Menopausal Management Options: an integrated approach

- Lifestyle
- HRT (hormone replacement therapy)

the most efficacious treatment for climacteric symptoms

- **Non estrogenic alternatives :**

Conventional non-hormonal treatments

Complementary and Alternative Medicines (CAM)

Controindication for HRT,CVD risk

Mild SNVG

Older ages

Personal beliefs

Alternative and complementary medicine (CAM)

Table 1
Classification of complementary and alternative medicine (CAM) according to the National Center for Complementary and Alternative Medicine.

Classification	Definition
Whole medical systems	Therapies based on systems of theory and practice. Examples include homeopathic medicine, naturopathic medicine, traditional Chinese medicine and Ayurveda
Mind–body interventions	Techniques designed to enhance the mind's capacity to affect bodily function and symptoms. Example are: patient support groups, cognitive-behavioral therapy and meditation
Biologically based therapies	Use substances found in nature such as herbs, foods, vitamins, and other natural substances
Manipulative and body based methods	Techniques based on manipulation and/or movement of one or more parts of the body. Examples are: chiropractic or osteopathic manipulation and massage
Energy therapies	Therapies that involve the use of energy fields. They are of two types: biofield therapies and bioelectromagnetic-based therapies

…a group of diverse medical and health care systems, practices, and products that are not generally considered to be part of conventional medicine"

Borrelli F ,Ernst E,Maturitas 2010

Cardini et al. BMC Women's Health 2010, 10:7
http://www.biomedcentral.com/1472-6874/10/7

BMC Women's Health

RESEARCH ARTICLE Open Access

The use of complementary and alternative medicine by women experiencing menopausal symptoms in Bologna

Francesco Cardini[1*†], Grazia Lesi[2†], Flavia Lombardo[3†], Corinne van der Sluijs[4†], MSCG - Menopause Survey Collaborative Group[2†]

Abstract

Background: The present study describes Complementary and Alternative Medicine (CAM) use amongst Italian women transitioning through menopause. Popularity and perceived effectiveness of CAM treatments, use of pharmaceutical medications, characteristics of CAM users, the extent of communication between medical practitioners and women about their use of CAM, and variables associated with CAM use were also investigated.

Methods: Women, aged 45-65 years attending Family Planning and Women's Health clinics or Menopause Centres in Bologna were invited to complete a voluntary, anonymous, self administered questionnaire, which was used in a previous study in Sydney. The questionnaire was translated and adapted for use amongst Italian women. Data on general demographic and health characteristics, menopause related symptoms and the use of CAM and pharmaceutical treatments during the previous 12 months were collected.

Results: In total, 1,203 women completed the survey, of which 1,106 were included in the final sample. Of women

Conclusions: The relatively high prevalence of CAM use by women transitioning through menopause should encourage research initiatives into determining which CAM treatments are the safest and effective. The increasing and likely concomitant use of CAM with HRT and other pharmaceuticals underlines the need for the implementation of a surveillance system to report and monitor possible drug-herb adverse events. The discrepancy between women preferring to seek information about CAM from their medical doctor and the difficulties noted in communication between doctor and patient should encourage educational initiatives on CAM by health-care agencies and institutions.

communication between doctor and patient should encourage educational initiatives on CAM by health-care agencies and institutions.

Complementary and Alternative Medicine (CAM) treatments for improving quality of life during the menopausal

- Come includere CAM in un algoritmo prescrittivo per la donna in postmenopausa?
- Ruolo del ginecologo nel counselling informativo sulla CAM
- Distinguere diverse classi terapeutiche
- Possibile fenotipizzazione della paziente target?

Alimenti particolari e integratori

A cura di:
Direzione generale della sicurezza degli alimenti e della nutrizione - Ufficio IV

Web editing:
Dr. D. DE CRINITO

INTEGRATORI ALIMENTARI

In generale

Gli integratori alimentari sono: "prodotti alimentari destinati ad integrare la comune dieta e che costituiscono una fonte concentrata di sostanze nutritive, quali le vitamine e i minerali, o di altre sostanze aventi un effetto nutritivo o fisiologico, in particolare, ma non in via esclusiva, aminoacidi, acidi grassi essenziali, fibre ed estratti di origine vegetale, sia monocomposti che pluricomposti, in forme predosate"

Altre sostanze ad effetto nutritivo o fisiologico

Nell' elenco delle sostanze ad effetto nutritivo o fisiologico sono incluse alcune delle sostanze impiegabili negli integratori

Probiotici

Il termine probiotico è riservato a quei microrganismi che si dimostrano in grado, una volta ingeriti in adeguate quantità, di esercitare funzioni benefiche per l'organismo

Vitamine e minerali

L'impiego di vitamine e minerali negli integratori e la loro aggiunta agli alimenti, con le relative fonti, è attualmente disciplinato dal regolamento (CE) 1170/2009 del 30 novembre 2009, che modifica la direttiva 2002/46/CE e il regolamento (CE) 1925/2006 "per quanto riguarda gli elenchi di vitamine e minerali e le loro forme che possono essere aggiunte agli alimenti, compresi gli integratori alimentari"

Estratti vegetali

Elenchi relativi agli estratti vegetali: impiegabili e non impiegabili

Coadiuvanti di diete ipocaloriche

Gli alimenti proposti come coadiuvanti di diete ipocaloriche per la riduzione del peso corporeo devono seguire i criteri relativi ad una corretta etichettatura e pubblicità

Ministero della Salute

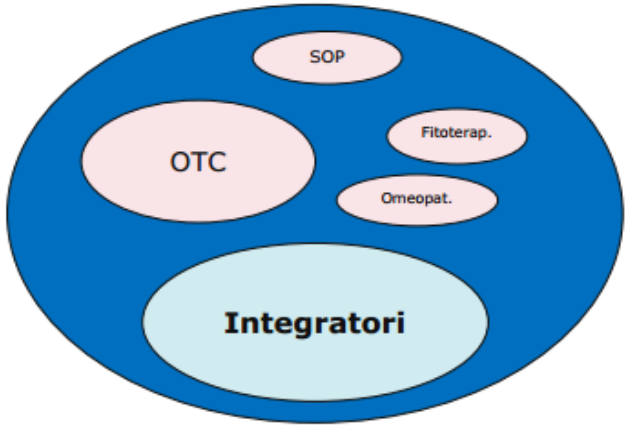
Il documento:

- nelle prime tre colonne con sfondo grigio riporta l'Allegato 1 al DM 9 luglio 2012 sulle "Sostanze e preparati vegetali ammessi"
- nella quarta colonna con sfondo bianco, che non è parte integrante del predetto DM, ripropone le "Linee guida ministeriali di riferimento per gli effetti fisiologici".

MINISTERO DELLA SALUTE **DECRETO 9 luglio 2012** **Disciplina dell'impiego negli integratori alimentari** **di sostanze e preparati vegetali** **(G.U. 21-7-2012 serie generale n. 169)**			**LINEE GUIDA MINISTERIALI** **DI RIFERIMENTO PER GLI EFFETTI FISIOLOGICI** applicabili in attesa della definizione dei claims sui "botanicals" a livello comunitario
ALLEGATO 1 aggiornato al 16 gennaio 2013			***Gli effetti fisiologici sono volti ad ottimizzare le funzioni dell'organismo nell'ambito dell'omeostasi, secondo il modello definito al riguardo dal Consiglio d'Europa [Homeostasis, a model to distinguish between foods (including food supplements) and medicinal products – 07.02.2008].***
NOME BOTANICO	**PARTE UTILIZZATA**	**NOTE**	
ABAREMA COCHLIOCARPOS (GOMES) BARNEBY & J. W. GRIMES	**oleum**		**oleum:** Naturali difese dell'organismo. Azione di sostegno e ricostituente.
ABELMOSCHUS ESCULENTUS (L.) MOENCH	**fructus**		**fructus:** Funzionalità delle mucose dell'apparato respiratorio. Benessere della gola. Azione emolliente e lenitiva (sistema digerente; vie urinarie)

I nutraceutici rientrano nella categoria dei prodotti notificati con finalità di integrazione e nutrizione, da non confondere con prodotti dietetici o alimenti funzionali

I nutraceutici in Farmacia, Parafarmacia e Corner GDO



- Gli integratori sono "**fonti concentrate di sostanze aventi un effetto nutritivo** (vitamine e minerali) o **fisiologico** (acidi grassi essenziali, estratti vegetali), il cui scopo è di **supplementare e integrare la normale dieta** e **contribuire al benessere** dell'organismo"
- L'immissione in commercio, in **forme esclusivamente orali**, è subordinata alla **procedura di notifica dell'etichetta** al Ministero della Salute (90 giorni di consenso/assenso → *time to market* accelerato) e le sostanze che lo compongono devono aver registrato un pregresso consumo significativo come prova di sicurezza

Gli integratori sono a tutti gli effetti degli alimenti
NO prodotti dietetici *(adatti ad uno specifico obiettivo nutrizionale, i.e. prodotti per celiaci e diabetici, etc.)*
NO alimenti funzionali *(alimenti freschi o trasformati che hanno proprietà benefiche sulla salute indipendentemente dal loro valore nutrizionale)*

Fonte: Direttiva 2002/46/CE in D.Lgs 21 maggio 2004, n. 169, Ministero della Salute

Three groups of recognised interventions for relief of menopausal vasomotor symptoms

Conventional	Alternative	Complimentary
Clonidine	Black cohosh	Homeopathy
SSRIs	Red clover	Aromatherapy
Gabapentin	Phytoestrogens	Acupressure
	Ginseng	Accupuncture
	Evening primrose	Stress management
	Dong quai	
	Vitamin E	

Fitoestrogeni – La biochimica

G Bonaccorsi,Unife

- 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.

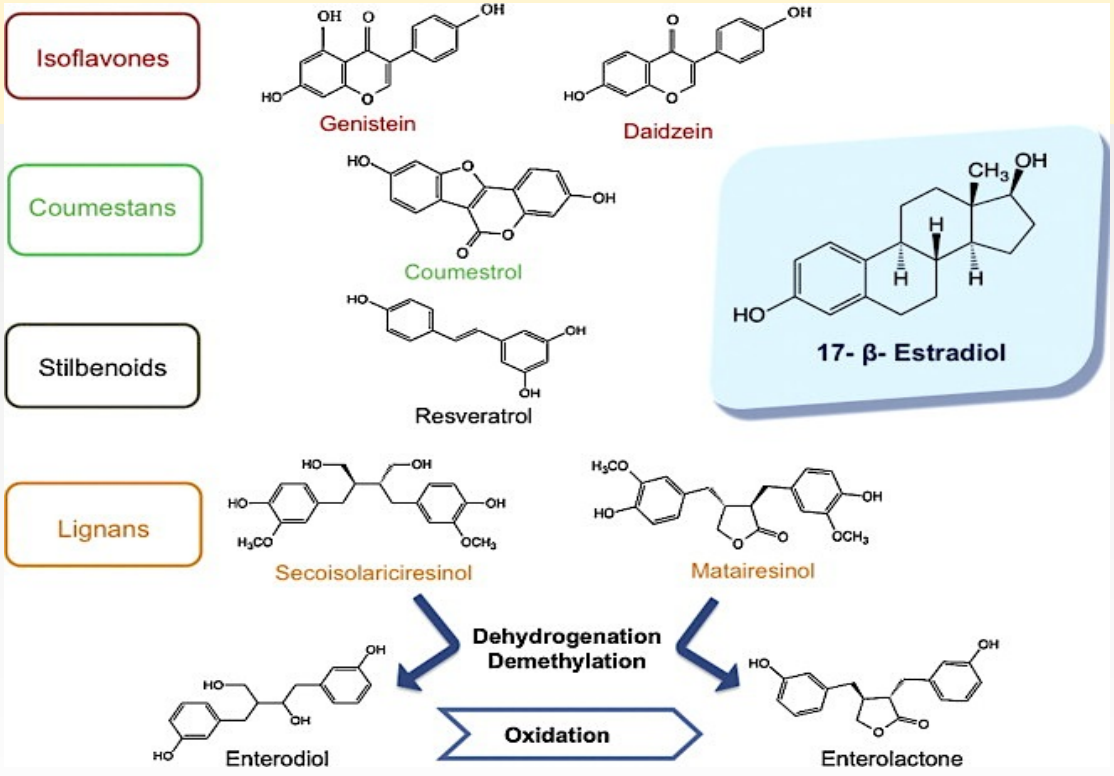
Fitoestrogeni

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

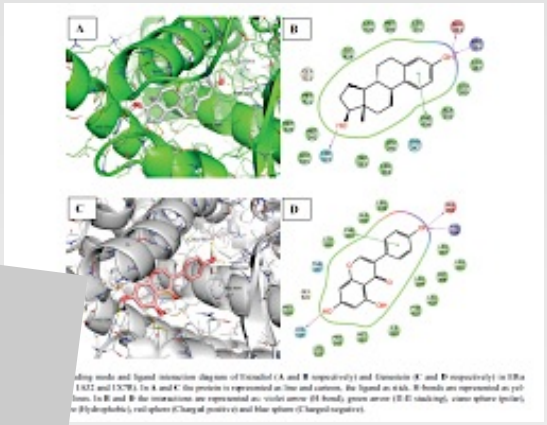


ISOFLAVONES: MECHANISM OF ACTION

Genomic:

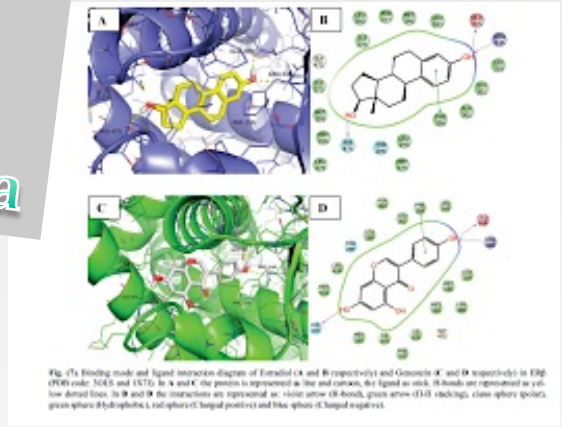
- Preferential link to ER beta:
- Link to ER alpha:
  - 100x less than Estradiol

Phyto-SERMs
Estrogeno "debole"
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 the toxicity of electrophiles and ROS

Isoflavones: complexity of the metabolism

HYDROLYSIS	in jejunum by β-glycosidases
METABO	by intestinal bacteria to equol and O-desmethylangolesin (O-DMA)
ABSORPTION	genistein and daidzein). tion function , stinal absorption
GLUCURONATION	by liver cells
BIOAVAILABILITY	depends on the food composition and the entero-hepatic circulatory efficiency
PEAK BLOOD LEVEL	reached 6-9 hrs after intake: to maintain sustained blood levels intake spread should be evenly distributed over the entire day.
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 .

Maturitas 78 (2014) 79–81

Contents lists available at ScienceDirect

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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.***

Efficacy
Safety

A systematic review and meta-analysis of the effects of isoflavone formulations against estrogen-deficient bone resorption in peri- and postmenopausal women

Max Norman Tandrup Lambert, Lin Meng Hu, and Per Bendix Jeppesen

Am J Clin Nutr 2017;106:801–11. Printed in USA.

Isoflavone treatments exert a moderately beneficial effect against estrogen-deficient bone loss in women

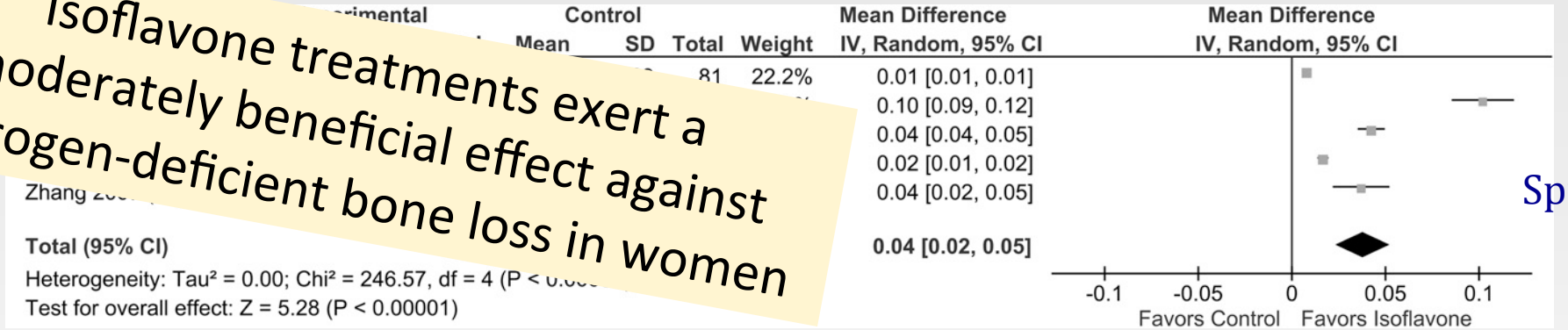

FIGURE 6 Forest plot showing the difference in bone mineral density change at the lumbar spine in studies providing isoflavone aglycones (n = 5) to treatment compared with control. Data calculated from the random-effects model are presented as weighted mean difference and 95% CI. IV, inverse varience.

Twenty-six RCTs (n = 2652) were included in the meta- analysis

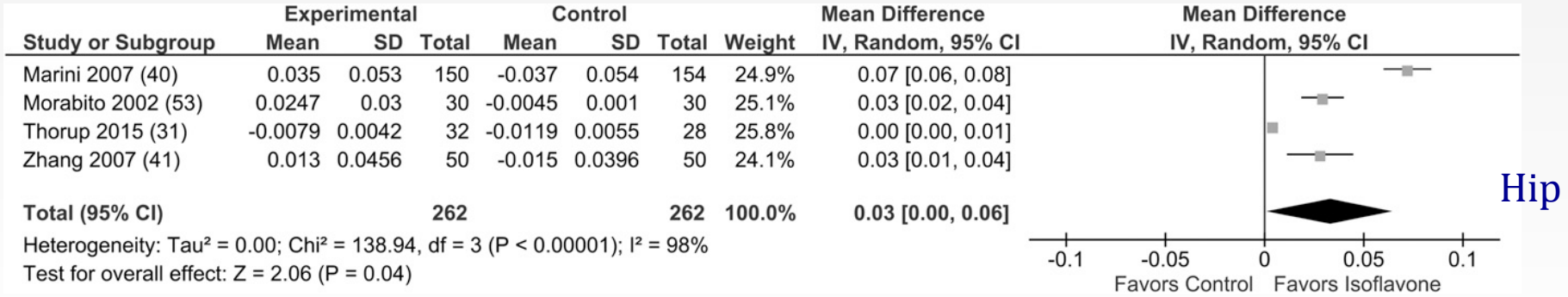

FIGURE 7 Forest plot showing the difference in bone mineral density change at the femoral neck in studies providing isoflavone aglycones (n = 4) to treatment compared with control. Data calculated from the random-effects model are presented as weighted mean difference and 95% CI. IV, inverse varience.

J. L. Marino,Menopause,2014

TABLE 3. *Vasomotor symptoms: menopause clinic and menopause symptoms after cancer clinic at King Edward Memorial Hospital*

	Noncancer participants	Cancer survivors		
	n (%)[a]	n (%)	Odds ratio (95% CI)	*P*
Current severe trouble				
Vasomotor symptoms			1.71 (1.06-2.74)	0.027
Hot flushes				0.022
Night sweats				
Past 24 h				
Any hot flushes				
Mild or moderate flushes				
Severe or very severe flushes	13 (15.7)		0.77 (0.44-1.36)	0.37
≥10 flushes		266 (61.3)	1.65 (0.93-2.91)	0.64
Past-week severe trouble	62 (60.8)	326 (74.6)	1.14 (0.66-1.97)	0.54
Poor sleep	55 (53.9)	252 (57.5)	0.82 (0.44-1.53)	
Hot flushes	47 (46.1)	104 (24.8)		
Night sweats	22 (22.0)			
Cold sweats				

Odds ratios adjusted for age at menopause, age at visit, and current use of hormone therapy. Denominators vary according to completion of instrument.
Boldface indicates statistically significant relationship ($P < 0.05$).
[a]Reference category.
[b]Denominator refers to women within the category reporting any hot flushes in the past 24 hours.

SNVG dopo neoplasia ginecologica/ breast cancer
più frequenti (>70% delle donne)
e più intensi vs menopausa fisiologica

Cancer survivors were more likely than non-cancer participants to be severely troubled by vasomotor symptoms (hot flushes and night sweats; 75 % vs 56% ,odds ratio, 1.71)

Only 21% of women experiencing HFs were receiving treatment for them, and most participants described **no knowledge or poor knowledge of HF treatment options.**
(Garcia MK,Cancer,2015)

Gynecological Endocrinology

Taylor & Francis
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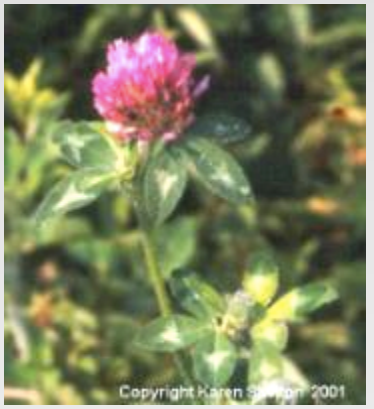
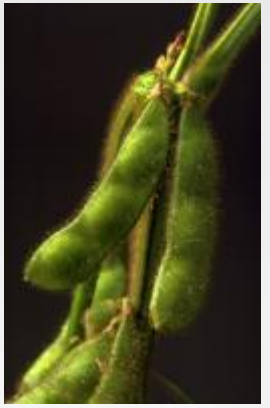
Marzo 2016

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

Mathias Schmidt, Karin Arjomand-Wölkart, Martin H. Birkhäuser, Andrea R. Genazzani, Doris M. Gruber, J. Huber, Heinz Kölbl, Samo Kreft, Sepp Leodolter, Doris Linsberger, Markus Metka, Tommaso Simoncini & Lucija Vrabic Dezman





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

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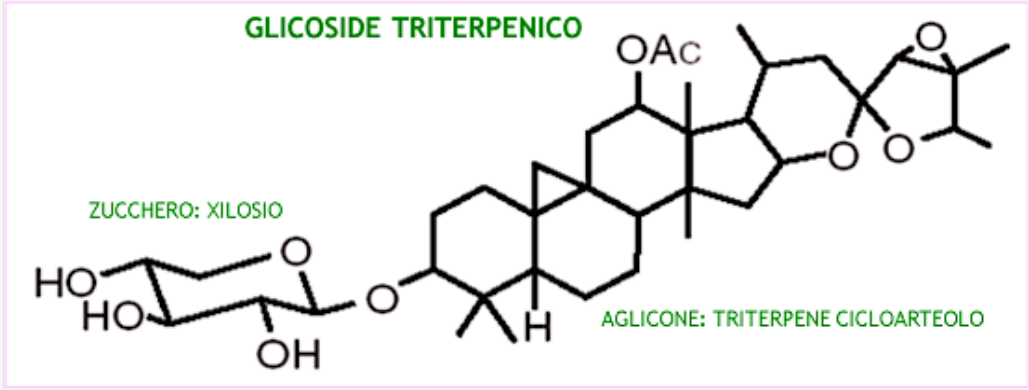
- ✓ High exposure to isoflavones is associated with **reduced breast cancer risk**
- ✓ Long-term studies in breast cancer patients indicate advantages for soy exposure, expressed as an improved cancer recurrence rate and a lack of undesired treatment interactions with tamoxifen and anastrozole. **Isoflavone exposure in breast cancer patients should no longer be discouraged**
- ✓ **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.**

CIMICIFUGA RACEMOSA (Black Cohosh,Actea racemosa)
pianta non alimentare
rizoma e radici vengono utilizzate fresche o in forma essiccata

Costituenti chimici



❖La Cimicifuga possiede diversi costituenti chimici:

❖I glucosidi triterpenici costituiscono la principale componente bioattiva presente nell'estratto alcolico responsabili degli effetti terapeutici.

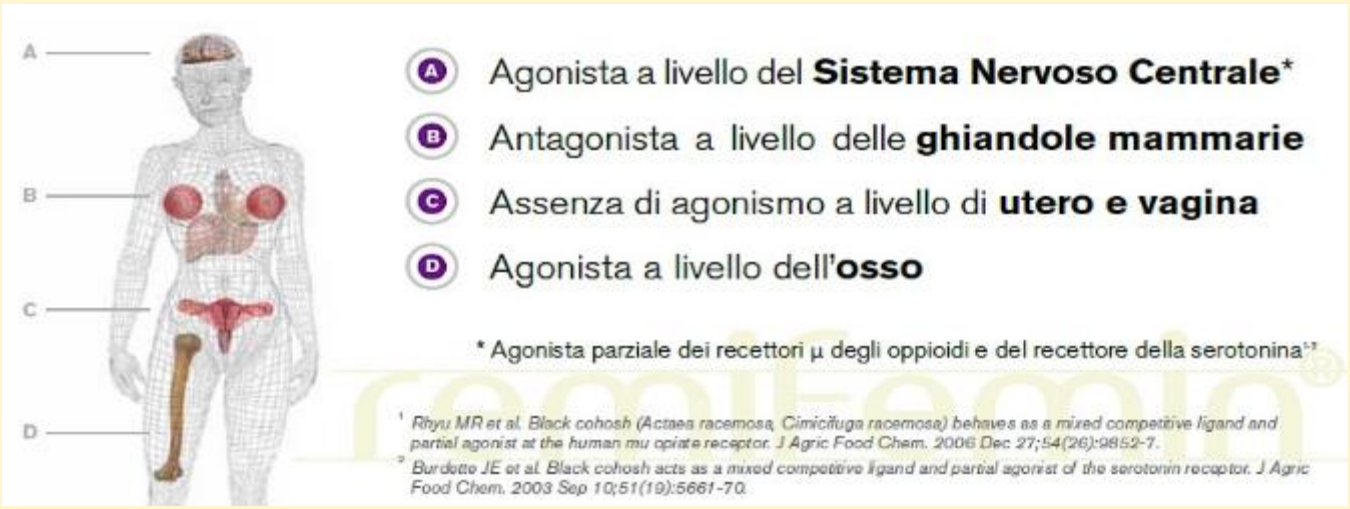
❖L'estratto alcolico isopropilico utilizzato in fitoterapia risulta **privo della componente fitoestrogenica fenolica della formononetina .**

Estratto alcolico di Cimicifuga racemosa

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)

Effetti della Cimicifuga racemosa (*estratto ICR)* ***sulla mammella***

I dati a disposizione su Cimicifuga racemosa e mammella sono sia 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**
- **di aumentare l'efficacia antiproliferativa del tamoxifene**

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

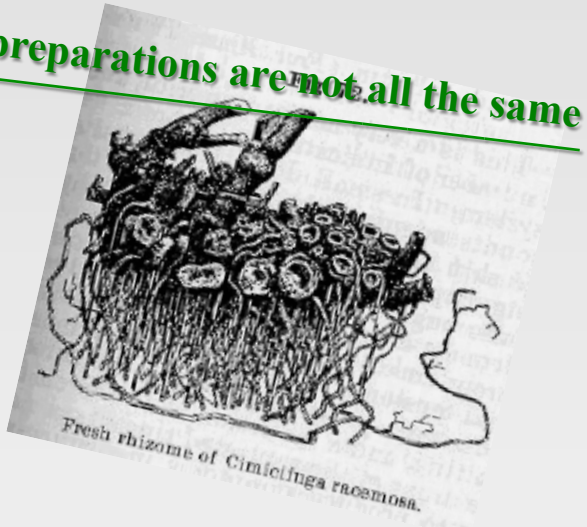
Black cohosh preparations are not all the same

Review Article

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

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

2013



- 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

ENDOCRINE DILEMMA

Managing menopausal symptoms after breast cancer

John Eden

...V, Locked bag 2000, Randwick,

Correspondence should be addressed to J Eden
Email
j.eden@unsw.edu.au

...east cancer offers some unique clinical challenges. For some ...and hormone therapy is at least relatively contraindicated. ...e, gabapentin and perhaps black cohosh extracts. ...urizers, although some may need specialized physiotherapy ...ay be the only treatment that works. The CO_2 laser may be a ...tom. Bone loss can be accelerated in some patients on AIs or

European Journal of Endocrinology
(2016) **174**, R71–R77

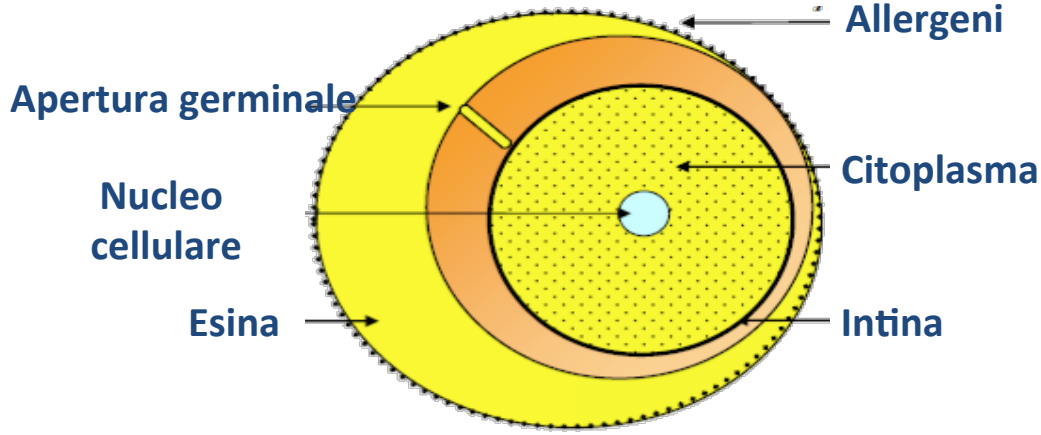
Table 1 Treatment options for menopausal women with a personal history of breast cancer.

Symptom	Treatment option
Hot flushes	Remifemin
	SSRIs
	Clonidine
	Gabapentin (Moderate-dose progestin) (HRT)
Vulvo-vaginal dryness	Soap-free washes
	Moisturizers
	Lubricants (CO_2 laser)
Osteoporosis	Bisphosphonates
	Denosumab
	Tamoxifen/Raloxifene

Cos'è Femal?

3 agenti attivi :

- **estratto di polline purificato** (GC Fem)
- mix di **polline citoplasmatico ed estratti di pistillo** (PI 82)
- **Vitamina E**



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

*Assicura una **concentrazione standard di agenti attivi in ogni compressa**:*
40 mg di GC Fem + 120 mg di PI + 5 mg di vitamina E

Non contiene fitoestrogeni

Meccanismo d'azione non ormonale

The pollen extract Femal—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.

- 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.

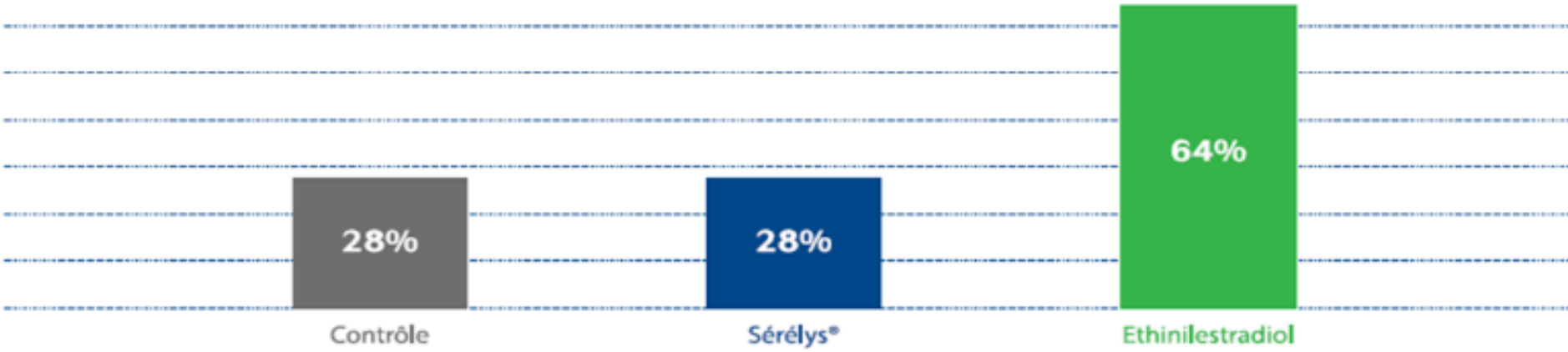
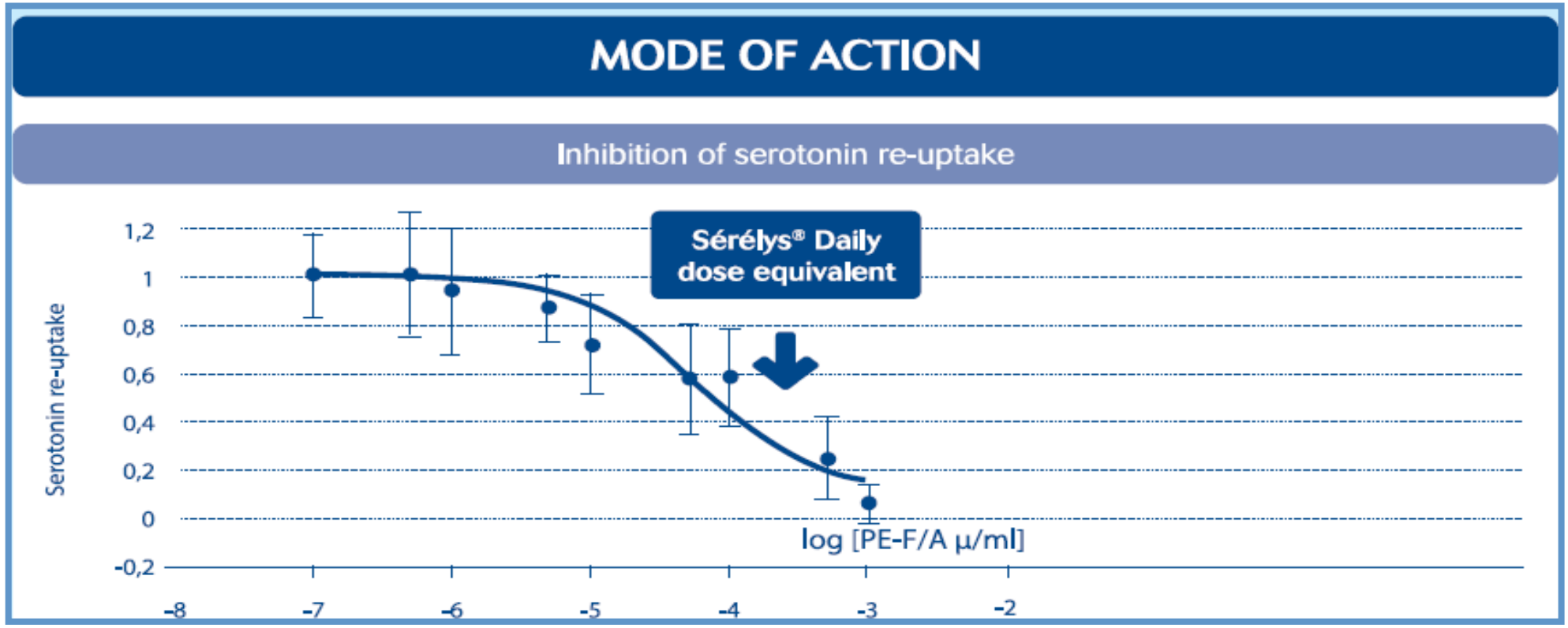


Figure 4. Uterotrophic effect of the PCP in Sérélys® and of the positive control Ethinilestradiol

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

Inibisce il re-uptake della serotonina nelle sinapsi della regione corticale



Druckman R, - EMAS 2015

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


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

- Studio in aperto;
- 417 donne in menopausa con sintomatologia quali vampate di calore, sudorazioni notturne, disturbi del sonno, alterazioni dell'umore;
- 2 compresse al giorno per 12 settimane.

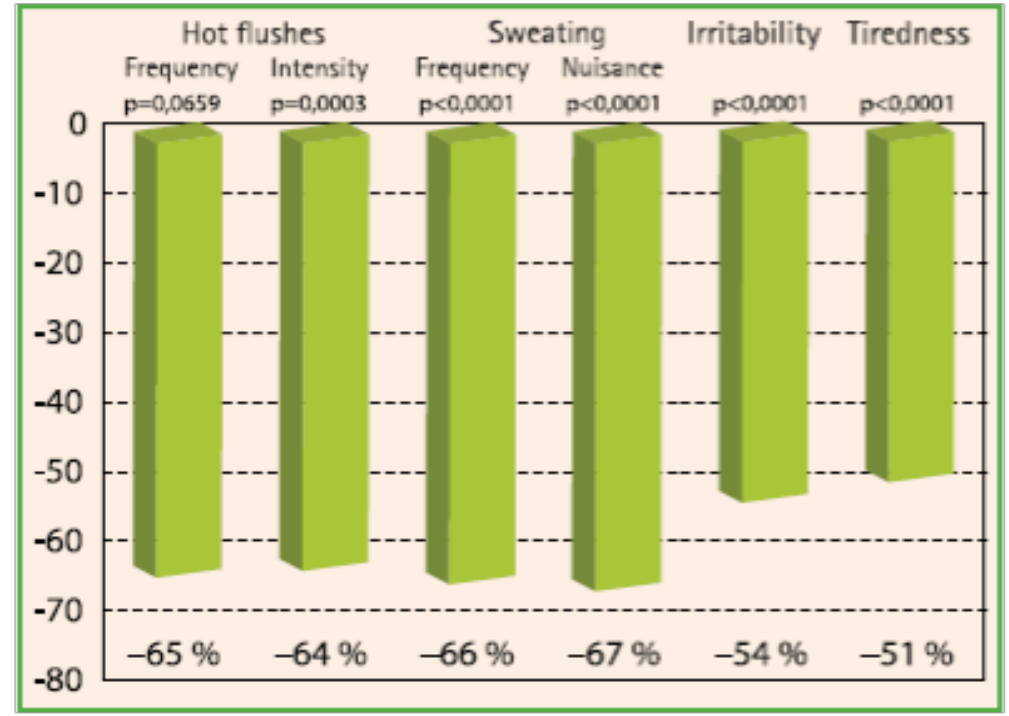
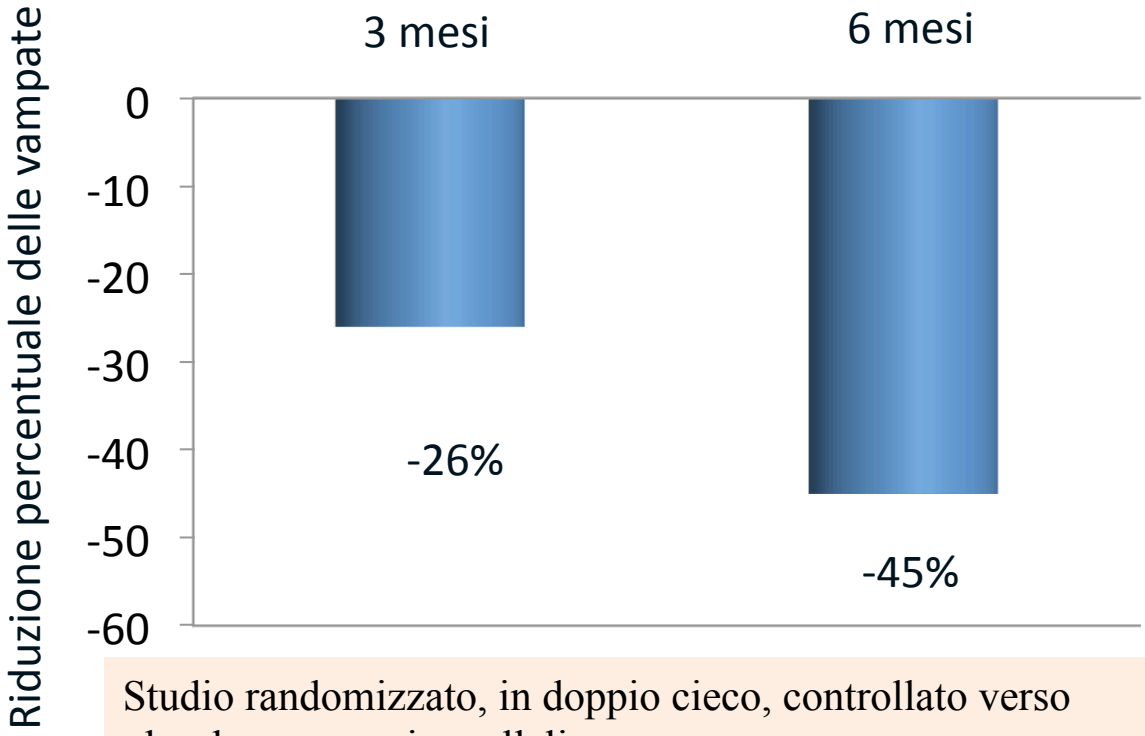


Figure 3: Reduction in symptoms on J84

Elia et al. Genesis 2008; 135

Significativa riduzione delle vampate di calore a 6 mesi con Femal (MRS)



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

Studio randomizzato, in doppio cieco, controllato verso placebo, a gruppi paralleli

64 donne in menopausa con sintomi da almeno 6 mesi

2 compresse di Femal o placebo al giorno

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

Femal non inibisce il complesso enzimatico che metabolizza il tamoxifene

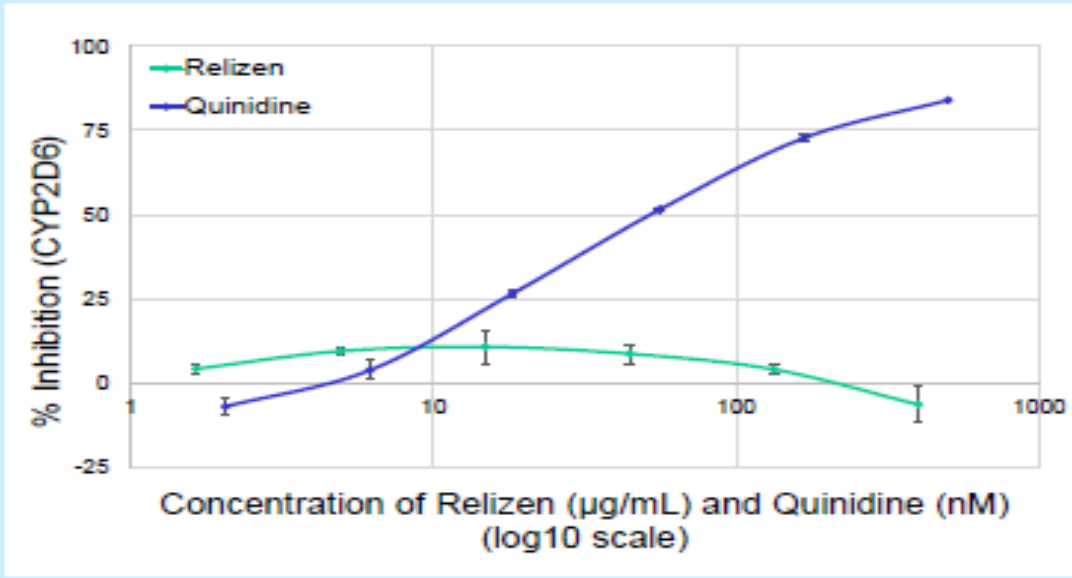


Figure 2. The *in vitro* dosage of Relizen (green) and Quinidine (blue) versus mean percent inhibition of CYP2D6 analyzed using LC-MS/MS. Each dosage was tested in triplicate. Percent inhibition increased linearly with Quinidine concentration, whereas percent inhibition failed to substantially increase with increased Relizen concentrations.

- 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