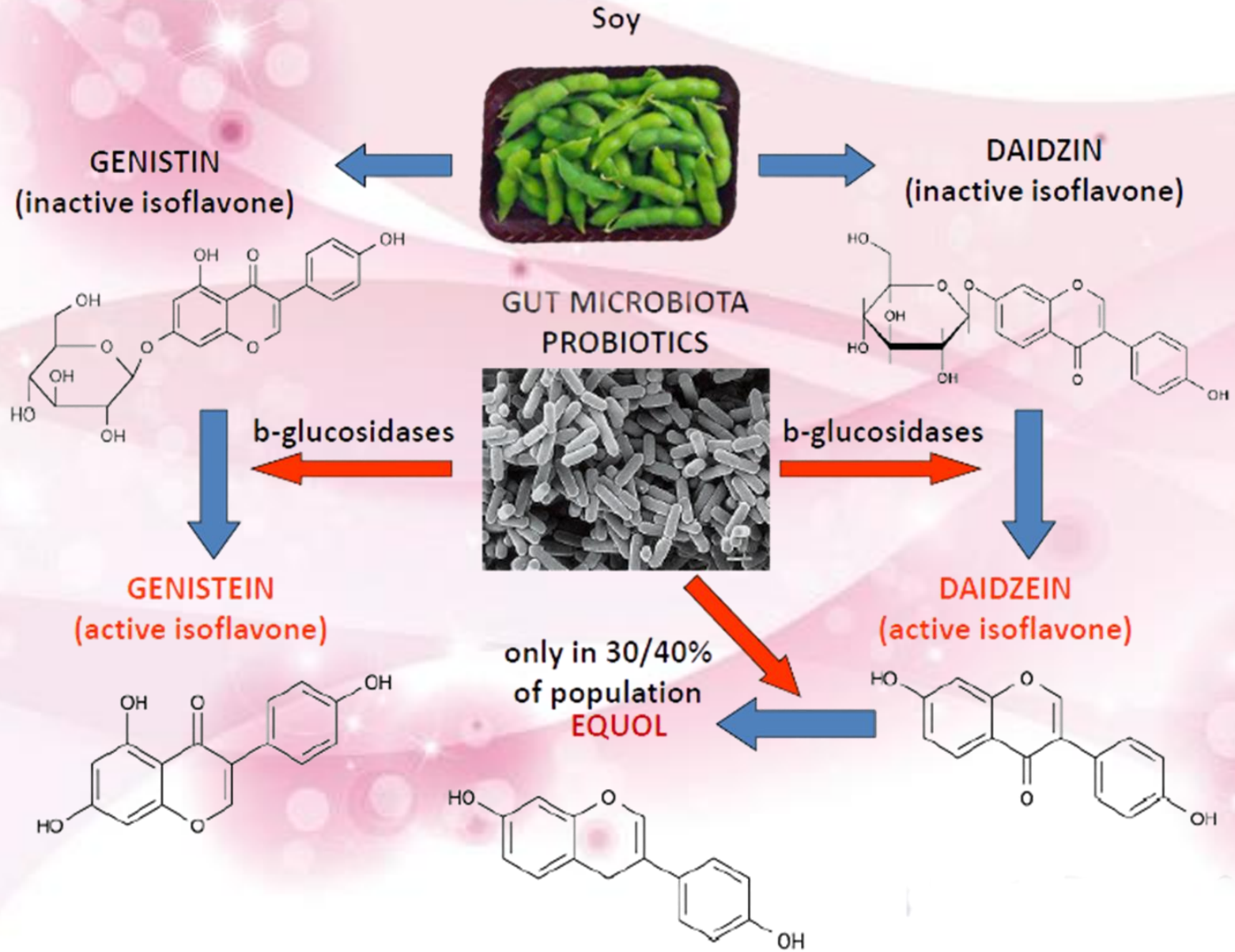
Phytoestrogens in plants are mainly present as glucosides, bonded with a sugar

Sugar removal is made by beta-glucosidases from intestinal bacteria

Aglycones can be either absorbed as they are or metabolized into specific metabolites

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# EQUOL



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# EQUOL

Derives from the biotransformation of daidzein

Not all adults produce Equol as a result of soy intake

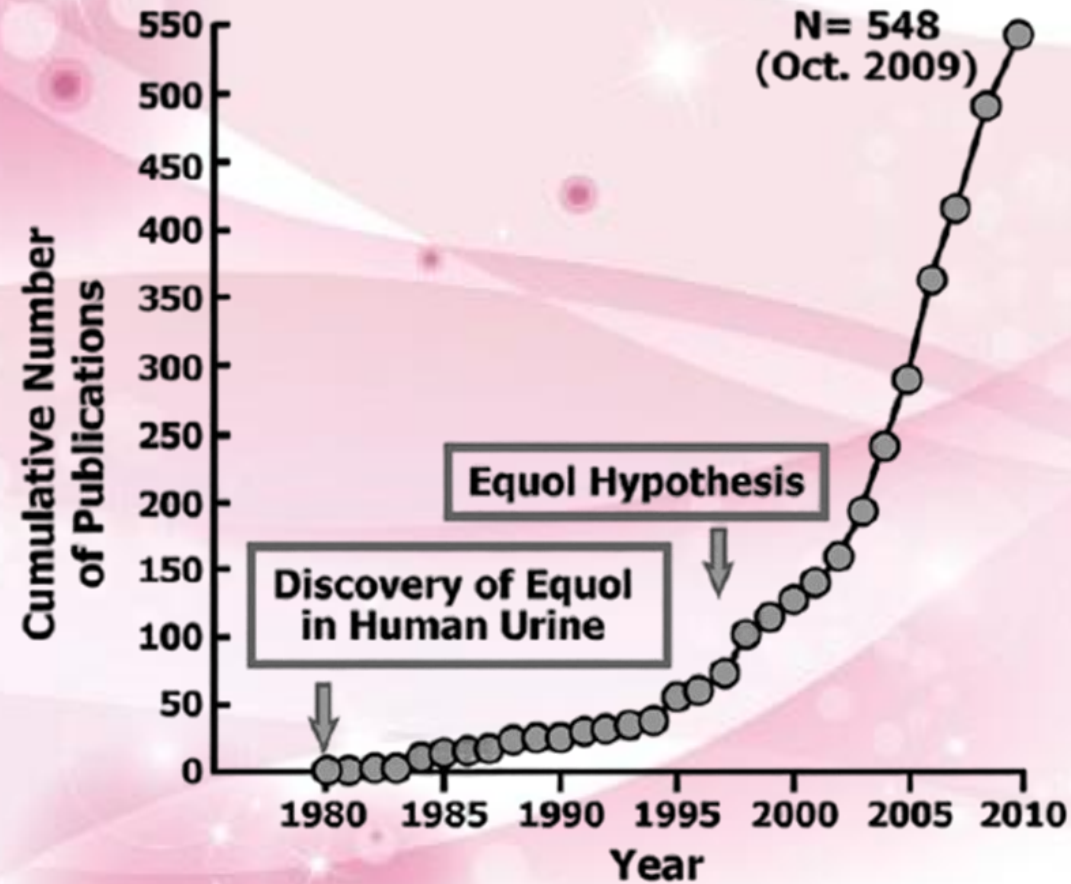
Only 30-40% of the Western population can transform daidzein into Equol by gut microbial flora

This percentage rises to 50-60% in the Asian population

Failure to distinguish between Equol-producing and non-producing individuals until the early 2000s accounts for the variability of data obtained in clinical trials regarding the efficacy of soy in reducing menopausal symptoms

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# EQUOL



Number of publications on equol since the year of its first identification in human urine.

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# EQUOL

## Western World

25-30%  
Equol-producers

Isoflavone intake  
from soy foods  
predominantly  
Glycosides

Clinical studies  
use mostly purified  
protein-based foods

## EQUOL

Soy food intake  
high  
in Aglycons

## Asia

50-60%  
Equol-producers

Aglycons may facilitate Equol production?  
Does Equol increase clinical efficacy of soy?

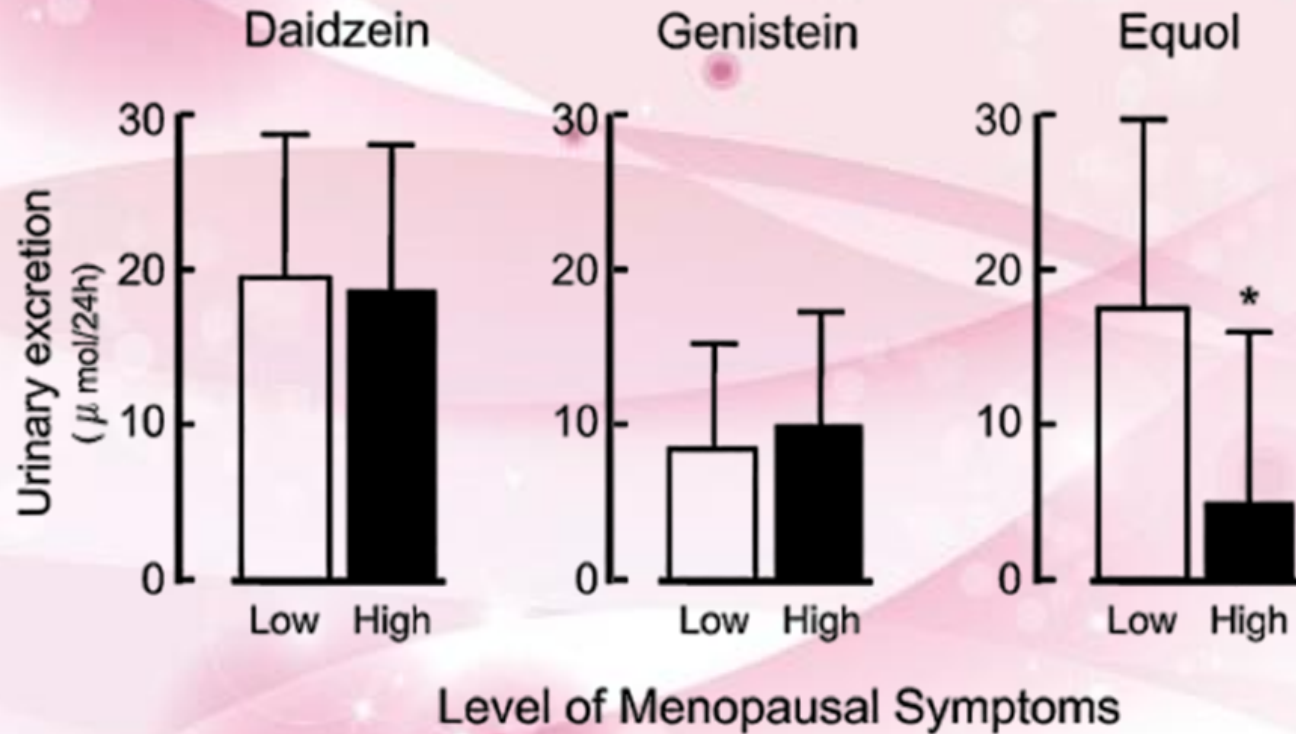
Different frequency of equol producers in the Western and Asian populations



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# EQUOL

## Inverse correlation between equol production and menopausal symptoms

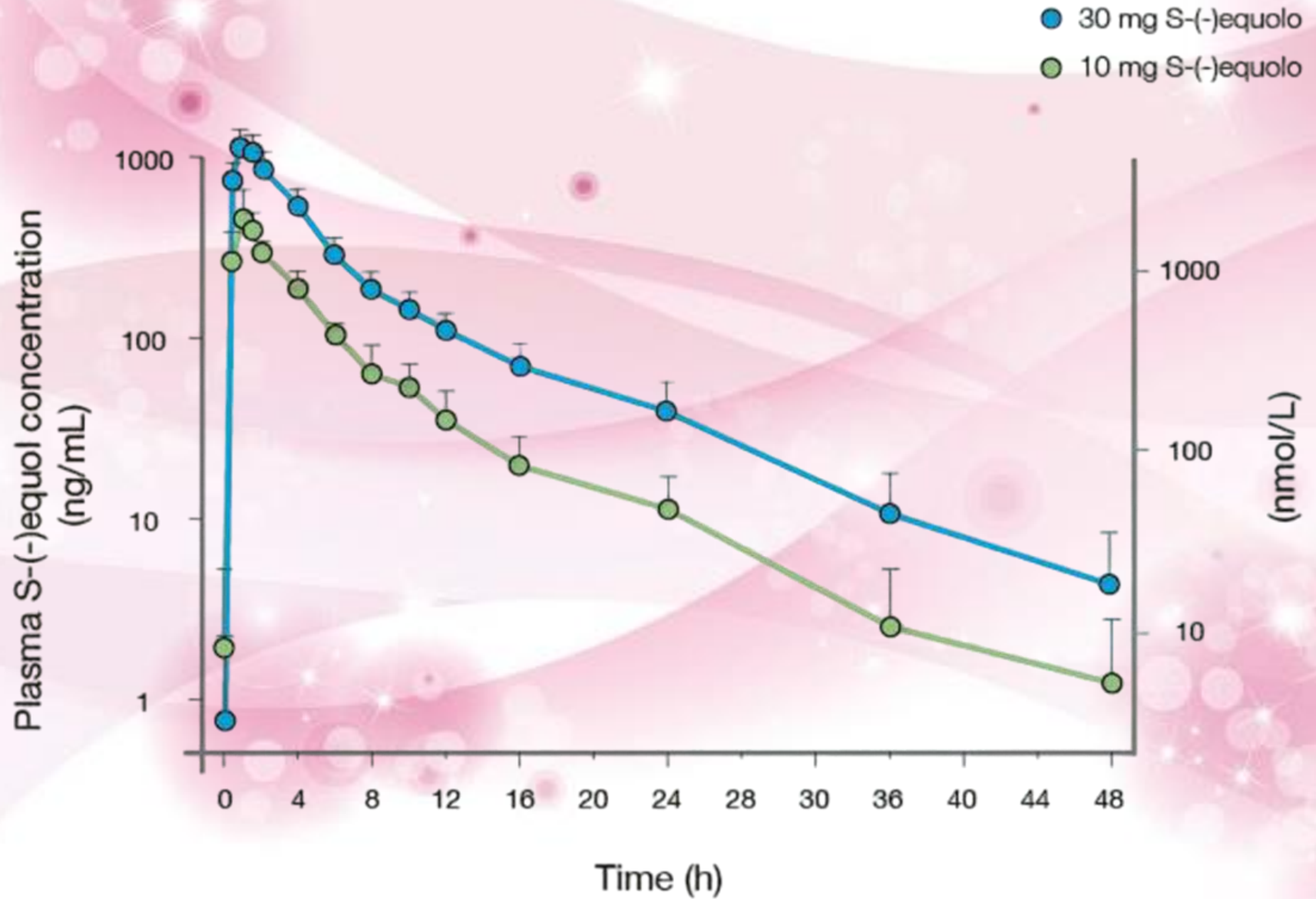


Data are means  $\pm$  SEM, n = 23. Low: SMI score .15; daily activities were not apparently disturbed. High: SMI score .15; daily life was disturbed. Statistical analysis was carried out using Wilcoxon's Rank Sum test. \*Different from low group, P , 0.05.

Uchiyama et al. "The cross-sectional study of the relationship between soy isoflavones, equol and the menopausal symptoms in Japanese women". J Jpn Menopause Soc. 2007;15:28-37.

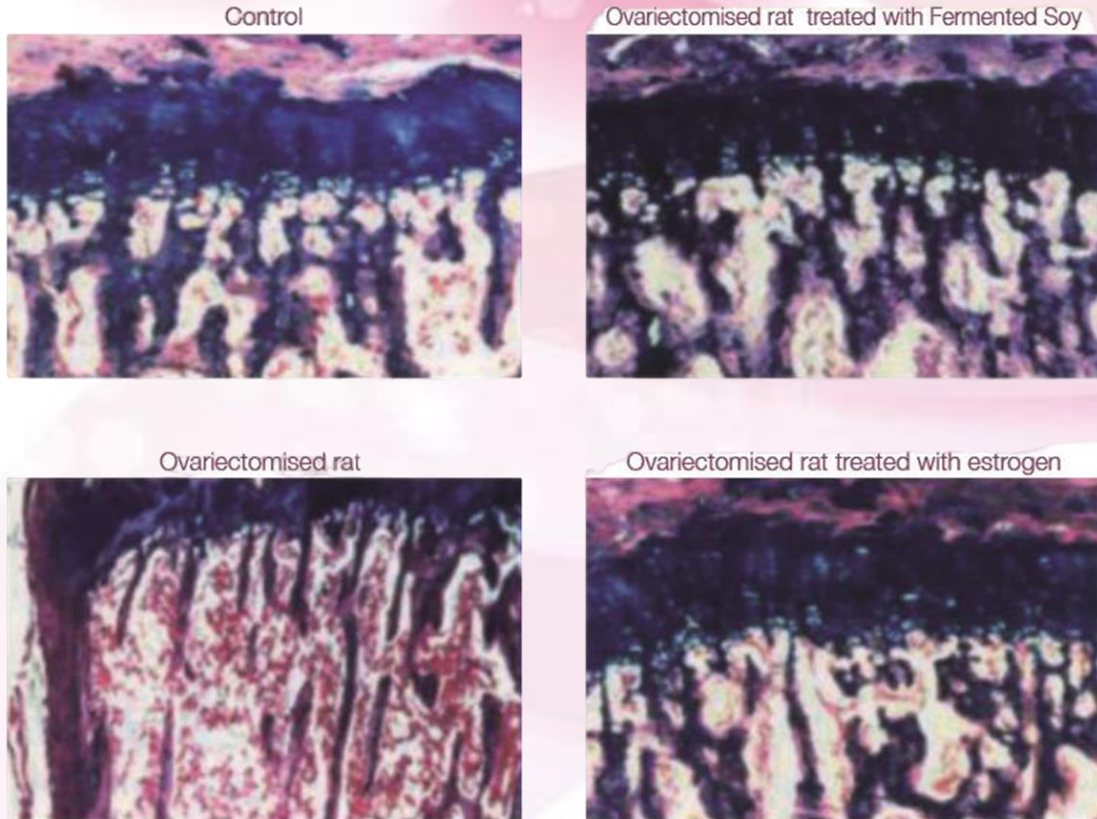
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## EQUOL PLASMATIC CONCENTRATION



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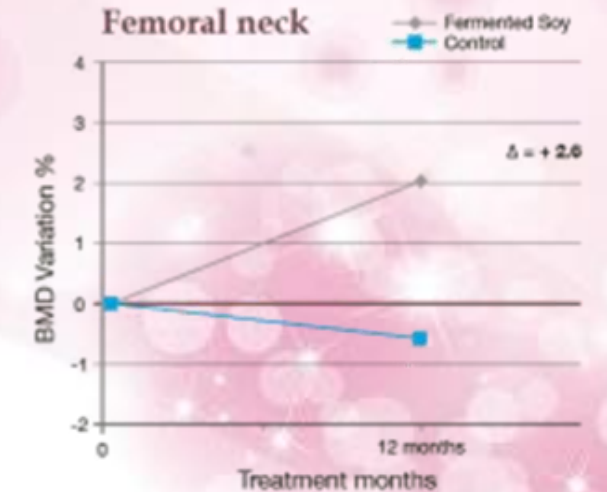
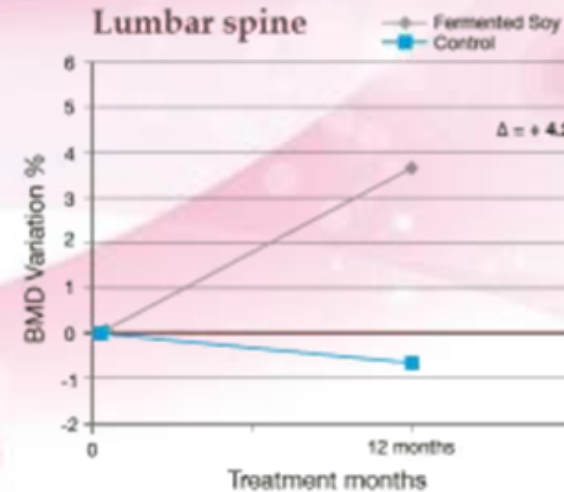
Fermented soy stimulates bone formation in female rats



# EQUOL & BONE DENSITY

Fermented soy efficacy in preserving bone mineral density (bmd)

	Soy fermented	Control	Effect
Lumbar spine	103.6%	99.4%	+4.2%
Femoral neck	102%	99.4%	+2.6%

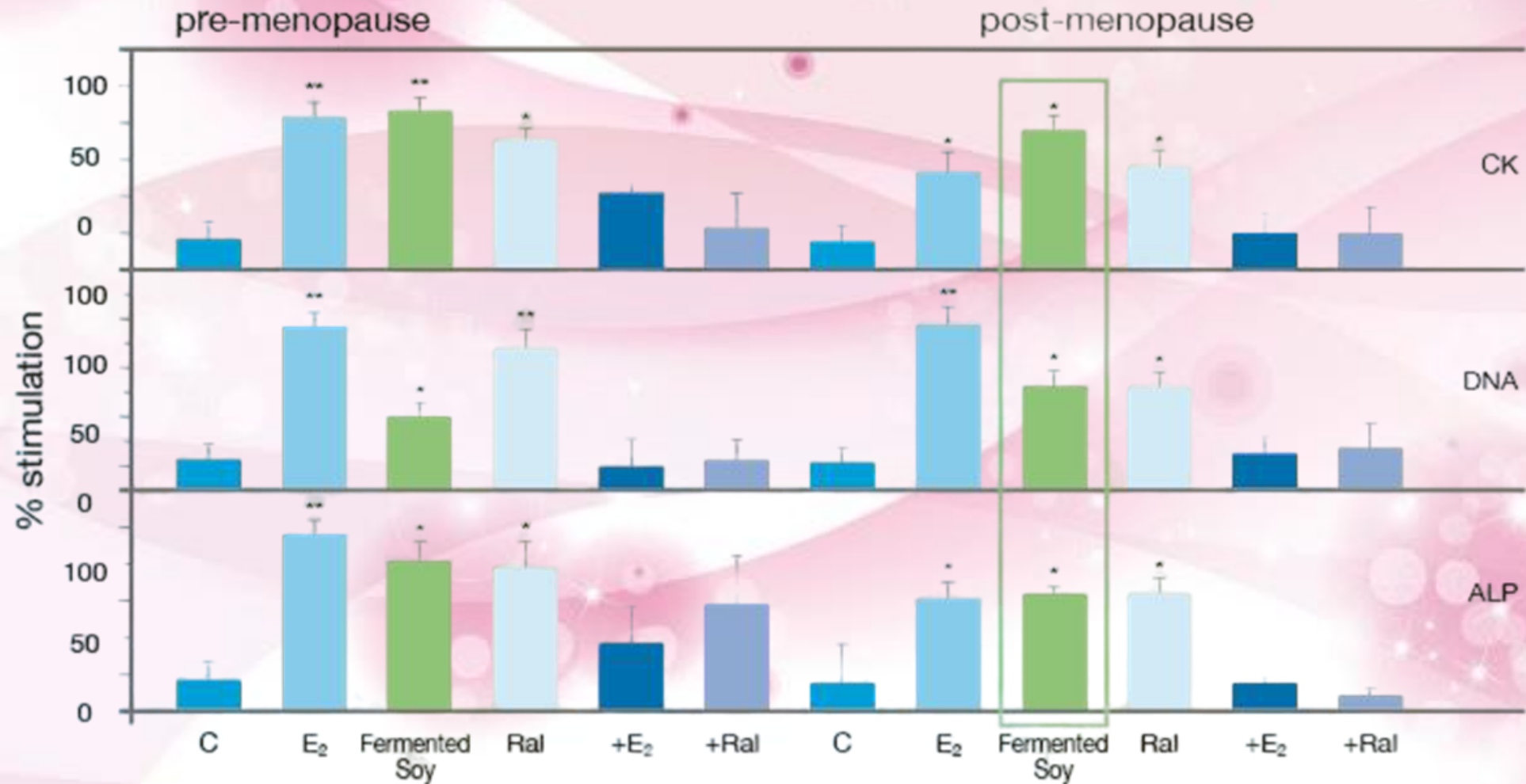


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## EQUOL & BONE DENSITY

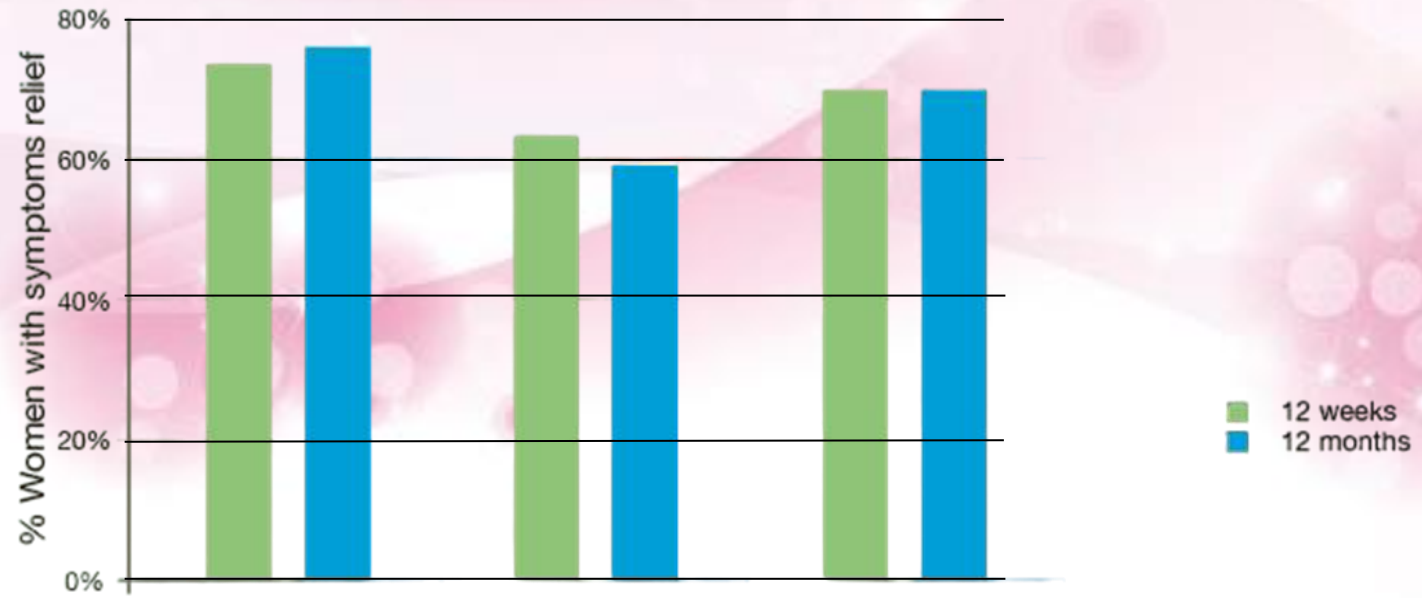
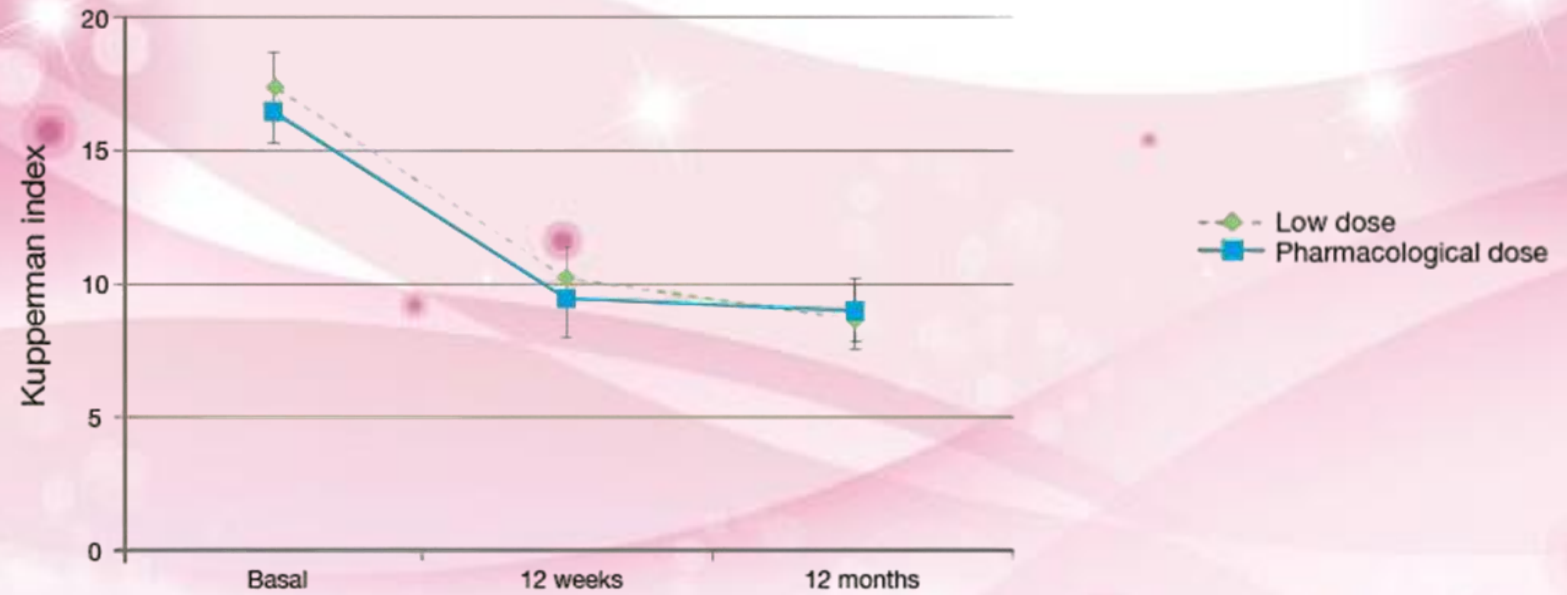
### Bone cells

- C = Control
- E<sub>2</sub> = Estrogen
- Ral = Raloxifene
- +E<sub>2</sub> = Fermented Soy + Estrogen
- +Ral = Fermented Soy + Raloxifene



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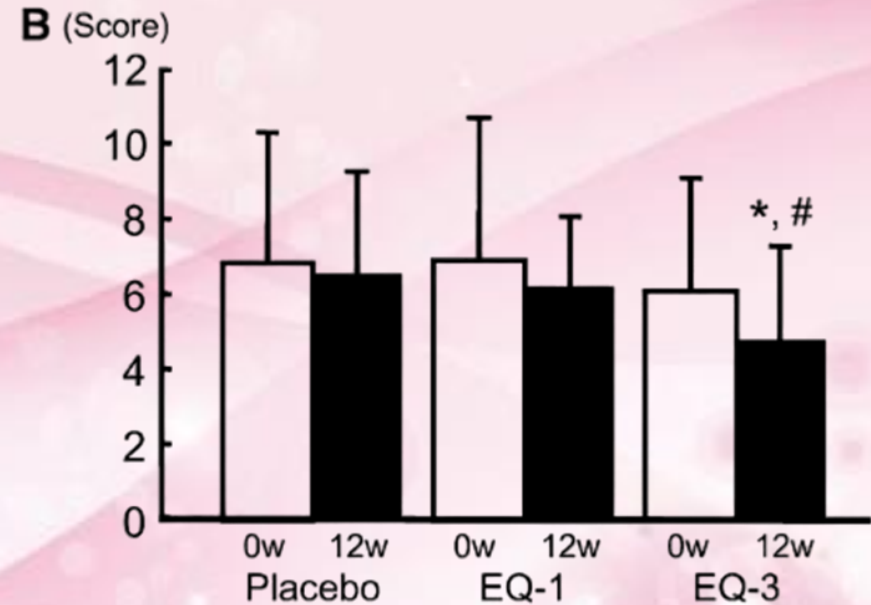
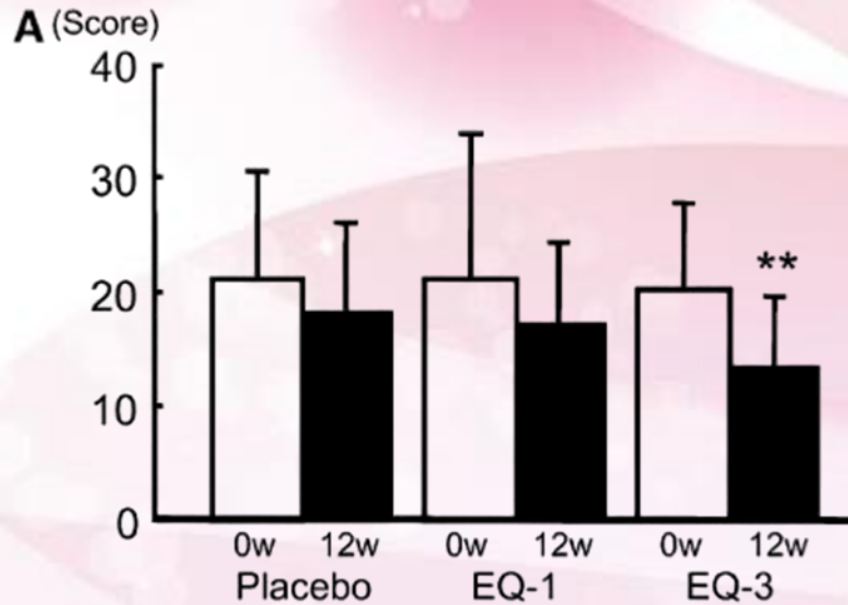
## EQUOL & MENOPAUSAL SYMPTOMS



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## EQUOL & MENOPAUSAL SYMPTOMS

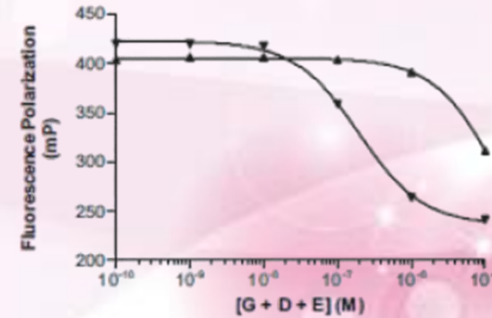
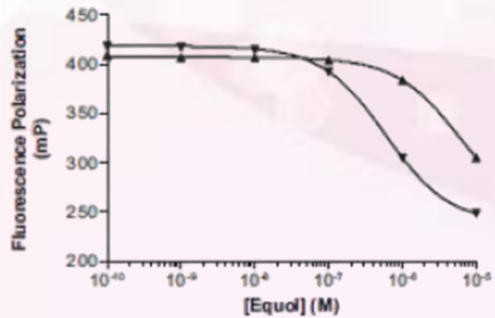
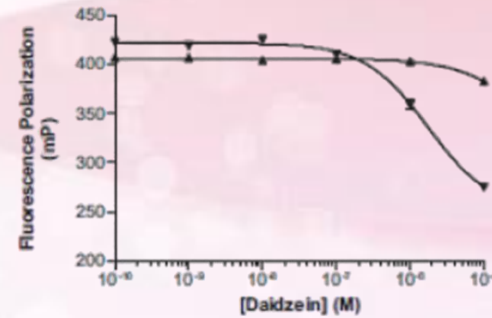
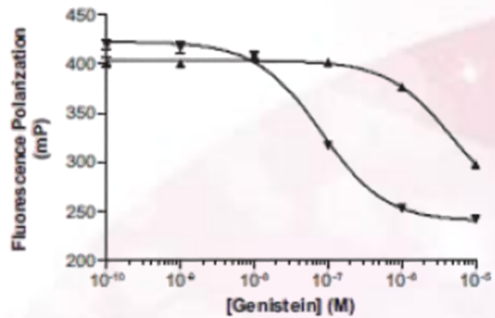
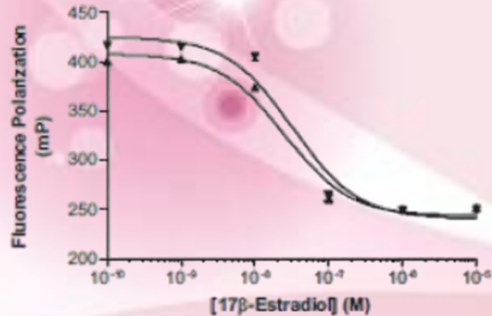
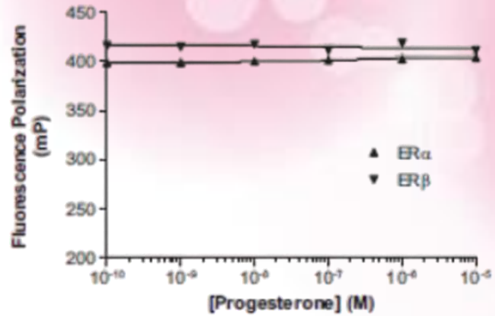
S equol contained in fermented soy improves menopause symptoms in women treated for 12 weeks



Effects of natural S equol on the menopausal symptom total score (A) and somatic score (Greene climacteric scale) (B) in Japanese women. Values are means  $\pm$  6 SD,  $n = 18$  or  $n = 17$ . \*,\*\*Different from wk 0,  $P < 0.05$  and  $P < 0.01$  (Wilcoxon's Rank Sum test). #Different from placebo in wk 12 changes,  $P < 0.05$  (Mann Whitney test).

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# EQUOL



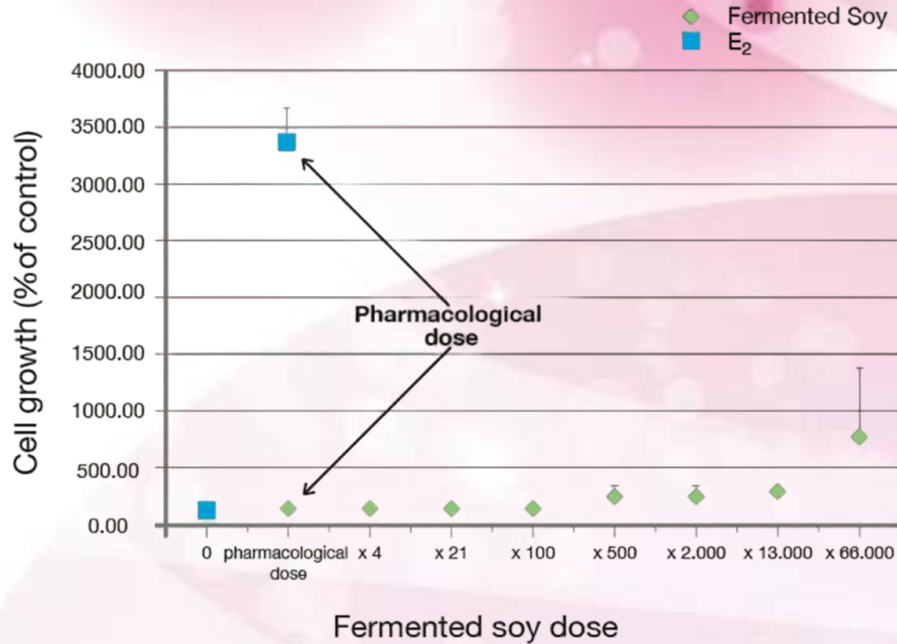
Compounds	Selectivity ( $\beta/\alpha$ ) <sup>d</sup>
Progesterone	
17 $\beta$ -E2	0.78
G	60.0
D	14.27
E	10.09
<b>combinations</b>	
G+D	62.87
G+D+E	82.60

The combination of genistein aglycone daidzein aglycone plus equol results in a greater binding selectivity for ER  $\beta$  and a better effectiveness/safety ratio profile compared to individual compounds.

Competition binding curves for Er  $\alpha$  and ER  $\beta$  Data were generated with a fluorescence polarization based competitive binding assay using full length human ER  $\alpha$  and ER  $\beta$  and plotted against the logarithm of serially diluted concentrations of the test compounds Progesterone served as a negative control 17  $\beta$  E 2 served as a positive control. - "A Select Combination of Clinically Relevant Phytoestrogens Enhances Estrogen Receptor Binding Selectivity and Neuroprotective Activities in Vitro and in Vivo L Zhao et al. Endocrinology 2009 150:770 783"

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Therapeutical dose of fermented soy has no effect on breast cancer cell-line



Lilling G. The European Journal of Obstetrics and Gynecology 2007; 130 (1)

# EQUOL & MENOPAUSAL SYMPTOMS

Endometrium and hormonal levels after 1 year treatment with fermented soy

	Study group		Control	
	Pre	Post	Pre	Post
Endometrium (mm)	3.2	2.8	3.7	3.4
Mean FSH (mIU/ml)	73.7	66.9	79.4	73.3
Mean E2 (Umol/L)	105	92	110	105

Menopause 2003; 10(6): 522-525



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## EQUOL: efficacy

“The administration of fermented soy and Equolo (10 mg) reduces all menopause symptoms”	Journal of Nutrition, n 140: 1386S 1389S, 2010. Clin. Exp. Obstet. Gynecol. 2004; 31(2):123 6
“More than 50 studies into isoflavones have been published since 1995, but their effectiveness on menopause symptoms is quite small”	Journal of Nutrition, n 139: 796S 802S, 2009
“Only 25-30% of the Western population are equol producers. In the East the percentage rises to 50 60%.”	Journal of Nutrition, n 140: 1355S 1362S, 2010
“The administration of Equol in the form of fermented soy reduces the pre and post menopause disorders affecting the CNS”	Menopause, vol. 16, n 1, 2009
“Fermented soy increases bone mineral density.”	Menopause 2003; 10(6):522 5.
“Preventing osteoporosis and weight increase depends on the capacity to produce equol”	Journal of Nutrition, n 140: 1377S 1379S, 1373S 1376S, 2010

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## EQUOL: efficacy

Scientific evidences from published in vitro and in vivo studies

Reduction of all menopausal symptoms

Neuroprotective action

Increased bone mineral density with stimulation of osteoblasts activity

The combination of genistein (aglycone) daidzein (aglycone) and equol results in increased binding selectivity for ER $\beta$  and an improved efficacy/safety ratio profile compared to individual the compounds

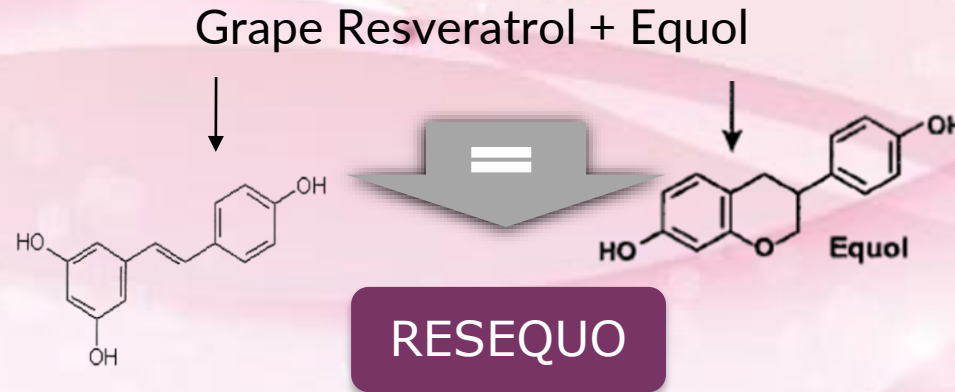
The clinical studies performed show that fermented Soja and Equol do not interfere with either estrogen receptors present in uterine tissue or those present in breast tissue

No significant alterations in the hormones FSH, LH, estradiol or progesterone were observed during the treatment

# FEMANIN

## THE HORMONAL RE-BALANCER

FEMANIN COMPLETE contains the exclusive patent



Synergic action in:

- Carry out an “hormone like” phytoestrogenic effect
- Encourage mitochondrial biogenesis for an anti-ageing action
- Inhibit matrix metalloproteases responsible for skin ageing during the menopause
- Activate lipolysis and reduce lipogenesis to inhibit the slowing down of the metabolism during the menopause

# FEMANIN

REDUCING ALL SYMPTOMS OF MENOPAUSE

## COMPONENTS FOR 1 TABLET

Fermented soy d.e.	200 mg
of which Isoflavones tot.	80 mg
of which Equol	8 mg
Resveratrol	10 mg
Magnesium	56,25 mg (15% VNR)
Melatonin	1 mg
Vitamin D	5 mcg (100% VNR)
Vitamin K	11,25 mcg (15% VNR)

## How to use:

1 tablet in the evening, before going to sleep, for at least three months



# FEMANIN

## THE ONLY SUPPLEMENT THAT:

Contains Fermented Soy rich in Equol for a “hormone-like” action without side effects and contraindications

Contains isoflavones in a form that is easier for the body to digest

Possesses a unique and patented fermentation process:

## RESEQUO

The exclusive patent, which combines the properties of Equol and Fermented Soy with Grape Resveratrol for a highly effective synergic action

Experimentally proven to be effective by the clinical studies carried out on Fermented Soy and Equol



## Influence of equol and resveratrol supplementation on health-related quality of life in menopausal women: A randomized, placebo-controlled study<sup>☆</sup>

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### ARTICLE INFO

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This paper is dedicated to the memory of Fulvio Marzatico passed away untimely on June 5, 2015.

#### Keywords:

Menopause  
Phytoestrogens  
Equol  
Resveratrol

### ABSTRACT

**Objective:** This study was designed to evaluate the effects of equol and resveratrol supplementation on health-related quality of life (HRQL) in otherwise healthy menopausal women with hot flashes, anxiety and depressive symptoms.

**Methods:** Sixty recently menopausal women aged 50–55 years were randomized in a 12-week, placebo-controlled trial to receive 200 mg of fermented soy containing 10 mg of equol and 25 mg of resveratrol (1 tablet/day). The primary outcome was the change in score on the Menopause Rating Scale (MRS), used to evaluate the severity of age-/menopause-related complaints. Additional outcome measures included the subject-reported score on the Hamilton Rating Scale for Depression (HAM-D) and Nottingham Health Profile (NHP), which was used specifically to assess sleep quality.

**Results:** The symptoms assessed by the MRS improved during treatment in the active group. Comparison between placebo and treatment groups revealed statistically significant improvement in particular for dryness of vagina (−85.7%;  $p < 0.001$ ), heart discomfort (−78.8%;  $p < 0.001$ ) and sexual problems (−73.3%;  $p < 0.001$ ). On the HAM-D significant improvements at week 12 were seen in work and activities (−94.1%;  $p < 0.001$ ). Subjects treated with equol and resveratrol also had significant differences in the sleep domain of the NHP ( $p < 0.001$ ).

**Conclusion:** These findings provide evidence that 12 weeks of dietary supplementation with equol and resveratrol may improve menopause-related quality of life in healthy women.

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### 1. Introduction

Menopause is characterized by falling levels of estrogen and progesterone, loss of reproductive function and permanent end of menstruation [1]. Although symptoms associated with menopause vary widely, they most often include hot flashes, sleep disturbances, anxiety, and depression [2]. There are still no specific and highly efficient medical interventions to alleviate these

symptoms and treat the clinical consequences of an estrogen-deficient state associated with menopause. For example, despite hormone replacement therapy (HRT) is the treatment of choice, its use has been linked to an increased risk of developing breast cancer and cardiovascular diseases [3,4]. The modern perspective to improve menopausal symptoms and enhance the quality of life may be the use of plant-based therapies [5,6]. In this context, there is substantial evidence that phytoestrogens and their derivatives have the potential to address several conditions associated with menopause [7]. Phytoestrogens are polyphenolic estrogenic compounds of plant origin and classified in four main classes: isoflavones, lignans, coumestans and stilbenes. The metabolism of phytoestrogens in humans is complex and their bioavailability is largely determined by intestinal microflora. Isoflavones are found mainly in soy-based foods and exhibit estrogenic activity by

Abbreviations: HRT, hormone replacement therapy; ERs, estrogen receptors; HRQL, health-related quality of life; MRS, Menopause Rating Scale; HAM-D, Hamilton Rating Scale for Depression; NHP, Nottingham Health Profile.

<sup>☆</sup> Trial Registration: ISRCTN registry ISRCTN10128742.

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+2,8% bone mineral  
density

-75% hot flashes

-85% vaginal dryness

-53% sleep problems



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## EFFICACY VS OSTEOPOROSIS

Results after one year of treatment chart

Analysis	12 MONTHS		n	Marker of
	Active	Placebo		
Deoxypyridinoline	-32.6%	+6.3%	30	Osseous reabsorption
Acid phosphatase	-8.8%	-2.5%	30	Osseous reabsorption
Osteocalcin	+49.7%	+19.1%	30	Osseous development
Alkaline phosphatase (isoenzyme osseous)	+7.9%	-2.8%	30	Osseous development
<b>Bone mineral density</b>	<b>+2.8%</b>	<b>+0.2%</b>	<b>15</b>	<b>Osseous development</b>

**Significant decrease of the markers indicating a osseous tissue reduction:**  
**+32,6% Deoxypyridinoline**  
**- 8,8% Acid phosphatase**

**New osseous tissue development marker increase:**  
**+49,7% Osteocalcin**  
**+7,9%Alkaline phosphatase**

**Femur bone mineral density increase (Osseous Densitometry via X-Ray)**

Double blind randomized test on 60 women (age 50-55) treated with 1 FEMANIN tablet a day for 12 months



# FEMANIN

## EFFICACY VS OSTEOPOROSIS

**Significant decrease of markers involved in bone tissue reduction**

- 32,6% Desossipiridinolin
- 8,8% Acid Phosphatase

**Significant increase of markers involved in bone tissue increment**

- +49,7% Osteocalcin
- +7,9% Alcalin phosphatase

**Bone mineral density increase**

- +2,8% DXA left thighbone



**2.8% bone mineral density increase**

# FEMANIN

REDUCING ALL SYMPTOMS OF MENOPAUSE

The only supplement with  
**EQUOL**

Supported by an in vitro study and  
two published clinical trials

**RESEQUO = equol + resveratrol**  
Italian Patent

Results after two weeks of  
treatment



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## THANK YOU