Soluzioni non ormonali in menopausa

G. BONACCORSI

Centro di Ricerca per lo Studio della Menopausa e dell'Osteoporosi

DIPARTIMENTO DI MORFOLOGIA, CHIRURGIA E MEDICINA SPERIMENTALE

Centro Universitario di Studi sulla Medicina di Genere

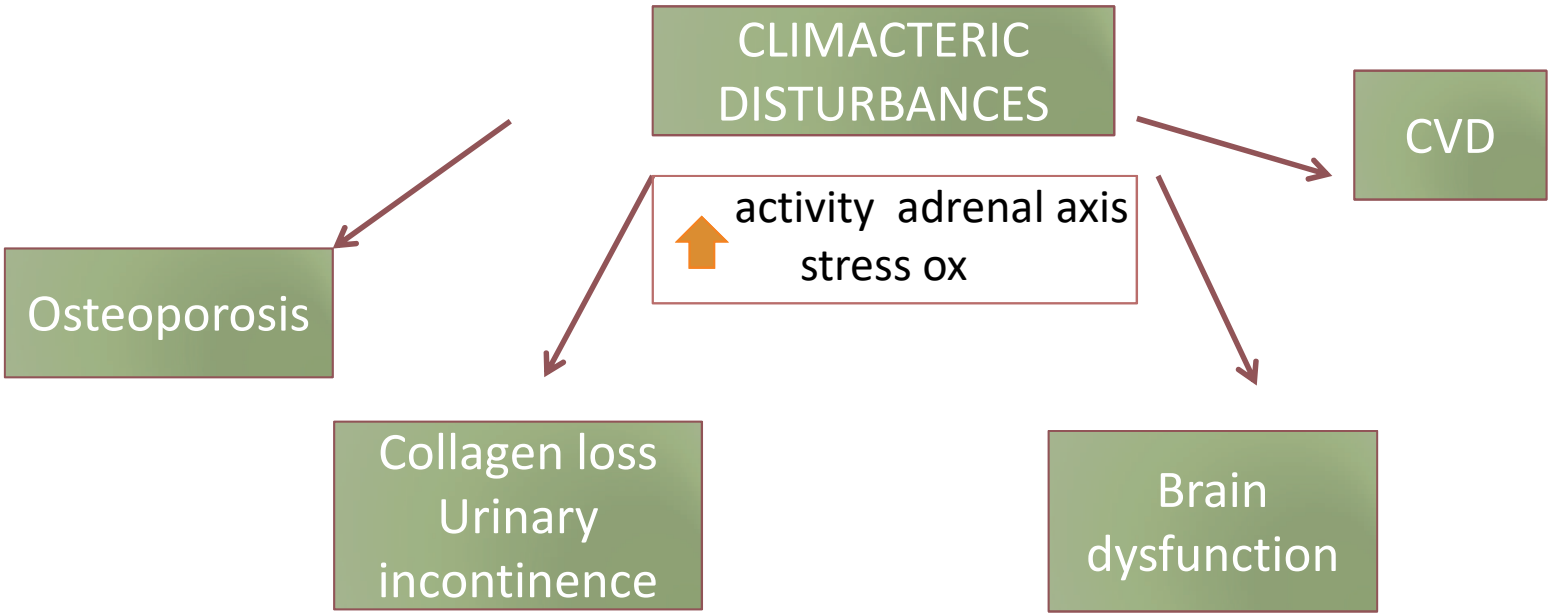
Università degli Studi di Ferrara

PROBLEMATICHE CLIMATERICHE

- **Sintomi vasomotori** e **neurovegetativi:**
  - ***Vampate, palpitazioni (50-70%)***
  - ***Disturbi del sonno ed emozionali, (45-63%)***
  - ***Calo di energia (68%)***
  - ***Artromialgie*** (58%)
- **S. uro-genitale** (57%-76%)
- **Malattia cardiovascolare** (I causa di morte dopo i 50 anni)
- **Osteoporosi** (3 donne su 5)
- **Declino cognitivo**
- **Secchezza cutanea e delle mucose**

Bonaccorsi, Cmo-Unife 2018

ASSOCIAZIONE TRA SINTOMI CLIMATERICI E PATOLOGIE CRONICHE



Menopause: The Journal of The North American Menopause Society
Vol. 17, No. 2, pp. 256-261
DOI: 10.1097/gme.0b013e3181e1ad3d
© 2010 by The North American Menopause Society

History of hot flashes and aortic calcification among postmenopausal women

Rebecca C. Thurston, PhD,[1,2] Lewis H. Kuller, MD, DrPH,[2] Daniel Edmundowicz, MD, MS,[3]

Menopause: The Journal of The North American Menopause Society
Vol. 16, No. 2, pp. 331-338
DOI: 10.1097/gme.0b013e318185c25b
© 2009 by The North American Menopause Society

Vasomotor symptoms are associated with a lower bone mineral density

Gerrie-Cor M. Gast, MSc,[1,2] Diederick E. Grobbee, MD, PhD,[1] Victor J.M. Pop, MD, PhD,[3] Jules J. Keyzer, PhD,[4] Colette J.M. Wijnands-van Gent,[4] Göran N. Samsioe, MD, PhD,[2] Peter M. Nilsson, MD, PhD,[5] and Yvonne T. van der Schouw, PhD[1]

Menopause: The Journal of The North American Menopause Society
Vol. 18, No. 3, pp. 273-278
DOI: 10.1097/gme.0b013e3181f31947
© 2011 by The North American Menopause Society

Increased cortisol level: a possible link between climacteric symptoms and cardiovascular risk factors

Angelo Cagnacci, MD, PhD, Marianna Cannoletta, MD, Simona Caretto, MD, Renata Zanin, MD, Anjeza Xholli, MD, and Annibale Volpe, MD

CLIMACTERIC 2015;18:631–636

Relation between oxidative stress and climacteric symptoms in early postmenopausal women

A. Cagnacci, M. Cannoletta, F. Palma, M. Bellafronte, C. Romani and B. Palmieri*

ASSOCIAZIONE TRA SINTOMI CLIMATERICI E PATOLOGIE CRONICHE

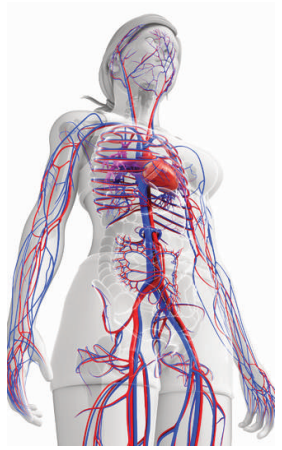
I sintomi climaterici , come markers di particolare suscettibilità alla carenza estrogenica, possono contribuire a modificazioni metaboliche responsabili di un aumentato rischio di patologie croniche nella donna dopo la menopausa

Trattare la «vampata»

❖Qualità di vita

\+

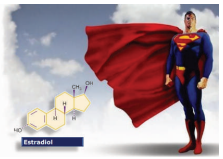
❖Prevenzione patologie croniche ?



by Boxmedia

- Lifestyle

- HT (hormone therapy)



the most efficacious treatment for climacteric symptoms

- **Non estrogenic alternatives :**

Conventional non-hormonal treatments

(neuroactive agents: drugs affecting the serotonin, the noradrenergic and, gabanergic sytem; NK3R neurokinin3 receptor antagonist)

Complementary and Alternative Medicines (CAM)

(herbal products, acupuncture, vitamins, biomagnets, yoga etc..)

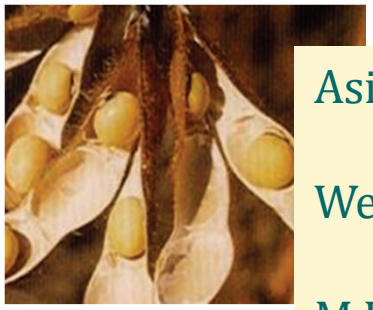
Alternative and complementary medicine (CAM): Biologically based therapies

Prepatati di origine vegetale con meccanismo d'azione :

- ❖ Estrogenico (phytoSERMs)
- ❖ Non estrogenico

Fitoestrogeni

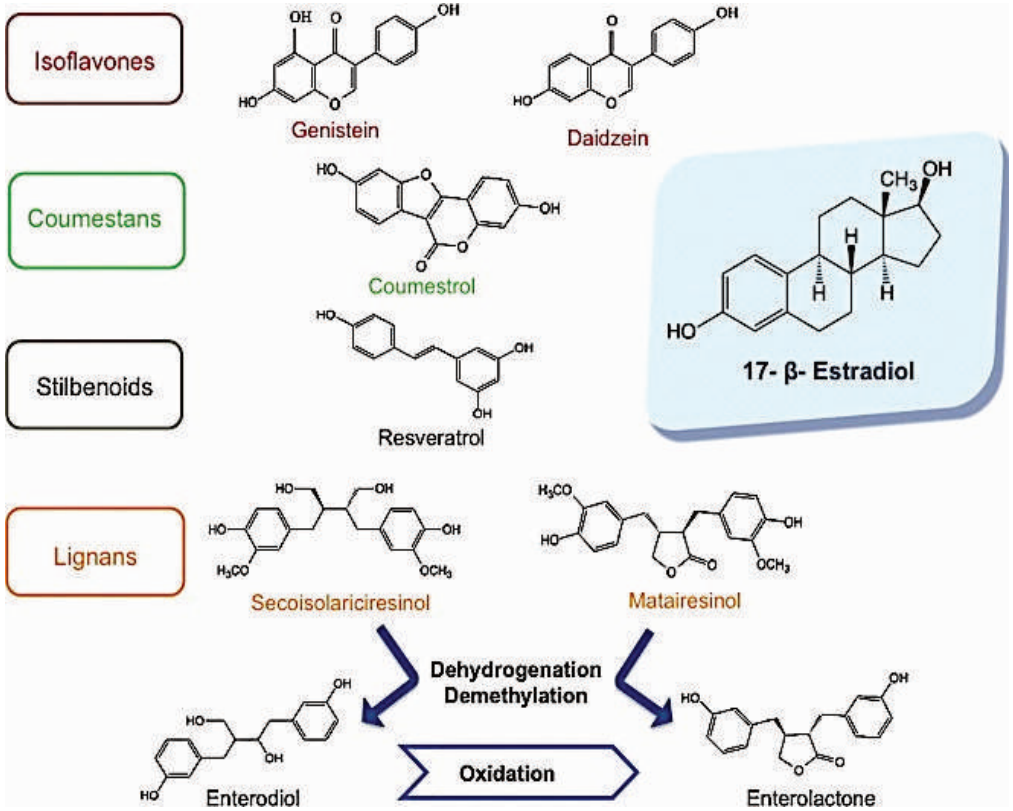
- Molecole presenti in diverse piante (alimentari e non) che presentano analogie strutturali e funzionali con gli estrogeni "nativi" presenti nell'essere umano.
- Sono classificati secondo differenti classi: isoflavoni, flavoni e lignani, prenil flavonoidi, sono le principali classi di fitoestrogeni presenti nelle piante ad uso alimentare umano.



Asian diet 15-50mg/die

Western diet 2 mg/die

M.Products 20-80mg/die



- **Lignani**: frutta, noci, cereali, semi di lino
- **Isolflavoni**: soia, piselli, fagioli, spinaci
- **Flavoni**: fagioli,verdure verdi, noci
- **Prenil flavonoidi**: luppolo, birra

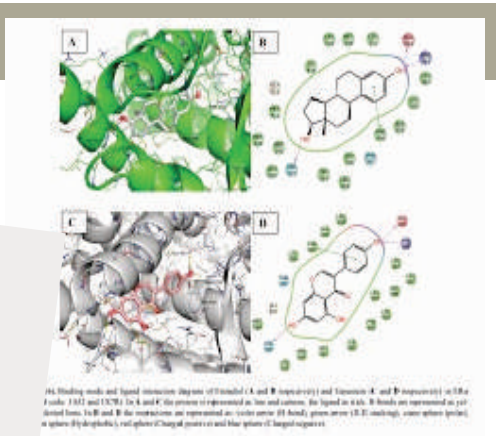
Isoflavones: mechanism of action

Genomic

- **Preferential link to ER beta:**

- **Link to ER alpha:**
  - 100x less than Estradiol

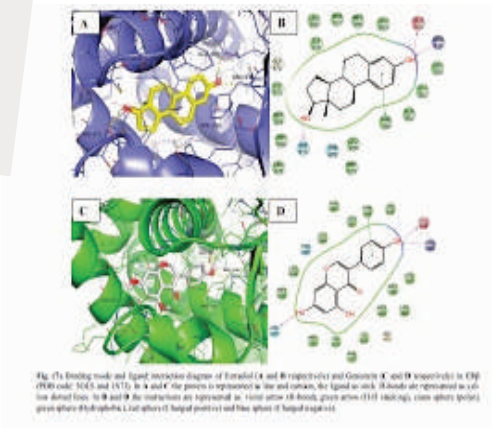
Phyto-SERMs
Estrogeno "debole"
Azione
Antiproliferativa
Antiossidante
Protezione metabolica



Non genomic

- **Througout growth factors:**
  - membrane receptors, EGF, VEGF, IGF1, PDGF

- **Througout enzyme factors:**
  - protein kinases, topoisomerases, 17β HSD, aromatases



Epigenetic

- **effects on DNA methylation, histone modification and microRNA regulation**

Increased cellular defence against toxicity of electrophiles and ROS

Isoflavones: complexity of the metabolism

HYDROLYSIS	in jejunum by β-glycosidases
METABOLIZATION	by intestinal l… …ria, to equol and O-desmethyl…
ABSORPTION	as aglycons (… daidzein), d… for the intes…
GLUCURONATION	by liver cell…
BIOAVAILABILITY	depends o… the entero… efficiency
PEAK BLOOD LEVEL	reached 6-9 hrs after intake
EXCRETION	20 to 50% of the ingested quantities are excreted within 24 hours

This existence of equol producers (30-40%) and non-producers could provide an alternative explanation for interindividual differences in the response to phytoestrogens

British Journal of Pharmacology (2017) **174** 1263–1280 1263

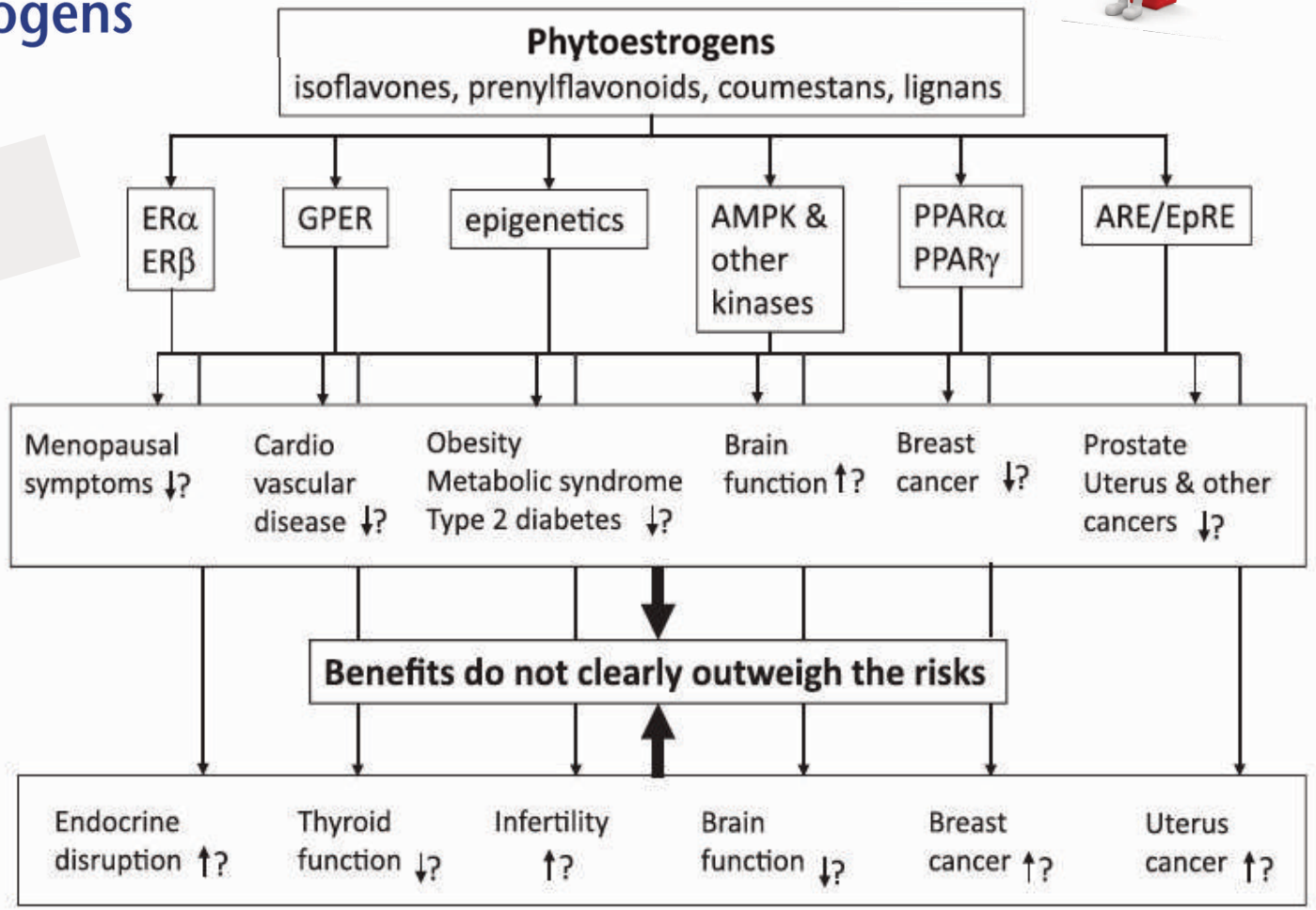
Themed Section: Principles of Pharmacological Research of Nutraceuticals

2017

REVIEW ARTICLE

The potential health effects of dietary phytoestrogens

Efficacy
Safety?



Maturitas 78 (2014) 79–81

Contents lists available at ScienceDirect

Maturitas

journal homepage: www.elsevier.com/locate/maturitas

Editorial

Phytoestrogens for menopausal vasomotor symptoms: A Cochrane review summary

2014

Journal of Steroid Biochemistry & Molecular Biology xxx (2013) xxx–xxx

Contents lists available at SciVerse ScienceDirect

Journal of Steroid Biochemistry and Molecular Biology

journal homepage: www.elsevier.com/locate/jsbmb

Review

The pros and cons of plant estrogens for menopause

2013

Sarah Bedell, Margaret Nachtigall, Frederick Naftolin*

Interdisciplinary Program in Menopausal Medicine, Department of Obstetrics and Gynecology, New York University School of Medicine, New York 10016, United States

- Overall, current research demonstrates that ***phytoestrogens are effective in reducing the intensity of hot flushes, and some phytoestrogen combinations result in a decreased frequency.***
- Certain phytoestrogens have also been shown to *decrease vaginal atrophy, improve sleep and cognition,* ***and positively affect bone health.***
- In terms of safety and reports of adverse reactions***, clinical trials*** have ***not shown an increase in breast cancer risk or increase in endometrial hyperplasia*** following phytoestrogen use, but trials explicitly designed to find neoplasia have not been reported**.**
- ***Phytoestrogens may provide a safe and "partially effective" alternative to HT.***

Bonaccorsi , Cmo Unife,2018

CLIMACTERIC 2015;18:260–269

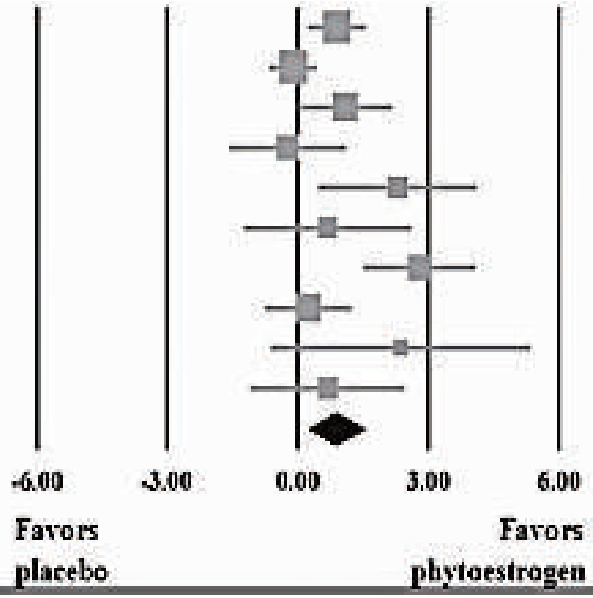
Efficacy of phytoestrogens for menopausal symptoms: a meta-analysis and systematic review

2015

M-N. Chen, C-C. Lin* and C-F. Liu†

Study name	Sample size	Mean difference (95%CI)	P-value	Relative weight
Aso T (2012)	60 vs. 66	0.90 (0.24, 1.56)	0.008	14.88
Atkinson C (2004)	103 vs. 102	-0.10 (-0.64, 0.44)	0.714	15.79
Ferrari A (2009)	94 vs. 82	1.10 (0.03, 2.17)	0.044	11.77
Lewis JE (2006)	33 vs. 33	-0.22 (-1.55, 1.11)	0.746	9.92
Nahas EA (2007)	38 vs. 38	2.30 (0.47, 4.13)	0.014	7.14
Penotti M (2003)	34 vs. 28	0.70 (-1.22, 2.62)	0.474	6.72
Petri Nahas E (2004)	25 vs. 26	2.80 (1.53, 4.07)	0.000	10.34
Tice JA (2003)	85 vs. 167	0.25 (-0.74, 1.24)	0.620	12.39
van de Weijer PH (2002)	14 vs. 16	2.37 (-0.60, 5.34)	0.118	3.59
Van Patten CL (2002)	64 vs. 59	0.70 (-1.06, 2.46)	0.435	7.46
Pooled mean difference in random model		0.89 (0.26, 1.52)	<0.005	

Forest plot for mean difference (95% CI)



Conclusion Phytoestrogens appear to reduce the frequency of hot flushes in menopausal women, without serious side-effect (Meta-analysis 10 RCTs)

Marzo 2016

Gynecological Endocrinology

ISSN: 0951-3590 (Print) 1473-0766 (Online) Journal homepage: http://www.tandfonline.com/loi/igye20

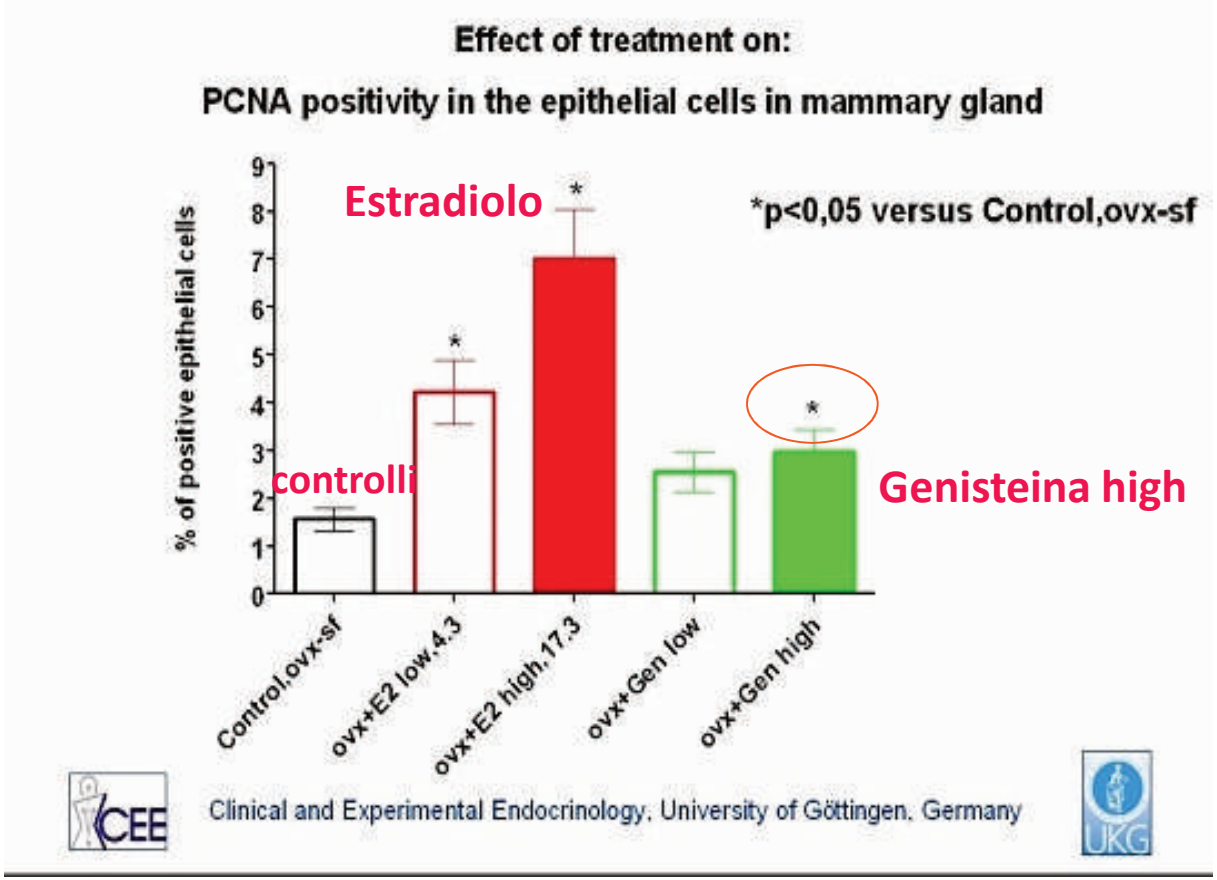
Consensus: soy isoflavones as a first-line approach to the treatment of menopausal vasomotor complaints

Conclusions on isoflavones and menopausal hot flushes

- ✓ The **efficacy of isoflavones against menopausal hot flushes has been confirmed** in independent meta-analyses, and has the evidence grade Ia
- ✓ **The effect against hot flush frequency and severity is 25% superior over placebo, and reaches 57% of the effect of estrogen replacement .Reaching the maximum effect takes more time than under treatment with estrogen.**
- ✓ Additional beneficial effects may be expected for the bones
- ✓ **Long-term safety** in hormone-sensitive tissues such as breast, endometrium and thyroid gland is undisputed and officially confirmed by the European Food Safety Authority (EFSA) with **exposures as high as 150mg isoflavones daily and a duration of intake of up to 3 years.**

Genisteina : effetto di stimolo sulla proliferazione di cellule di ghiandola mammaria di ratto

PCNA (proliferating cell nuclear antigen) : marker di proliferazione cellulare



- **Cell biological experiments**
- **Animal experimental studies**

Wuttke W,IMS,2008

Non estrogenic alternatives

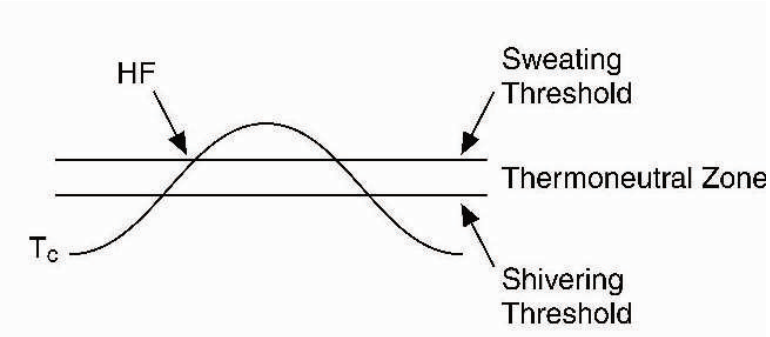
5-HT in the mechanism of flushing

The menopausal hot flush: a review

D. W. Sturdee, M. S. Hunter, P. M. Maki, P. Gupta, J. Sassarini, J. C. Stevenson & M. A. Lumsden

After the menopause:
decreasing levels of 5-HT and endorphin
increase in 5-HT receptors
increase of norepinephrine

Decrease thermoneutral zone



Thus, any substance that increases 5-HT, estrogen, endorphins or decreases norepinephrine may widen the thermoneutral zone and therefore be expected to reduce HFs.

Inibitori selettivi del re-uptake della serotonina **SSRIs** (fluoxetina, paroxetina, escitalopram,citalopram)
Inibitori selettivi del re-uptake della serotonina e noradrenalina **SNRIs** (venlafaxina, duloxetina)

- Utilizzati, in genere a dosi inferiori rispetto a quelle usate per depressione **(off-label)**
- Dimostrata efficacia nel ridurre in media del 50-70% intensità e frequenza delle vampate
- ***Effetti collaterali*** più frequenti , diversi a seconda della molecola, sono limitati a sonnolenza/insonnia, nausea, stipsi, alterazioni libido, secchezza delle fauci nei primi giorni di assunzione
- Trattamento di almeno 6 mesi. Sospensioni graduali.

-La paroxetina e la fluoxetina possono interferire con il metabolismo del tamoxifene in quanto capaci di inibire in modo irreversibile il CYP2D6

-utilizzo è da evitare in corso di trattamento ormonale adiuvante

Taghreed S.

"SSRI NATURALI"

Natural botanicals with potential serotonergic efficacy

1521-0081/68/4/1026–1073$25.00
PHARMACOLOGICAL REVIEWS
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http://dx.doi.org/10.1124/pr.115.010843
Pharmacol Rev 68:1026–1073, October 2016

ASSOCIATE EDITOR: ERIC BARKER

Botanicals and Their Bioactive Phytochemicals for Women's Health

Birgit M. Dietz, Atieh Hajirahimkhan, Tareisha L. Dunlap, and Judy L. Bolton

University of Illinois at Chicago/National Institutes of Health Center for Botanical Dietary Supplements, Department of Medicinal Chemistry and Pharmacognosy, College of Pharmacy, University of Illinois at Chicago, Chicago, Illinois

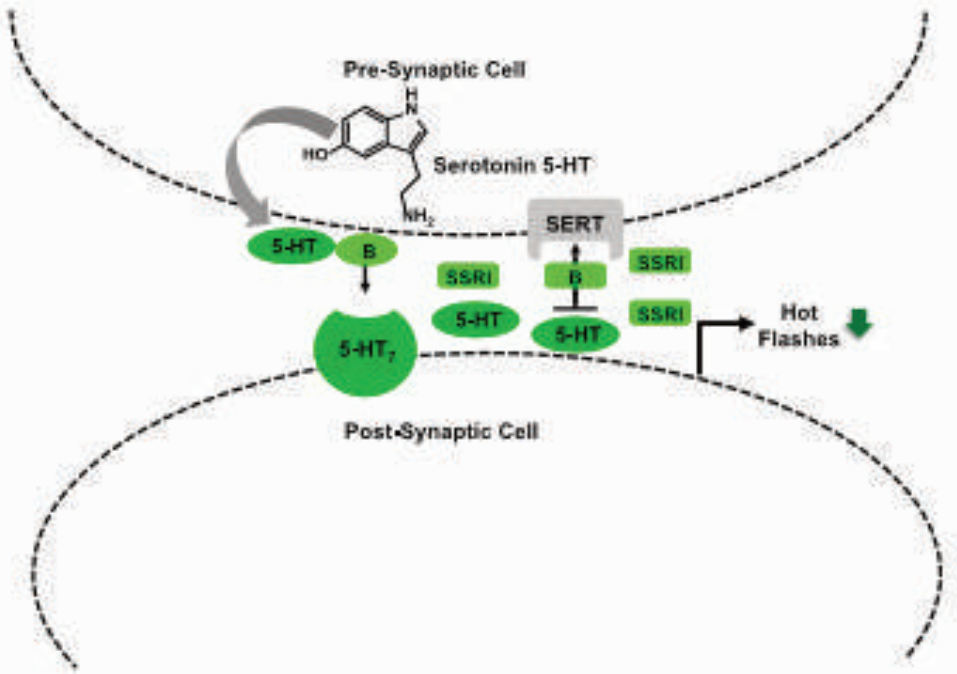


Fig. 22. Serotonergic mechanism. In synapses, botanicals can directly act on the serotonin receptors (5-HT receptors) or reduce serotonin reuptake through inhibiting serotonin transporters (SERTs) to elicit a reduction in menopausal symptoms such as hot flashes.

Iperico, griffonia, valeriana

CIMICIFUGA RACEMOSA (Black Cohosh,Actea racemosa)

pianta non alimentare

rizoma e radici vengono utilizzate fresche o in forma essiccata

Attualmente la Cimicifuga è commercializzata come **Rimedio erboristico** negli USA per il trattamento della sintomatologia menopausale.

È commercializzato in Italia con autorizzazione ministeriale come **Integratore alimentare**, mentre in Germania e in molti paesi europei è approvato e commercializzato come **Medicinale vegetale**.

L'utilizzazione dell'estratto di Cimicifuga racemosa è ben tollerato alla dose raccomandata di 40 mg/die di estratto secco.

La Cimi

❖I *c* principale compo alcolico respo

❖L'estratto alcolico iso apia risulta **privo della componente fitoestrog olica della formononetina**

Hindawi Publishing Corporation
Evidence-Based Complementary and Alternative Medicine
Volume 2013, Article ID 860602, 21 pages
http://dx.doi.org/10.1155/2013/860602

Hindawi

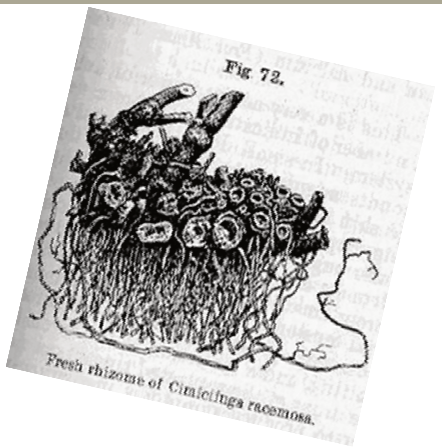
Black cohosh preparations are not all the same

Review Article

Differentiated Evaluation of Extract-Specific Evidence on *Cimicifuga racemosa*'s Efficacy and Safety for Climacteric Complaints

2013

A.-M. Beer[1] and A. Neff[2]



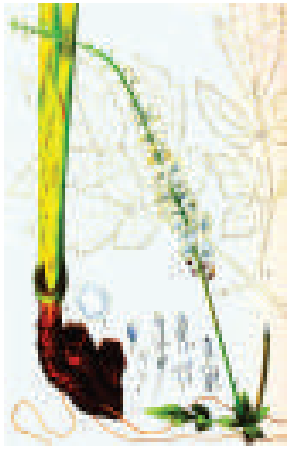
- A literature search for clinical studies examining CR's efficacy and safety for menopausal complaints was conducted.
- ***The results were sorted by type of extract, regulatory status***
- ***(pharmaceutical quality), and indication.***
- *CR extracts demonstrated a good to very good safety in general, on estrogen-sensitive organs and the liver.*
- *However,* ***only registered CR medicinal products (ICR ,BNO) were able to prove their efficacy.***

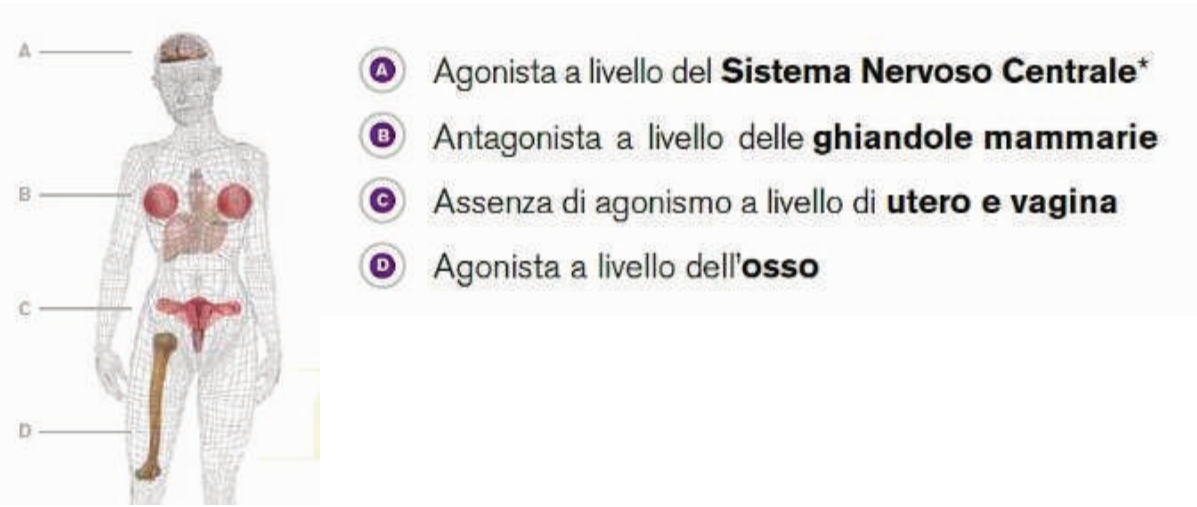
**Risposta differenziata in basa alla identificazione degli estratti e dello stato regolatorio,
efficacia e sicurezza dimostrati per estratto isopropilico ed estratto alcolico, titolati e standardizzati**

Effetti biologici

• **antagonista competitivo degli estrogeni** modulazione a livello dei recettori estrogenici con solo effetti di tipo **inibitorio**

NON AZIONE ESTROGENICA genomica





•**agonista serotoninergico e dopaminergico** a livello dei neurocettori di membrana del **SNC** ; capacità di modulare l'azione di diversi neurotrasmettitori a livello del recettore GABA, del recettore dopaminergico D2, del recettore serotoninergico 5HT (1A ,1D e 7) e dei recettori oppioidi mu (hMOR)

EFFICACY OF CIMICIFUGA RACEMOSA ON CLIMATERIC COMPLAINS: A RANDOMIZED STUDY VERSUS LOW-DOSE TRANSDERMAL ESTRADIOL

Nappi R, et al *Gynecological Endocrinology,* January 2005; 20(1):30-35

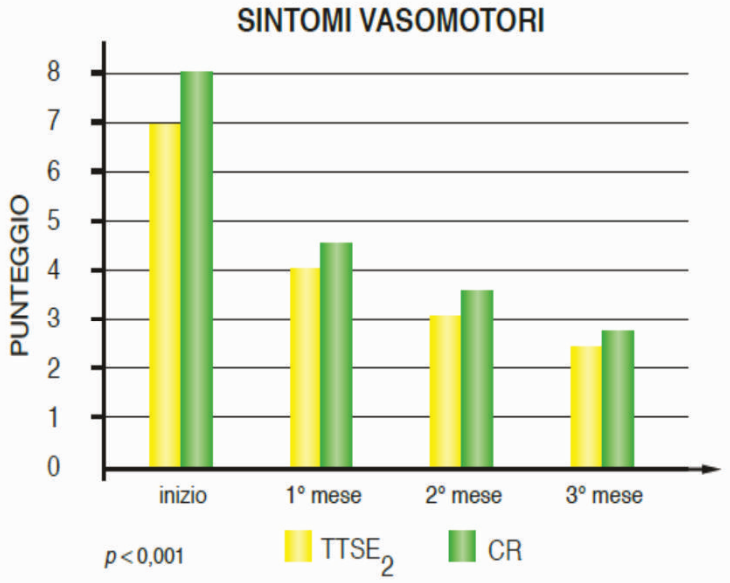
▼ Studio prospettivo multicentrico randomizzato

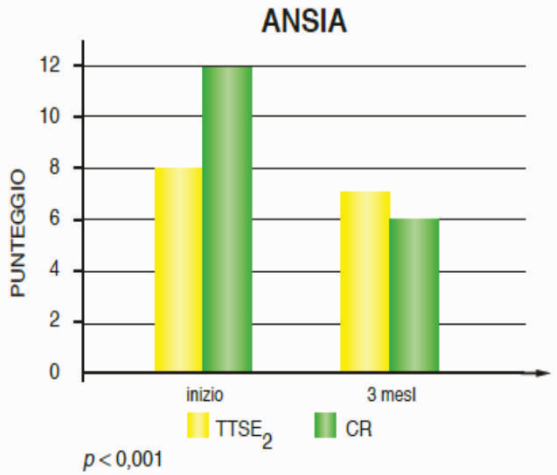
64 DONNE IN POSTMENOPAUSA

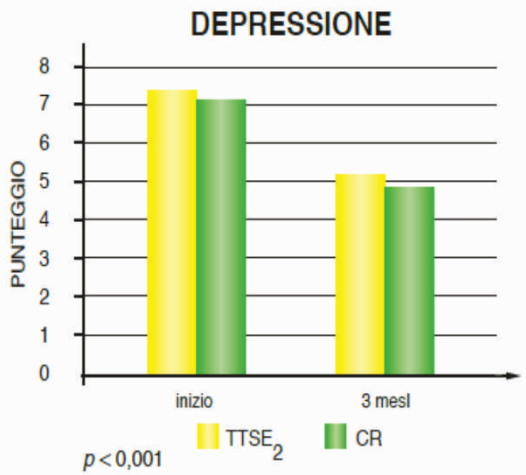
Terapia 1° gruppo: 25 µg estradiolo per via transdermica (TTSE2) per 3 mesi.

Terapia 2° gruppo: (CR) 2 cpr/die per 3 mesi

Valutati: sintomi vasomotori, neurovegetativi, parametri ormonali, profilo lipidico e spessore endometriale.



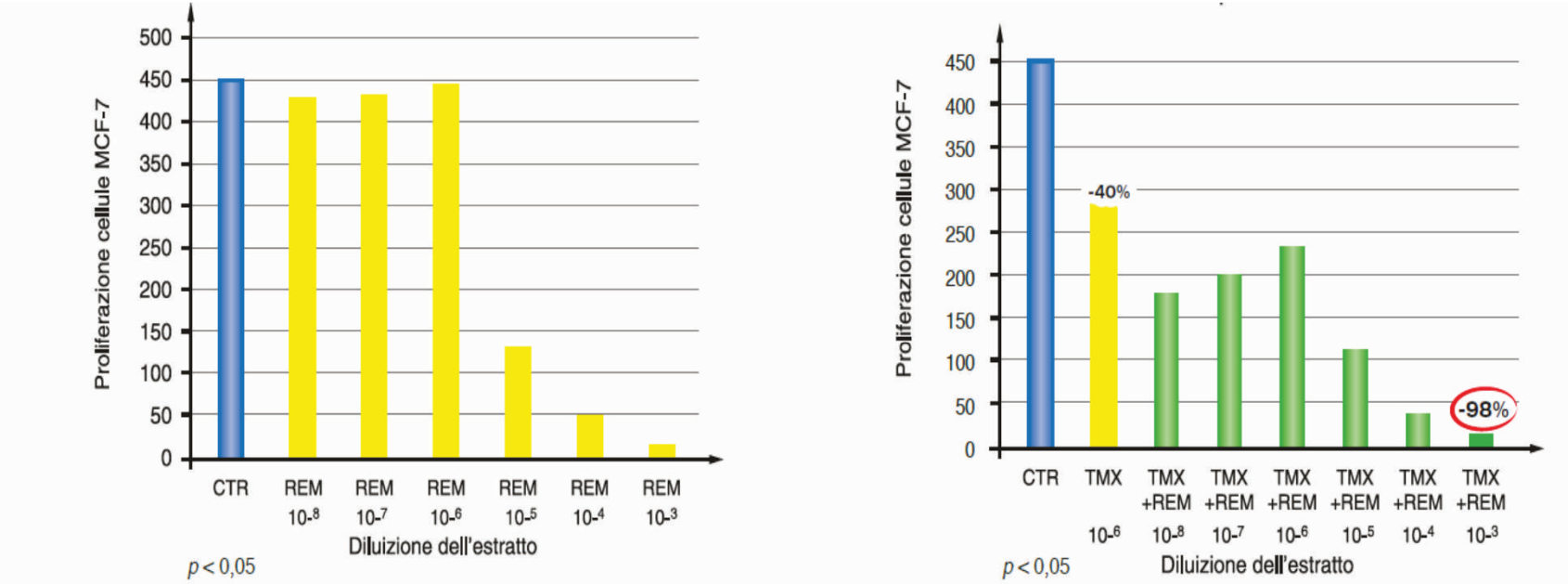




Effetti della Cimicifuga racemosa (estratto ICR) sulla mammella

I dati di ordine biochimico-biologico che clinico-epidemiologici
I dati biologici condotti su cellule di adenocarcinoma mammario in cultura MCF7 dimostrano che **l'estratto di Cimicifuga è in grado:**

- **di inibire la proliferazione spontanea cellulare**
- **di inibire la proliferazione indotta da estrogeni** (inibizione enzima steroide- solfatasi (STS) con inibizione sintesi E1e E2)
- **di aumentare l'efficacia antiproliferativa del tamoxifene**



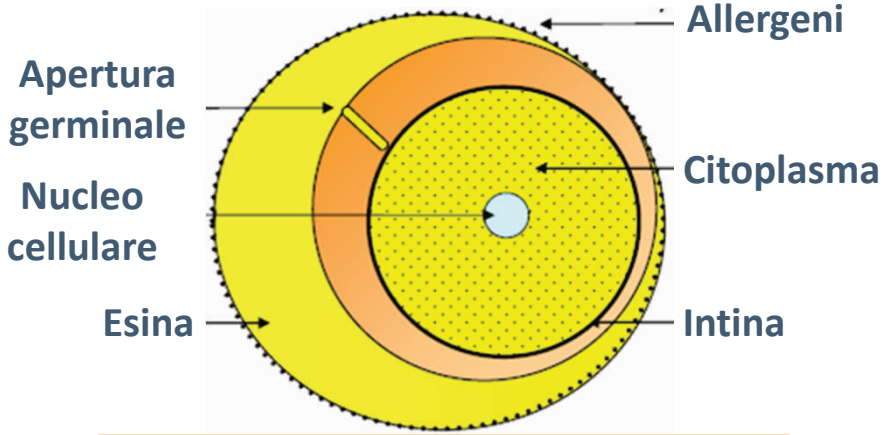
Bodinet C, Freudenstein J Influence of Cimicifuga racemosa on the proliferation of estrogen receptor-positive human breast cancer cells. Breast Cancer Res Treat. 2002 Nov; 76(1):1-10.

Estratto di polline citoplasmatico purificato

Cosa contiene?

concentrazione standard di agenti attivi in ogni compressa:

- ✓ **Estratto di polline purificato** (320 mg)
- ✓ **Vitamina E** (10 mg)



Metodologia produttiva controllata da coltivazioni selezionate

Elia D et al. *Genesis*. 2008 November; 135: 12-15

Meccanismo d'azione non ormonale

The pollen extract —a nonestrogenic alternative to hormone therapy in women with menopausal symptoms

Ann-Cathrin Hellström, MD, PhD,[1] and Jonas Muntzing, PhD[2]

- I campioni di estratto di polline sono stati sottoposti a cromatografia liquida ad alte prestazioni per l'analisi di fitoestrogeni: **concentrazioni non clinicamente rilevanti di agliconi**

- L'estratto di polline è stato testato per l'attività estrogenica su saggio biologico uterotropico nel ratto immaturo.

Hellstrom AC et al. Menopause; 2012, Vol. 19, No. 7, pp. 825/829

Nessun effetto uterotrofico

Non-estrogenic mode of action

UTEROTROPHIC TEST:

The purified cytoplasm of pollen were tested for any estrogenic action in vivo in immature female rats using the uterotrophic assay [Hellström, 2012]. Sérélys® pollen extracts did not show a uterotrophic effect in the animals.

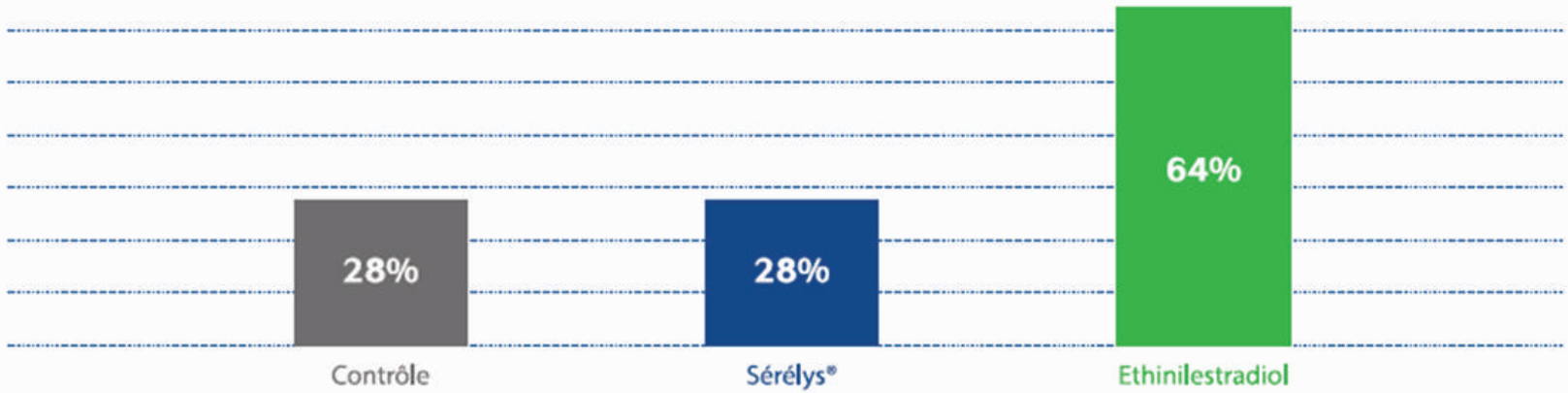


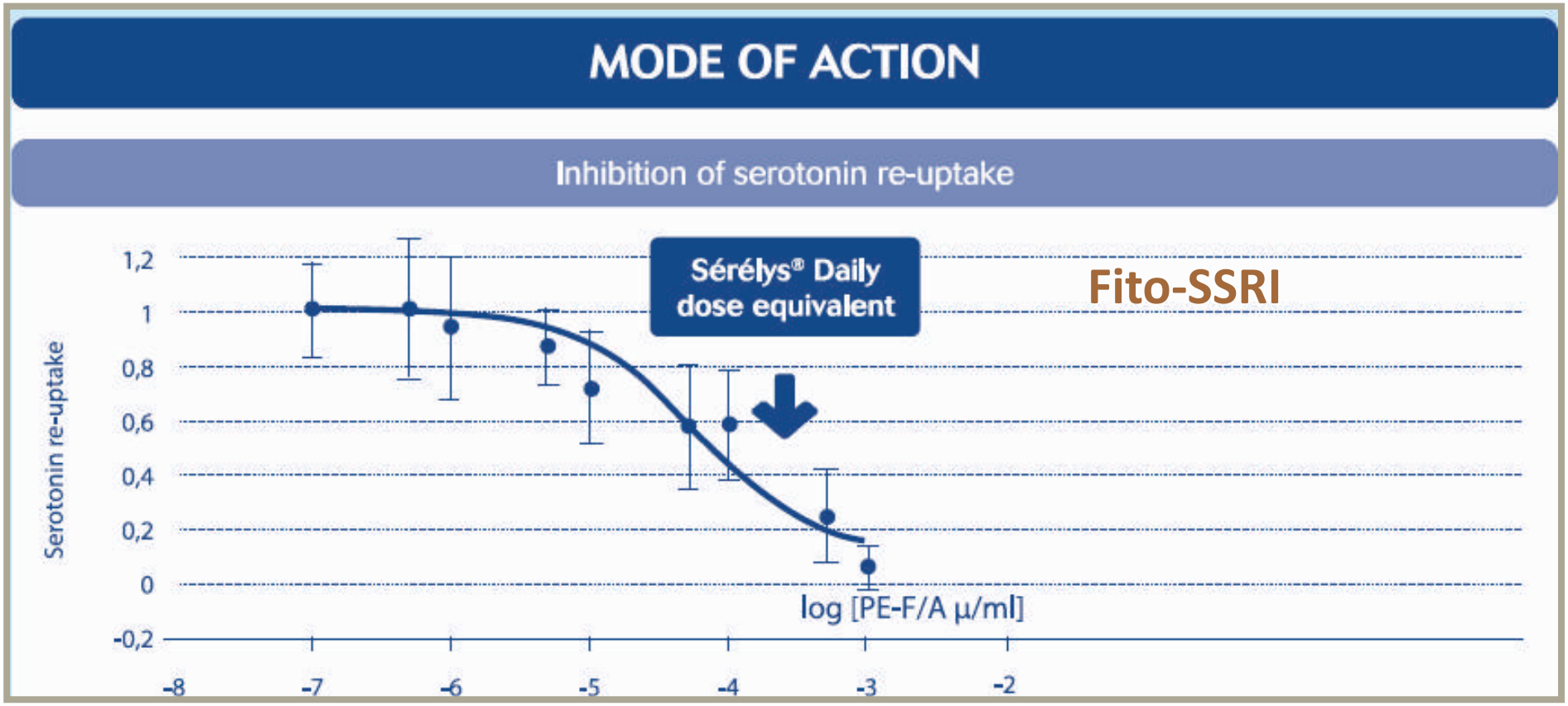
Figure 4. Uterotrophic effect of the PCP in Sérélys® and of the positive control Ethinilestradiol

L'estratto di polline ad alti dosaggi (500 mg kg^{-1} day^{-}) non ha causato alcuna crescita uterina in ratti immaturi di sesso femminile.

Hellstrom AC et al. Menopause 2012; Vol. 19, No.7 pp 825-829

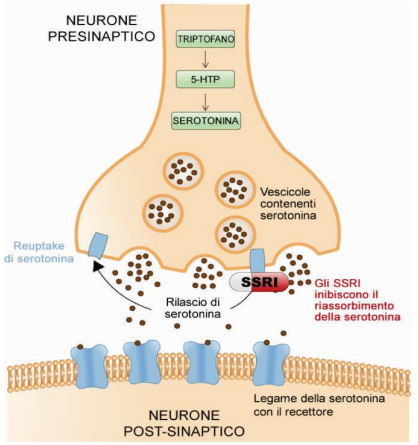
Inibisce il re-uptake della serotonina nelle sinapsi della regione corticale in modello animale

(studio su estrazioni di sinapsi di ratto in vitro)



Druckman R, - EMAS 2015

Estratto di polline citoplasmatico purificato (PCP)

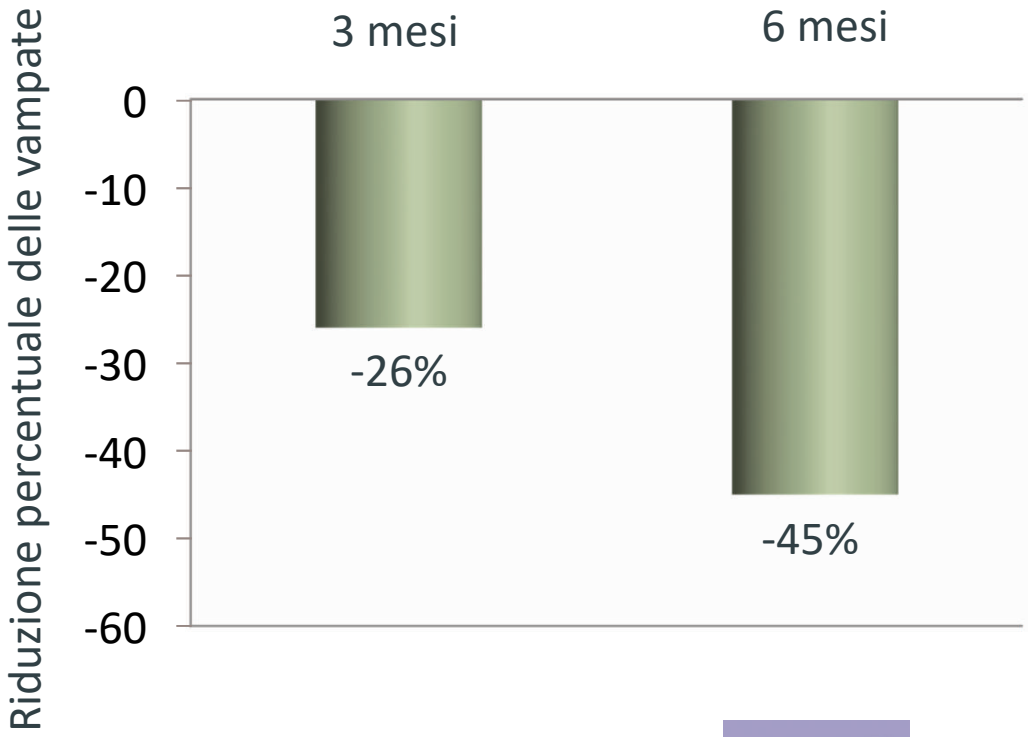


- Azione a livello del sistema nervoso centrale ***simile agli SSRI***, efficaci sui sintomi menopausali

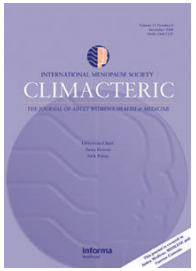
A non –hotmonal treatment for vasomotor symptoms in femal patients with and after breast cancer carcinoma. Druckman R, - EMAS 2015

Efficacia sul controllo delle vampate e sulla QoL

Significativa riduzione delle vampate di calore con PCP (diario delle pazienti) a 3 mesi e a 6 mesi



- Riduzione progressiva delle vampate nei pazienti che ricevono un secondo ciclo di PCP
- ***Nessun aumento significativo di eventi avversi a sei mesi***



Winther K et al. *Climacteric* 2005;8:162–170

Estratto di polline citoplasmatico purificato (PCP) :efficacia

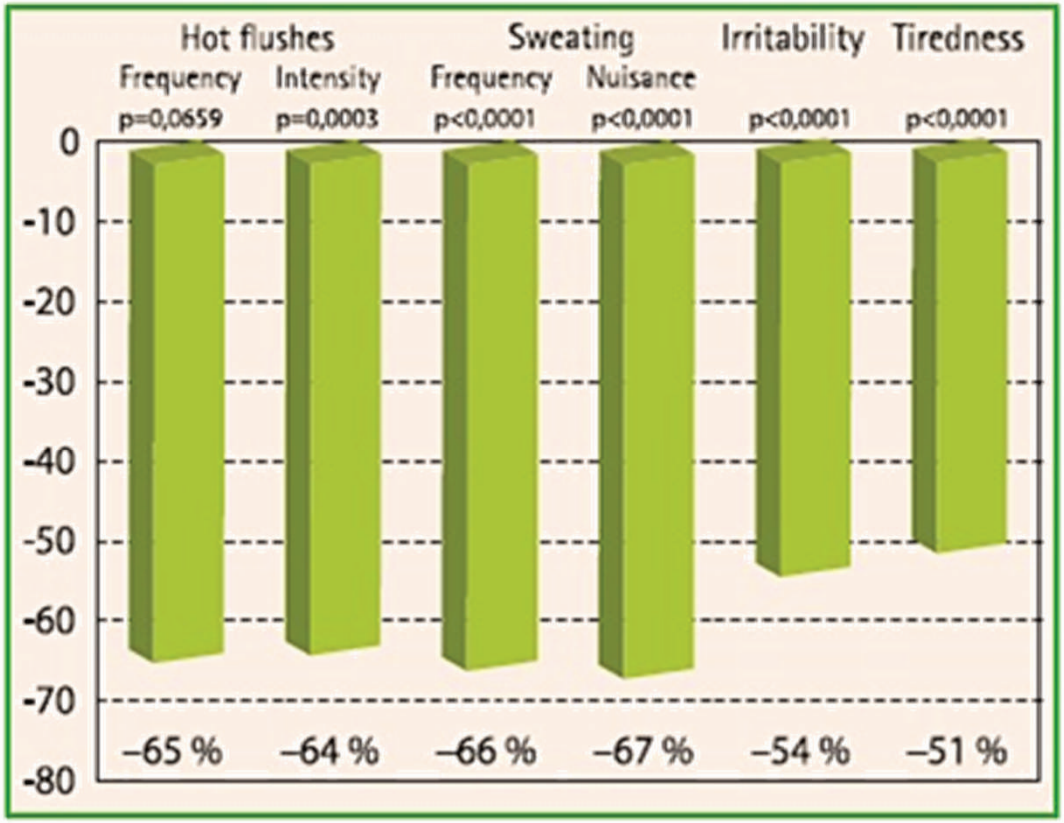


Figure 3: Reduction in symptoms on J84

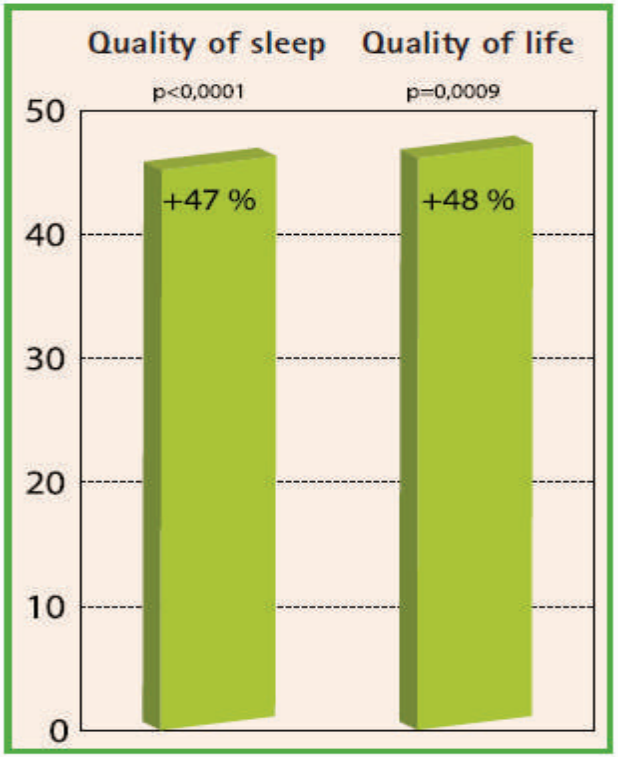
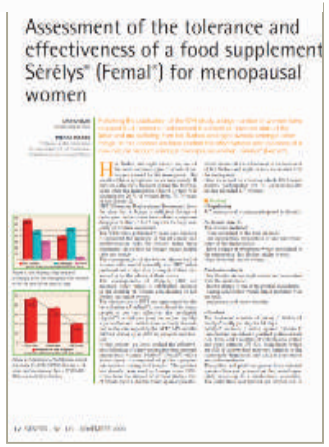


Figure 4: Improvement in the quality of sleep and quality of life on J84

- Studio in aperto;
- **417** donne in menopausa con sintomatologia climaterica
- 2 compresse al giorno per **12 settimane**.

Elia et al. Genesis 2008; 135


Assessment of the tolerance and effectiveness of a food supplement Sérélys® (Femal®) for menopausal women

A non-hormonal treatment, efficient and safe on symptoms during ***pre-menopause and menopause***, improve women's quality of life

Studio in aperto: **324 pazienti**

Trattamento: ***PCPl 2cpr/die per 3 mesi***

Valutazione: Sintomatologia climaterica con **scala VAS + questionario**

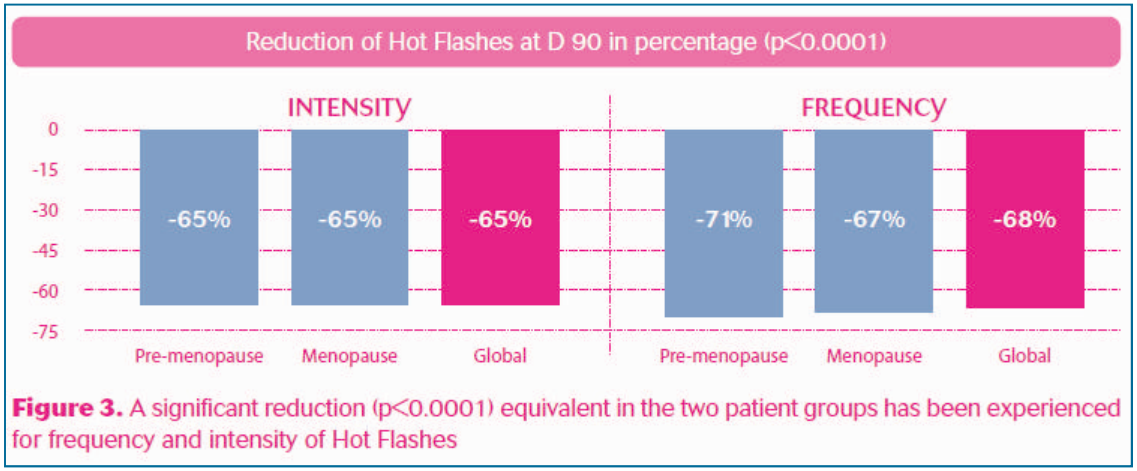


Figure 3. A significant reduction (p<0.0001) equivalent in the two patient groups has been experienced for frequency and intensity of Hot Flashes

FATIGUE AND IRRITABILITY:
Respectively 62.0% and 60.8% of the patients have experienced improvement in irritability and fatigue.

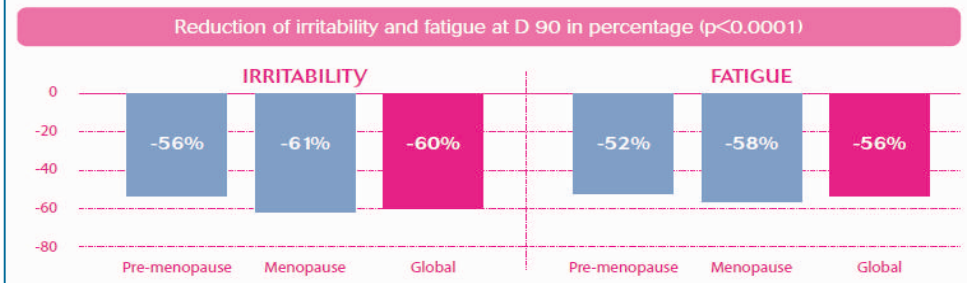
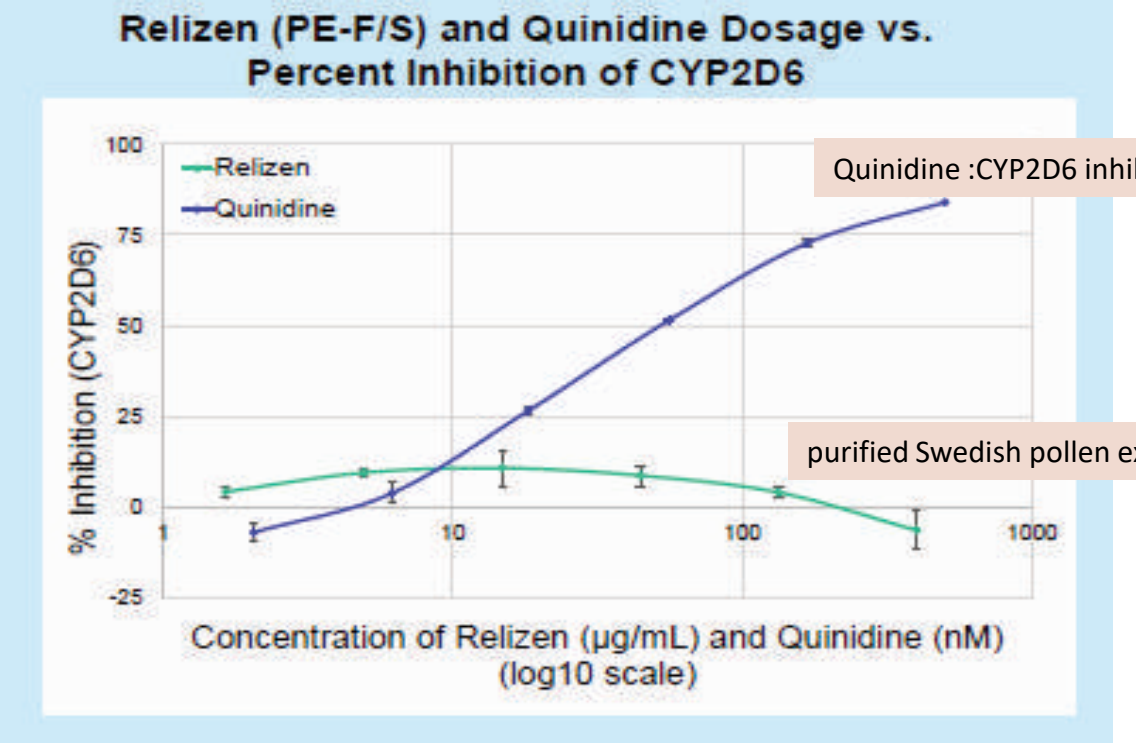


Figure 4. A significant reduction (p<0.0001) equivalent in the two patient groups has been shown for irritability and fatigue

Druckmann et al. EMAS, 2015

L'estratto di polline non inibisce il complesso enzimatico che metabolizza il tamoxifene, a differenza di altri SSRI (paroxetina,fluoxetina)



- Questo dato può avere un'importante utilità clinica nelle donne che utilizzano tamoxifene per il trattamento adiuvante del carcinoma mammario e che lamentano sintomi vasomotori

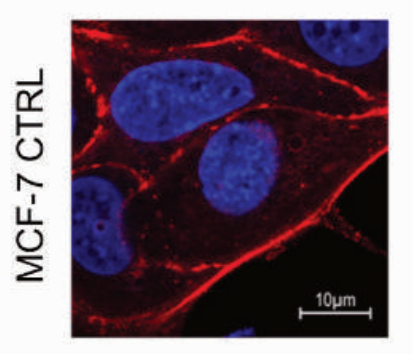
Goldstein et al. EMAS 2015

"Non stimola la proliferazione delle cellule di carcinoma mammario"

Disegno dello studio

- Studio *in vitro* su due linee cellulari di carcinoma mammario trattate con:
- **PCP** (a concentrazioni diverse fino a 400 µg/ml, ~ 50 vv la dose quotidiana)
- **GF o estradiolo,** da soli o in combinazione, per 6 giorni.

- **Analisi:**
  - Proliferazione cellulare mediante MTT-test
  - Morte cellulare mediante apoptosi mediante kit ELISA



- Seeger et al. Gynecological Endocrinology 2017

PCP non stimola la proliferazione delle cellule mammarie

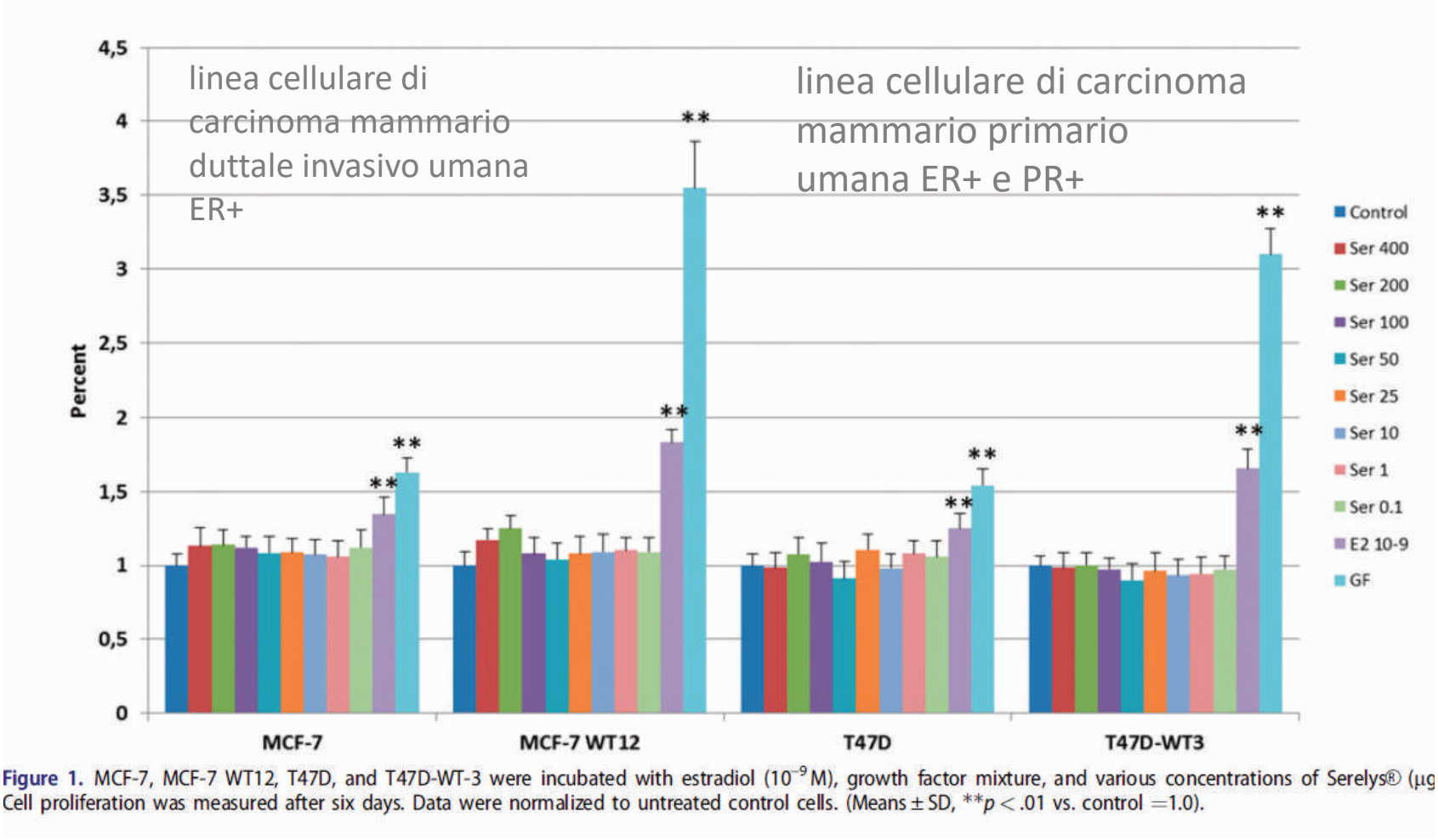


Figure 1. MCF-7, MCF-7 WT12, T47D, and T47D-WT-3 were incubated with estradiol (10^{-9} M), growth factor mixture, and various concentrations of Serelys® (µg Cell proliferation was measured after six days. Data were normalized to untreated control cells. (Means ± SD, $^{**}p < .01$ vs. control =1.0).

Seeger et al., Gynec Endocrinol 2017

PCP non deregola l'apoptosi nelle cellule mammarie

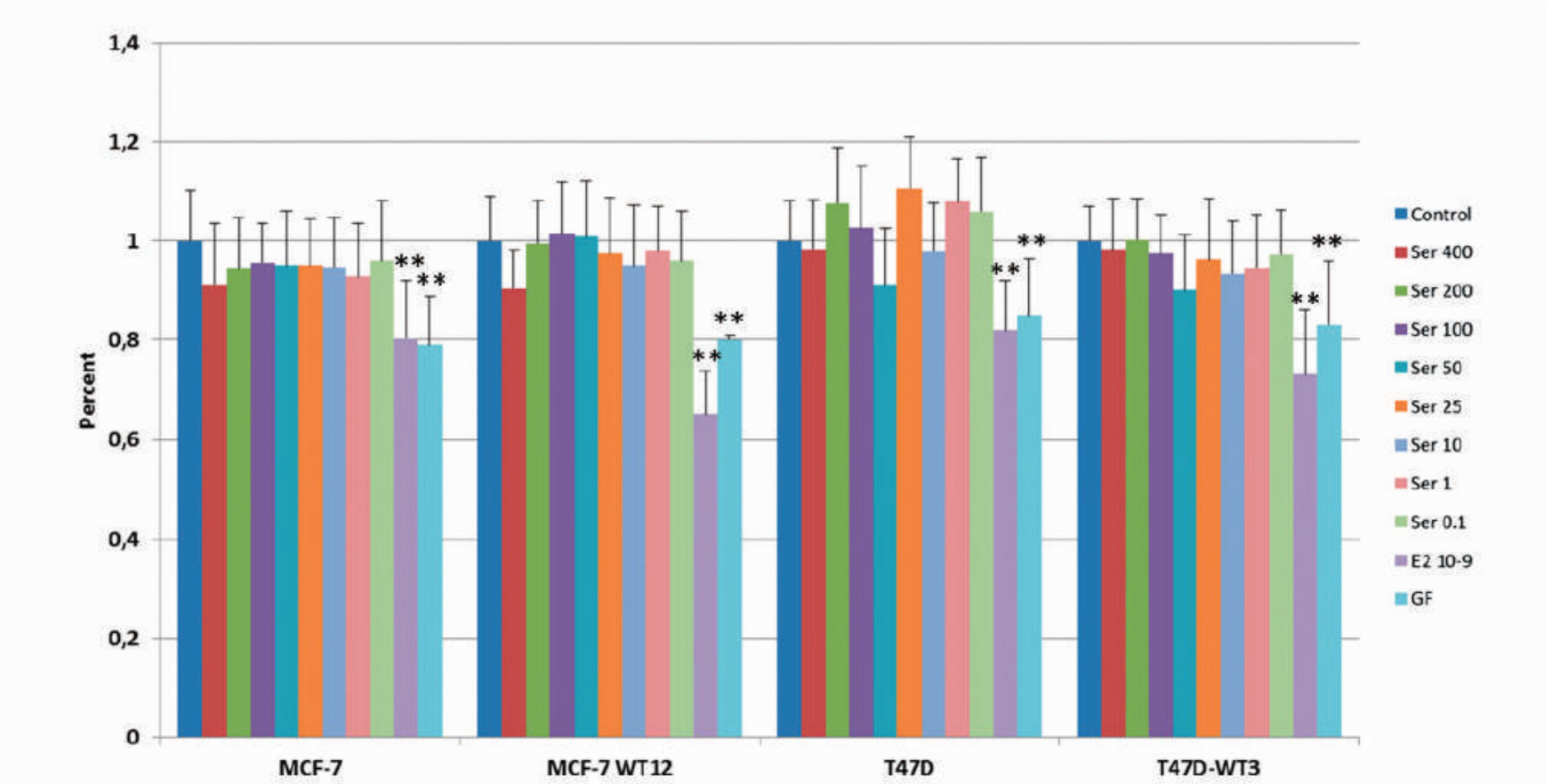
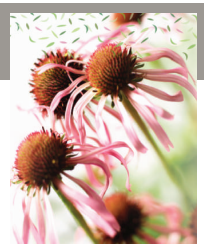


Figure 2. MCF-7, MCF-7 WT12, T47D, and T47D-WT-3 were incubated with estradiol (10^{-9} M), growth factor mixture, and various concentrations of Serelys® (µg/ml). Cell death was measured after six days. Data were normalized to untreated control cells. (Means ± SD, $^{**}p < .01$ vs. control = 1.0).

Seeger et al., Gynec Endocrinol , 2017



Principali fitoterapici negli integratori per la Menopausa:

	Meccanismo d'azione	Dati di efficacia	Sicurezza/ Aree di incertezza
Fitoestrogeni 60- 80 mg/die	Fito-SERM estrogeno «debole», Az metaboliche e anti-ox	Vampate, -25% vs placebo Intensità e frequenza Effetti metabolici Effetti osteoprotettivi (BMD e BTM)	Sicurezza mammaria? Protezione vascolare ?
Cimicifuga racemosa estratto isopropilico tit. e standardizzati 80mg/die	Agonista 5HT e DOPA a livello dei neurocettori di membrana del SNC, modulatore recettore GABA e oppioidi	Sintomi vasomotori e neurovegetativi	Nessuna azione proliferativa estrogenica, non contrasta ter. adjuvante
Esratto concentrato di **Polline purificato** 640 mg/die	Inibisce il re-uptake della serotonina nelle sinapsi della regione corticale	Sintomi vasomotori e neurovegetativi	Nessuna azione proliferativa estrogenica non contrasta ter. adjuvante

Menopause. 2014 September ; 21(9): 924–932. doi:10.1097/GME.0000000000000196.

RISK OF LONG TERM HOT FLASHES AFTER NATURAL MENOPAUSE: EVIDENCE FROM THE PENN OVARIAN AGING COHORT

Ellen W. Freeman, PhD[a,b], Mary D. Sammel, ScD[c], and Richard J. Sanders, MS[d]

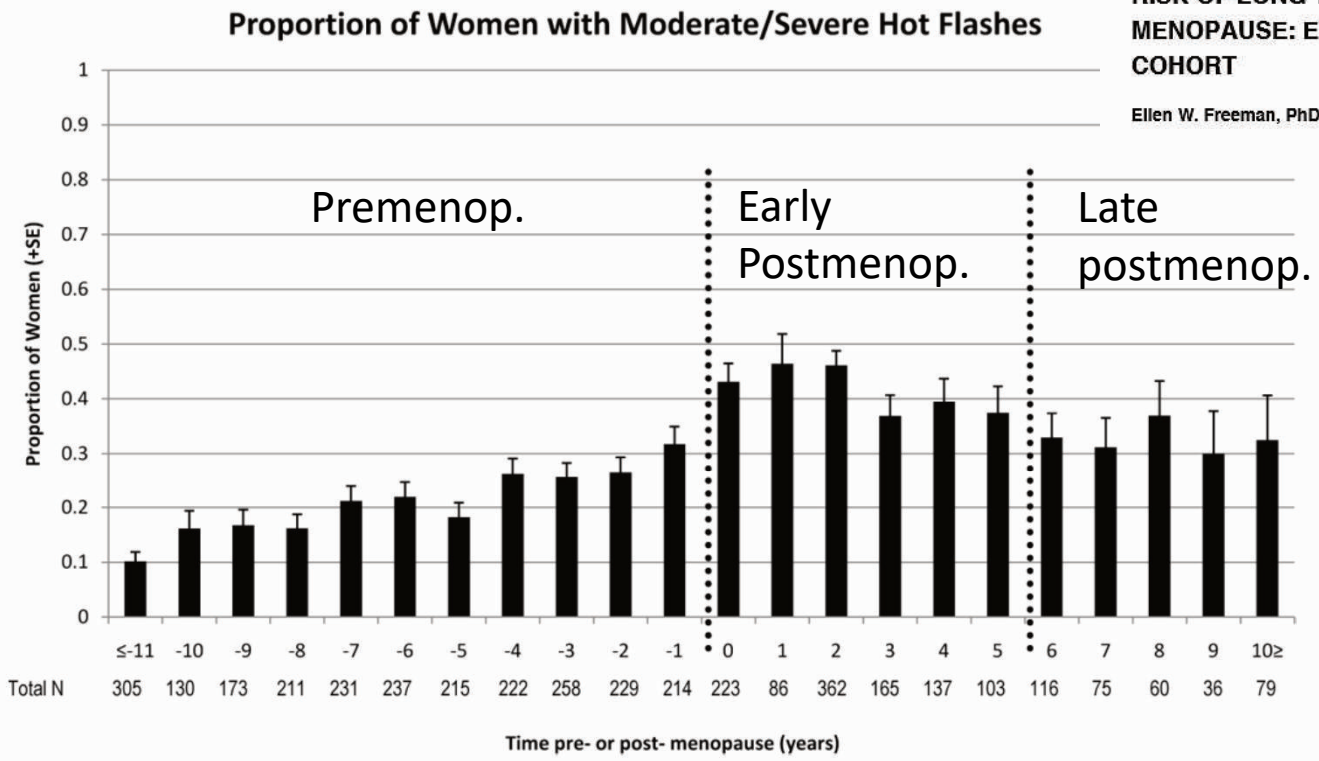


Figure 1.

- 255 women
- natural menopause
- 16 years of follow-up.

- ✓ *Moderate/severe hot flashes continued* ***on average for nearly 5 years following menopause****; more than one- third of women observed for 10 or more years following menopause had moderate/severe hot flashes.*
- ✓ *Continuation of hot flashes for more than 5 years following menopause underscores the* ***importance of determining individual risk/benefit when selecting hormone or non-hormonal therapy*** *for menopausal symptoms*