Nutraceutica e benessere femminile in menopausa

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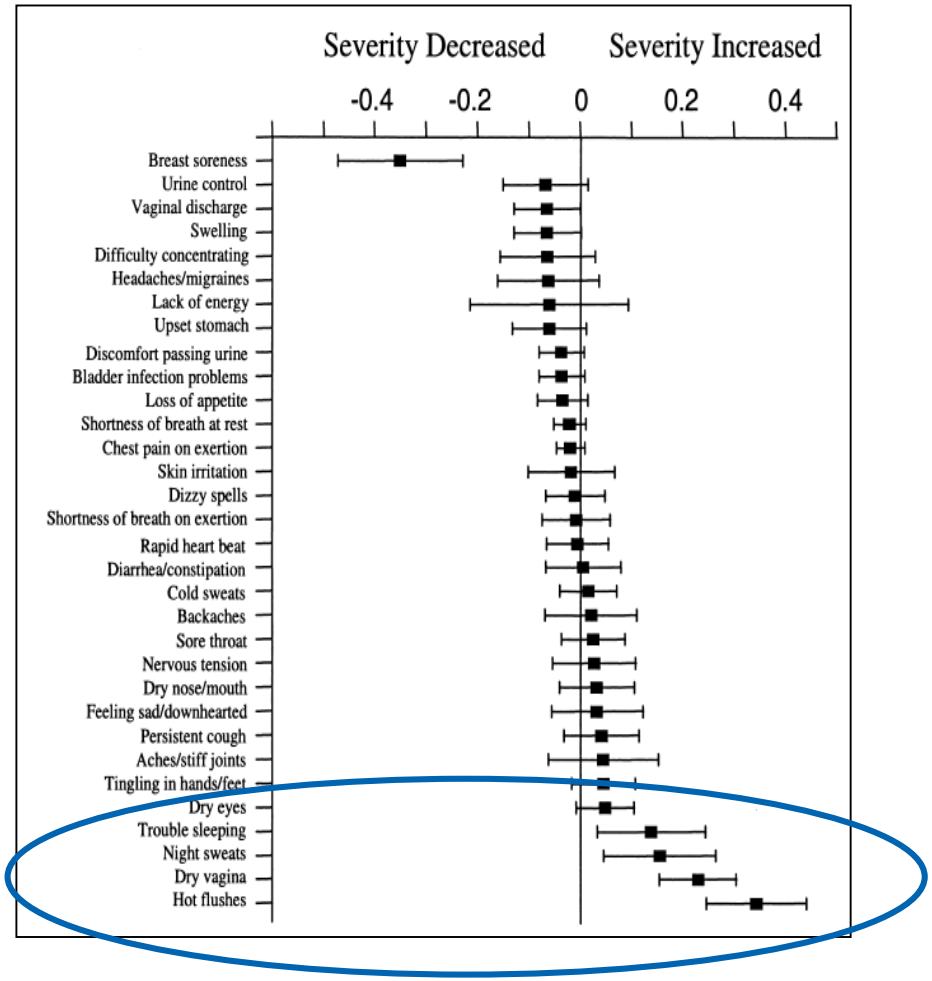
SINTOMI CLIMATERICI



Dennerstein et al. Obstet Gynecol 2000

Precoci

- Sintomi vasomotori e neurovegetativi:
  - *Vampate, palpitazioni (50-70%)*
  - *Disturbi del sonno e dell'umore (45-63%)*

Tardivi

- Osteoporosi
- Sindrome genito-urinaria
- Alterazioni connettivali
- Malattia cardiovascolare
- Declino cognitivo

CLIMACTERIC, 2017
http://dx.doi.org/10.1080/13697137.2017.1315089

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REVIEW

Vasomotor symptoms in menopause: a biomarker of cardiovascular disease risk and other chronic diseases?

N. Biglia[a], A. Cagnacci[b], M. Gambacciani[c], S. Lello[d], S. Maffei[e] and R. E. Nappi[f]

ABSTRACT

Menopausal disorders may include shorter-term symptoms, such as hot flushes and night sweats (vasomotor symptoms, VMS) and longer-term chronic conditions such as cardiovascular disease (CVD), osteoporosis, and cognitive impairment. Initially, no clear link between the shorter-term symptoms and longer-term chronic conditions was evident and these disorders seemed to occur independently from each other. However, there is a growing body of evidence demonstrating that VMS may be a biomarker for chronic disease. In this review, the association between VMS and a range of chronic postmenopausal conditions including CVD, osteoporosis, and cognitive decline is discussed. Prevention of CVD in women, as for men, should be started early, and effective management of chronic disease in postmenopausal women has to start with the awareness that VMS during menopause are harbingers of things to come and should be treated accordingly.

ARTICLE HISTORY
Received 7 December 2016
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KEYWORDS
Menopause; hot flushes; cardiovascular disease; vasomotor symptoms; biomarker; chronic disease

There is now a body of evidence demonstrating that menopausal symptoms, in particular VMS, may be considered precursors or biomarkers of chronic disease, such as CVD, osteoporosis, and cognitive decline.

Trend assunzione TOS in Italia (2000-2010)

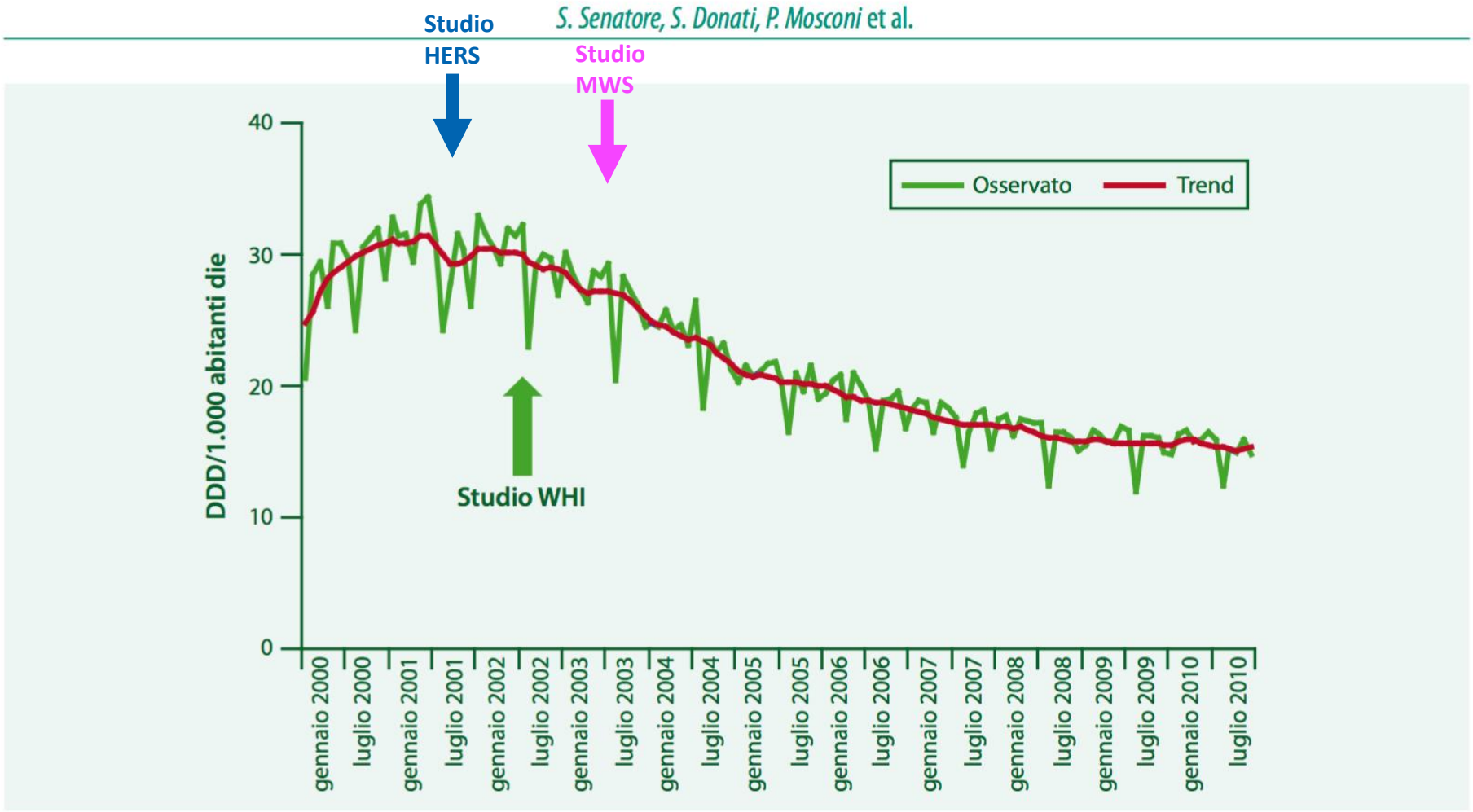

Figura 1 - Farmaci per la terapia ormonale in menopausa, andamento temporale del consumo territoriale di classe A - Servizio Sanitario Nazionale (2000-2010). Fonte: OsMed (elaborazione dati: Reparto di Farmacoepidemiologia, CNESPS, ISS)

Maturitas 81 (2015) 410–413

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

EMAS position statement: Non-hormonal management of menopausal vasomotor symptoms

Gesthimani Mintziori[a], Irene Lambrinoudaki[b], Dimitrios G. Goulis[a,*], Iuliana Ceausu[c], Herman Depypere[d], C. Tamer Erel[e], Faustino R. Pérez-López[f], Karin Schenck-Gustafsson[g], Tommaso Simoncini[h], Florence Tremollieres[i], Margaret Rees[j]

- **Lifestyle modifications and diet**

- **Non-hormonal pharmacological interventions**

(neuroactive agents: selective serotonin-reuptake inhibitors (SSRIs), serotonin norepinephrine-reuptake inhibitors (SNRIs) and gabapentin; NK3R neurokinin3 receptor antagonist)

- **Alternative and complementary medicine**

(acupuncture, hypnosis, yoga, etc)

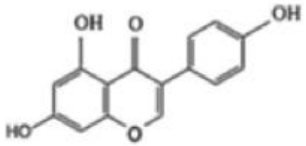
FITOESTROGENI

- ✓ Ubiquitari nel **mondo vegetale**, concentrazioni elevate si riscontrano nella soia e, anche se in quantità inferiori, in molti tipi di frutta, verdure e cereali integrali.
- ✓ Sono classificati secondo differenti classi: **isoflavoni, cumestani, lignani e prenil-flavonoidi**, sono le principali classi di fitoestrogeni presenti nelle piante ad uso alimentare umano.
- ✓ Pur non essendo di natura steroidea (sono fenoli eterociclici), funzionalmente e anche in parte strutturalmente, sono **simili al 17 beta estradiolo**.
- ✓ In virtù di questa analogia strutturale, essi competono per gli **stessi siti recettoriali** degli estrogeni endogeni dei quali condividono la stessa affinità, possedendo, però, una capacità di attivazione mille volte inferiore.
- ✓ Per le loro caratteristiche biochimiche e funzionali, possono avere **sia effetti estrogenici che antiestrogenici,** modulando eventuali carenze o eccessi degli steroidi endogeni.

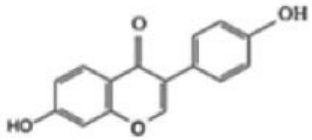
Chawalitpong et al., European Journal of Pharmacology, 2016

Fitoestrogeni

Isoflavones



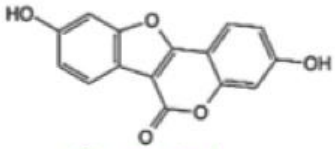
Genistein



Daidzein

Soia, legumi, trifoglio rosso

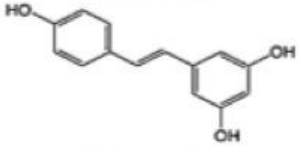
Coumestans



Coumestrol

Broccoli, cavoli di Bruxelles, semi di girasole

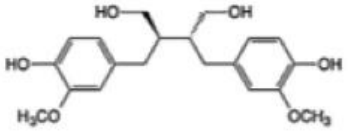
Stilbenoids



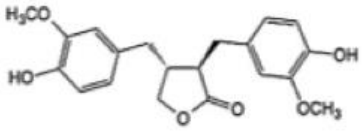
Resveratrol

Vitis vinifera

Lignans

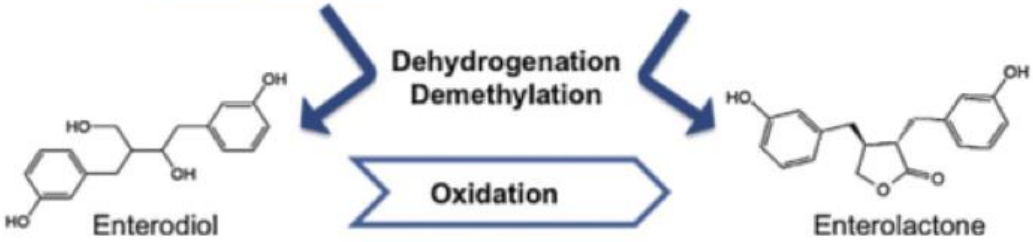


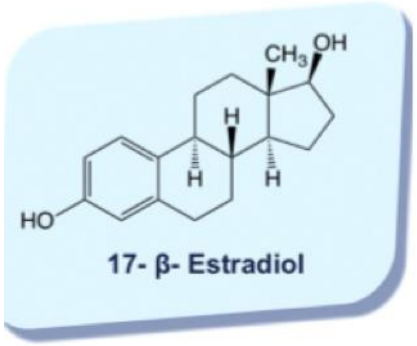
Secoisolariciresinol



Matairesinol

Frutta, noci, cereali, semi di lino





Moreira et al., Journal of Steroid Biochemistry and Molecular Biology, 2014

Affinità recettoriale selettiva

phytoSERMs

- Potenza 500-10000 volte inferiore a quella di E2
- Selettività specifica per ER-β
- **Isoflavoni e lignani** (struttura simile ad E2):
  - Agonista se E2 basso
  - Antagonista se E2 alto
- **Coumestrolo e Genisteina** maggiore potenza estrogenica

Potenza estrogenica relativa	
Estradiolo	100
Genisteina	0.084
Equolo	0.061
Daidzeina	0.0013

Affinità recettoriale		
	ER-α	**ER-β**
Estradiolo	100	100
Genisteina	4	87
Daidzeina	0.1	0.5

Fitoestrogeni: meccanismo d'azione

- Interazione con i recettori estrogenici per modulare l'espressione dei geni estrogeno-rispondenti;
- Inibizione degli enzimi coinvolti nel metabolismo e nella biosintesi degli estrogeni (chinasi-proteica, aromatasi, topoisomerasi,…);
- Interazione con i componenti del ciclo cellulare (proliferazione, differenziazione e apoptosi);
- Reazioni antiossidanti.

Chawalitpong et al., European Journal of Pharmacology, 2016

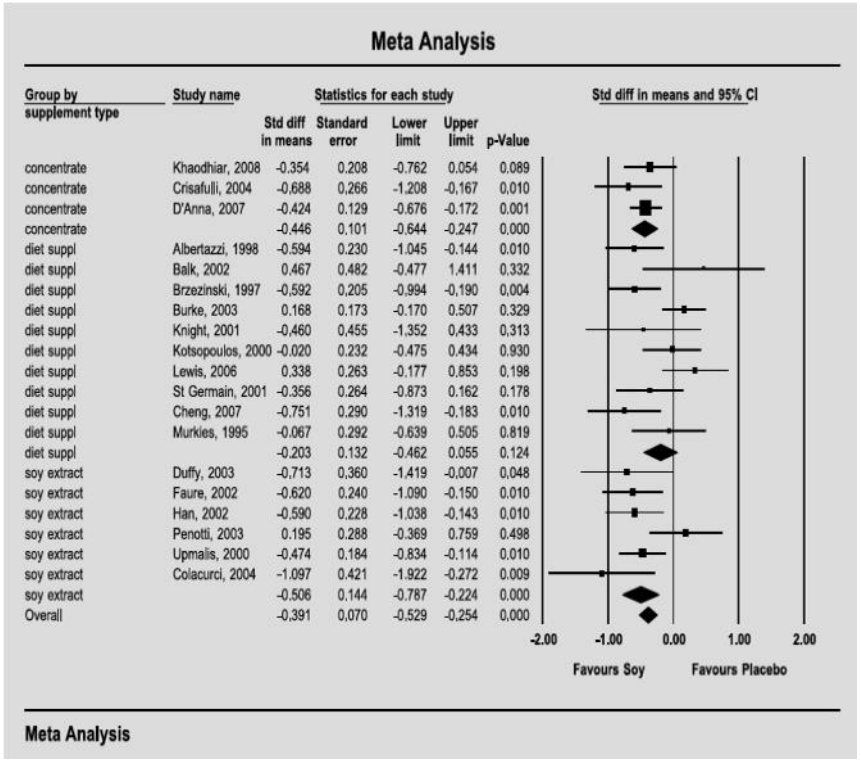
Menopause: The Journal of The North American Menopause Society
Vol. 17, No. 3, pp. 660-666
DOI: 10.1097/gme.0b013e3181cb4fb5

19 RCTs, Review 2010

REVIEW ARTICLE

Soy isoflavones versus placebo in the treatment of climacteric vasomotor symptoms: systematic review and meta-analysis

Rafael Bolaños, MD, MSc,[1] Angélica Del Castillo, MD,[2] and José Francia, MD, MSc[3]

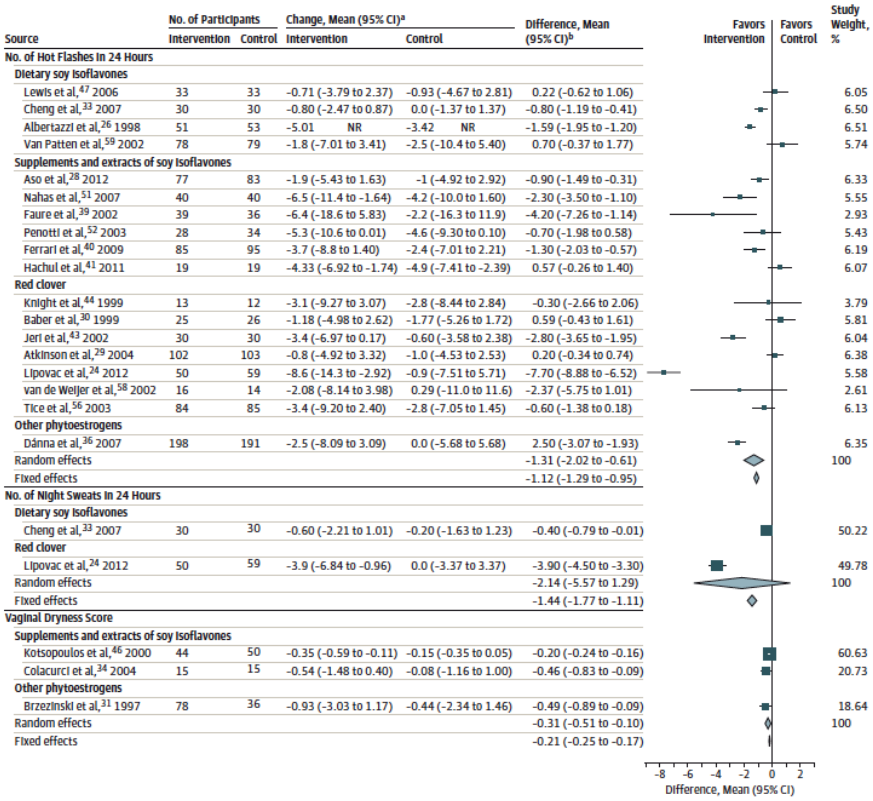


Original Investigation

Use of Plant-Based Therapies and Menopausal Symptoms
A Systematic Review and Meta-analysis

Oscar H. Franco, MD, PhD; Rajiv Chowdhury, MD, PhD; Jenna Troup, MSc; Trudy Voortman, PhD; Setor Kunutsor, MD, PhD; Maryam Kavousi, MD, PhD; Clare Oliver-Williams, PhD; Taulant Muka, MD, PhD

21 RCTs, Review 2010



Conclusions: Although the overall combined results and the results by subgroups (according to the type of supplement used) showed a **significant tendency in favor of soy**, **it is still difficult to establish conclusive results given the high heterogeneity found in the studies**.

Phytoestrogens for menopausal vasomotor symptoms (Review)

Lethaby A, Marjoribanks J, Kronenberg F, Roberts H, Eden J, Brown J

43 RCTs, 2013

THE COCHRANE COLLABORATION®

Authors' conclusions

No conclusive evidence shows that phytoestrogen supplements effectively reduce the frequency or severity of hot flushes and night sweats in perimenopausal or postmenopausal women, although benefits derived from concentrates of genistein should be further investigated.

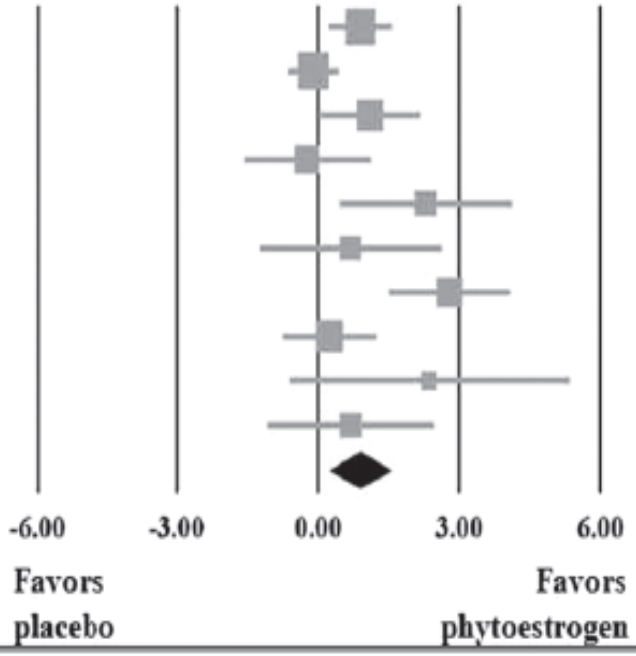
CLIMACTERIC 2015;18:260–269

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

10 RCTs, 2015

M-N. Chen, C-C. Lin and C-F. Liu†*

Study name	Sample size	Mean difference (95%CI)	P-value	Forest plot for mean difference (95% CI)	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		



Conclusion: Phytoestrogens appear to reduce the frequency of hot flushes in menopausal women, without serious side-effects.

GYNECOLOGICAL ENDOCRINOLOGY
https://doi.org/10.1080/09513590.2019.1621835

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ORIGINAL ARTICLE

Acupuncture or phy(F)itoestrogens *vs.* (E)strogen plus progestin on menopausal symptoms. A randomized study

Federica Palma[a], Francesca Fontanesi[b], Fabio Facchinetti[a] and Angelo Cagnacci[c]

Arm 1 - low dose HRT per os for 12 weeks (Conjugated Equine Estrogens 0.3 mg + acetate medroxyprogesterone 1.5 mg daily).

Arm 2 - Soy isoflavones per os for 12 weeks (75 mg twice daily).

Arm 3 - Acupuncture, performed once a week for 12 consecutive weeks.

No serious adverse effects

	HT ($n = 25$)	Acupuncture ($n = 24$)	Phytoestrogens ($n = 23$)
Greene			
Vasomotor	$-2.0 \pm 1.9^{*}$	$-2.2 \pm 2.3^{*,\S}$	$-0.8 \pm 2.0^{*,**}$
Anxiety	-1.4 ± 3.1	$-3.0 \pm 4.2^{*}$	-0.6 ± 3.5
Depression	-0.8 ± 2.7	-0.5 ± 2.2	$-1.1 \pm 2.6^{*}$
Somatic	-1.3 ± 0.9	-0.8 ± 3.2	-0.8 ± 2.7
Sexuality	0.0 ± 0.7	-0.4 ± 1.3	-0.1 ± 1.3
Total	$-5.6 \pm 3.1^{*}$	$-6.9 \pm 4.5^{*}$	$-3.4 \pm 4.3^{*,**}$

Results of a *post-hoc* analysis comparing the effect of the different treatments is also reported.
Data are presented as mean ± SD.
$^{*}p < .05$, measured by paired t-test (3 months-baseline).
$^{**}p < .05$ *vs.* HT; by ANOVA, followed by the *post-hoc* test of Dunnett.
§significant *vs.* phytoestrogens (see text).

Fitoestrogeni e funzionalità sessuale

TRIGONELLA
(*Trigonella foenum-graecum*)

Trigonella foenum-graecum migliora la funzione digestiva e il metabolismo dei carboidrati, trigliceridi e del colesterolo. Aumenta I livelli di testosterone libero e incrementa eccitazione e desiderio nelle donne.[1]

TRIBULUS
(*Tribulus terrestris*)

Tribulus terrestris ha un'azione tonica sulla fatica fisica e mentale. Ha dimostrato di migliorare la funzione sessuale nelle donne con disturbo del desiderio sessuale ipoattivo. [2]

DAMIANA
(*Turnera aphrodisiaca*)

La Damiana ha un azione tonica sulla fatica fisica e mentale e aiuta il drenaggio dei liquidi corporei. Inibisce l'aromatasi, l'enzima che trasforma il testosterone in estradiolo. [3]

FITOSOMAS DE *Ginkgo biloba*

Ha azione antiossidante, sulla memoria e sulle funzioni cognitive, contribuisce alla normale circolazione sanguigna e alla funzionalità del microcircolo. Questi effetti sono parte della risposta sessuale nelle donne. [4]

1. Rao A, Steels E, Beccaria G, Inder WJ, Vitetta L. Influence of a specialized Trigonella foenum-graecum seed extract (Libifem), on testosterone, estradiol and sexual function in healthy menstruating women, a randomised placebo controlled Study. Phytother Res. 2015;29(8):1123–30.
2. Akhtari E, Raisi F, Keshavarz M, Hosseini H, Sohrabvand F, Bioos S, Kamalinejad M. Ghobadi A. Tribulus terrestris for treatment of sexual dysfunction in women: randomized double-blind placebo - controlled study. Daru. 2014;22:40.
3. Zhao J, Dasmahapatra AK, Khan SI, Khan IA. Anti-aromatase activity of the constituents from Damiana (Turnera diffusa). J Ethnopharmacol. 2008;120(3): 387–93.
4. Meston CM, Rellini AH, Telch MJ. Short- and long-term effects of Ginkgo biloba extract on sexual dysfunction in women. Arch Sex Behav. 2008 August ; 37(4): 530–547.

Palacios *et al. BMC Women's Health* (2019) 19:58
https://doi.org/10.1186/s12905-019-0755-9

BMC Women's Health

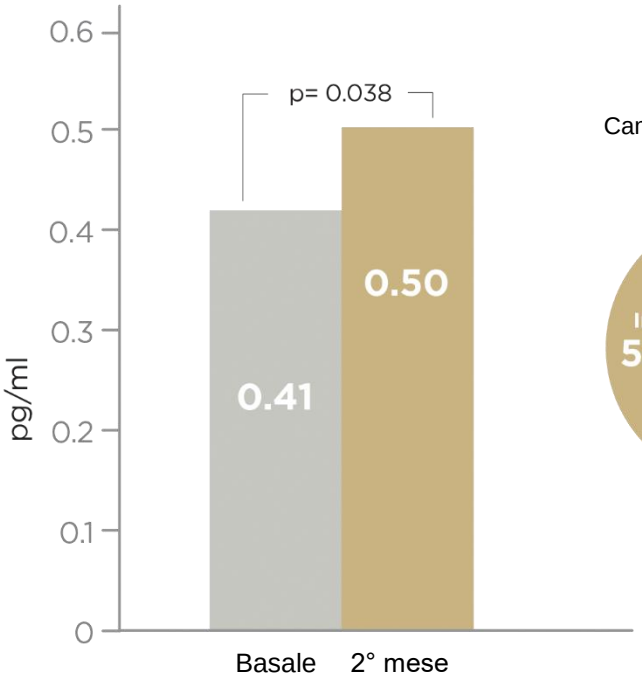
RESEARCH ARTICLE Open Access

Effect of a multi-ingredient based food supplement on sexual function in women with low sexual desire

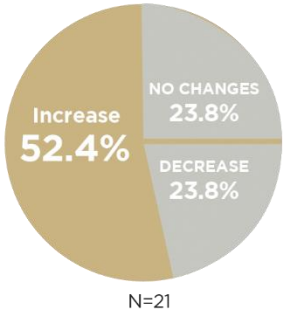
S. Palacios[1*], E. Soler[1], M. Ramírez[1], M. Lilue[1], D. Khorsandi[2,3] and F. Losa[4]

29 pazienti (età media: 53.9 anni)

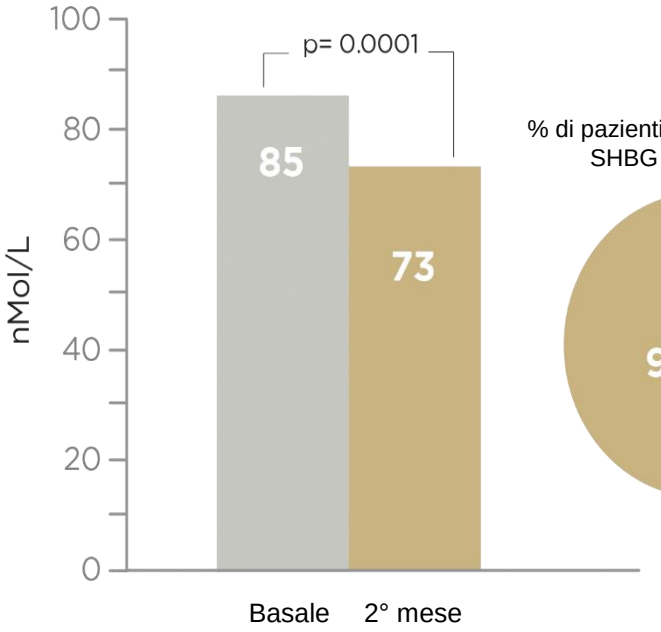
LIVELLI DI TESTOSTERONE E SHBG



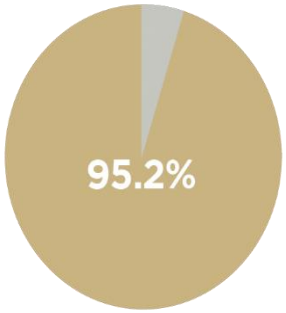
Cambiamenti nei livelli di testosterone (% di pazienti)



N=21

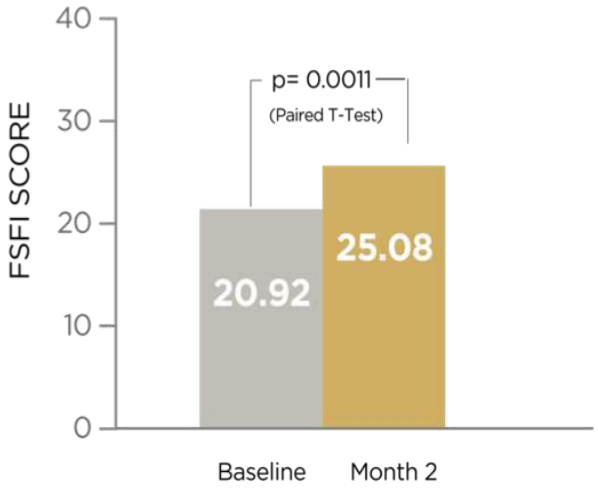


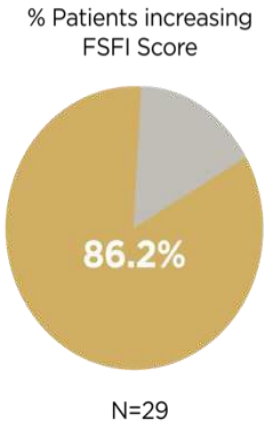
% di pazienti nelle quali i livelli di SHBG sono diminuiti



N=21

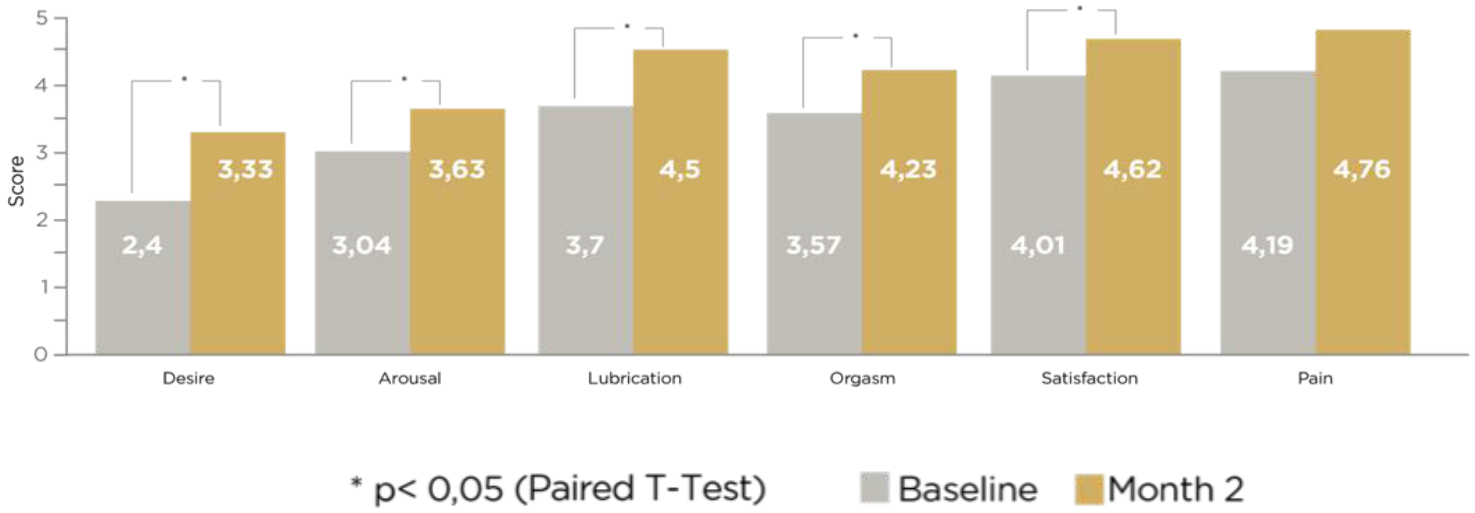
FSFI TOTAL SCORE





Nessun evento avverso segnalato.

FSFI DOMAIN SCORES



Palacios et al.; BMC Women's health 2019, 19:58

Risultati contrastanti: perché???

- La capacità dei fitoestrogeni di esplicare le loro proprietà è in funzione di:

- ***assorbimento,***
- ***metabolismo,***
- ***distribuzione negli organi target,***
- ***escrezione***.

- Le variabili che influenzano la farmacocinetica dei fitoestrogeni sono:

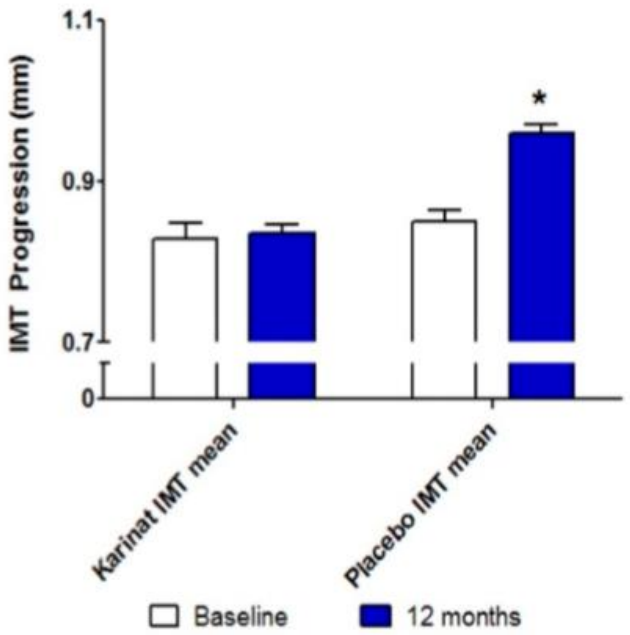
- ***la composizione della flora batterica intestinale,***
- ***il tempo di transito intestinale,***
- ***le malattie intestinale,***
- ***i farmaci,***
- ***la dieta, etc***.

Fitoestrogeni e rischio cardiovascolare

Assetto metabolico

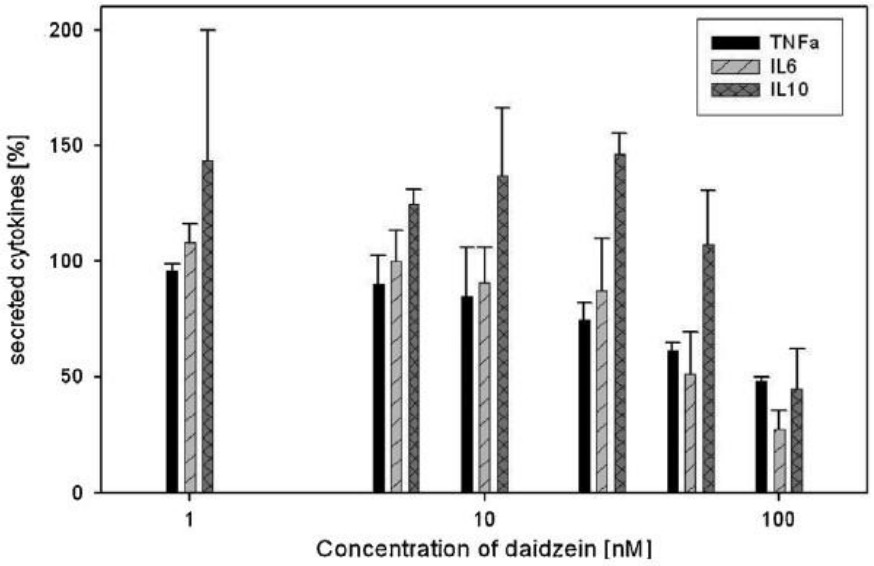
Variable	Isoflavonoid-Rich Herbal Preparation Recipients, $n = 56$		Placebo Recipients, $n = 71$	
	Change	p-Value	Change	p-Value
Body mass index, kg/m^2	−0.01 (0.8)	0.978	−0.07 (1.6)	0.708
Systolic BP, mm·Hg	5 (19)	0.051	−1 (18)	0.666
Diastolic BP, mm·Hg	−1 (8)	0.806	−1 (9)	0.150
Total cholesterol, mg/dL	−17 (46)	0.011	−13 (41)	0.020
Triglycerides, mg/dL	−9 (53)	0.232	−9 (40)	0.106
HDL-C, mg/dL	−3 (11)	0.114	−3 (12)	0.038
LDL-C, mg/dL	−13 (45)	0.040	−8 (39)	0.126

Aterosclerosi carotidea

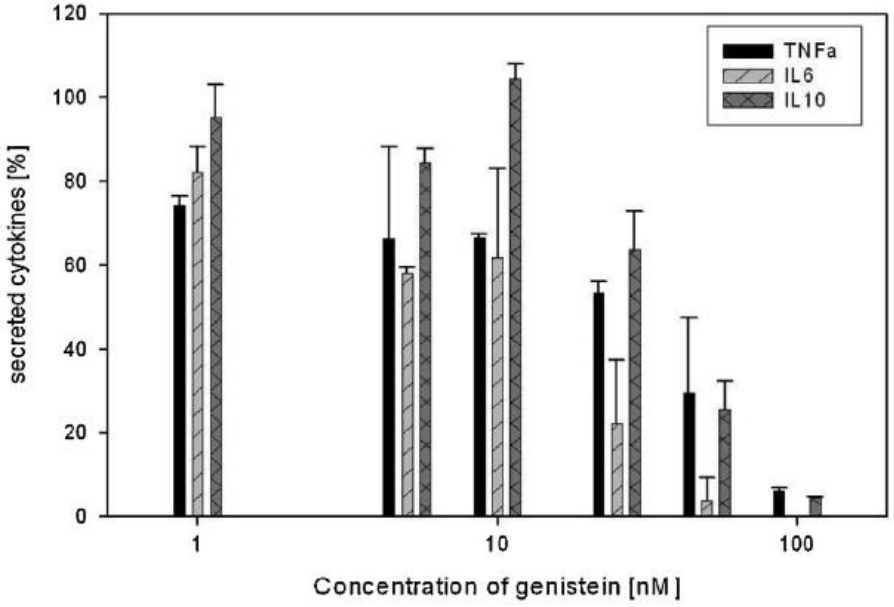


Myasoedova et al., International Journal of Molecular Sciences, 2016

Effetto antinfiammatorio



DAIDZEINA

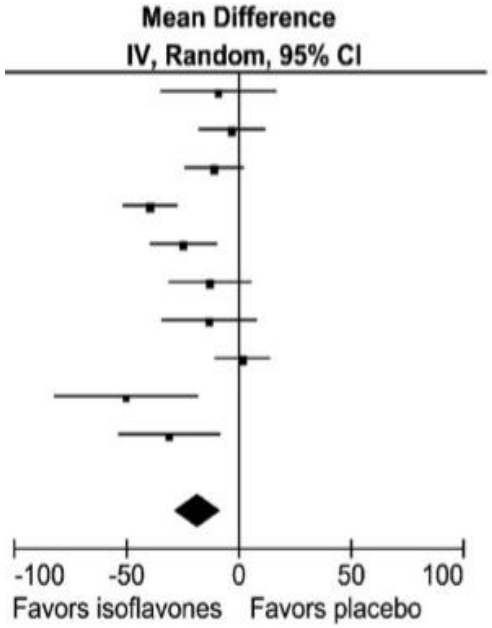


GENISTEINA

Jungbauer et al., Journal of Steroid Biochemistry and Molecular Biology, 2012

Fitoestrogeni e osso

Urine DPD



- ✓ Aumento significativo del **BMD solo a livello della colonna vertebrale** e non effetti significativi sul BMD femore (3 meta-analisi);
- ✓ **Riduzione significativa del marker di riassorbimento osseo DPD** e non effetti sui markers di osteoformazione (fosfatasi alcalina e osteocalcina) (2 meta-analisi);
- ✓ Risultati significativi se:
  - durata di trattamento di almeno 6 mesi;dosi >= 75 mg/die di Isoflavoni (estratti) o proteinato di soia
  - donne in postmenopausa osteopeniche e/o osteoporotiche;
- ✓ Significativa eterogenieità tra gli studi;
- ✓ **No studi clinici sulla prevenzione delle fratture**.

Atmaca et al., Menopause, 2008
Wel et al., Asian Pacific J Trop Med, 2012
Lambert et al., Am J Clin Nutr, 2017
Taku et al., Bone, 2010

Fitoestrogeni:recidiva e sopravvivenza x k mammella

Ref	Cohort Name	CohortN	Cases N	Geographic area	Menopause status	Tamoxifen Use?	Anastrozole Use?	Herceptin Use?	Exposure*	High quartile	Study duration	Years f/u**	Outcome
Kang 2012	Mongolia Medical College	288	125	China	Pre and post	Y: 206	NR	NR	Soy protein & IF	>15.78g protein; >35.30mg IF	2004-2011	5-7y	↑Survival
Woo 2012	Korean cohort	339	25	Korea	Pre and post	Y: n=195	NR	Y: n=28	Soyfoods& soy IF	≥65.7g soyfood; ≥15.2mg IF	2007-2008+	32.6mo	↔Recurrence
Zhang 2012	Mongolia Medical College	616	79 (deaths)	China	Pre and post	40-60%	NR	NR	Soy protein & IF	>13.03g protein; >28.83mg IF	2004-2006+	52.1mo	↑Survival
Caan 2011	WHEL	2736	271	USA	Pre and post	~66%	NR	NR	Soy IF	>16.33mg IF	1991-2006	7.3	↔Survival ↔Recurrence
Kang 2010	Harbin, China	524	185 (recur)	China	Pre and post	100% T or A	100% T or A	NR	Soy IF	>42.3mg IF	2002-2008	5.1	↔Survival ↓Recurrence (postM)
Guha 2009	LACE	1954	282	USA	Pre and post	20-40%	NR	NR	Genistein intake	>13.02mg genistein	2000-2008	6.31	↔Recurrence
Shu 2009	SBCSS	5042	534 (recur)	Shanghai	Pre and post	Y: n=2622	NR	NR	Soy protein & IF	>15.31g protein; >62.68mg IF	2002-2009	3.9	↓Recurrence ↑Survival
Fink 2007	Long Island BrCa Study	1210	113 (deaths)	USA	Pre and post	NR	NR	NR	Soy IF	≥7.48mg IF	1996-2002	~6	↑Survival
Boyapati 2005	Shanghai Breast Cancer study	1459	216 (deaths)	Shanghai	Pre and post	NR	NR	NR	Soyfoods	NR	1996-2002	5.2	↔Survival

Fritz et al., Plos One, 2013

Gynecological Endocrinology

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

Marzo 2016

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

- 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**. This is an important message to give to the patients. On the risk side fewer adverse effects and a high patient compliance can be expected.
- Additional **beneficial effects** may be expected for the **bones**.
- High exposure to isoflavones is associated with **reduced breast cancer risk**.

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- 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 150 mg isoflavones daily and a duration of intake of up to 3 years**.

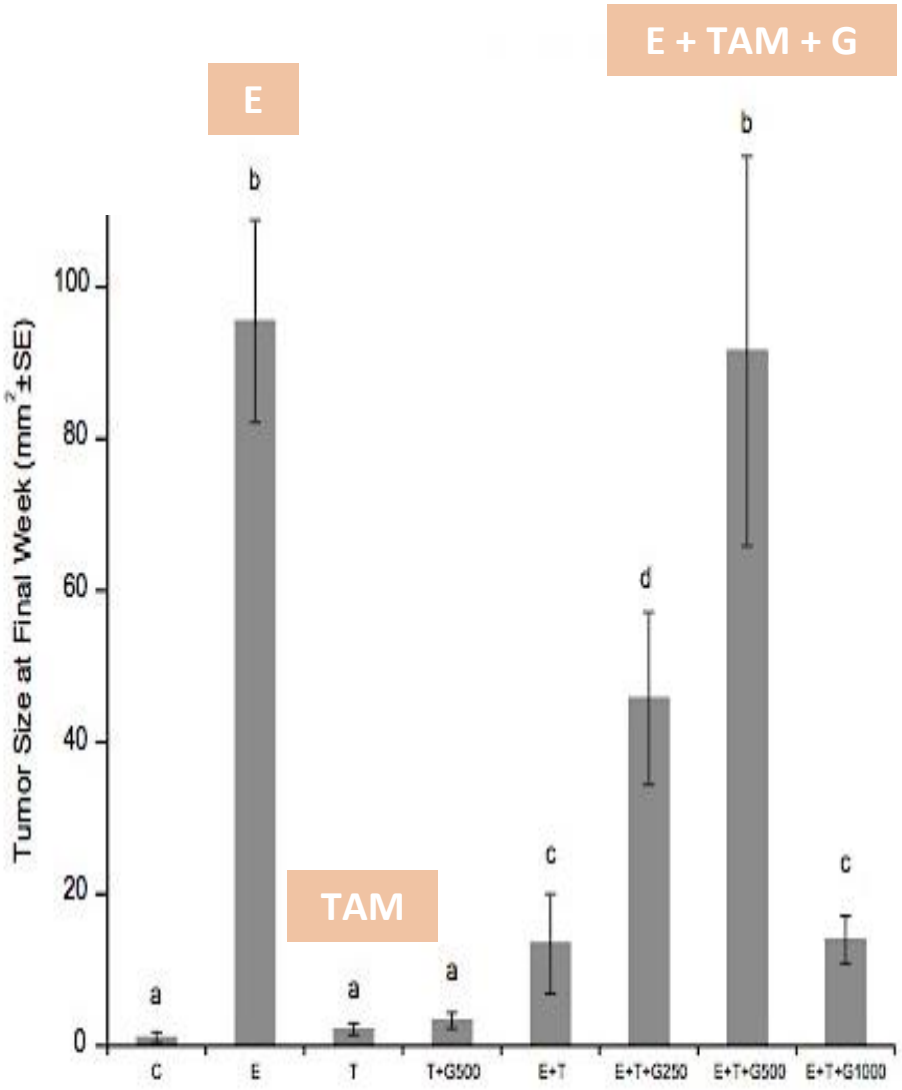
- Summarizing, isoflavones can be recommended as first-line treatment of natural menopausal hot flushes.

Carcinogenesis vol.33 no.4 pp.895–901, 2012
doi:10.1093/carcin/bgs017
Advance Access publication January 20, 2012

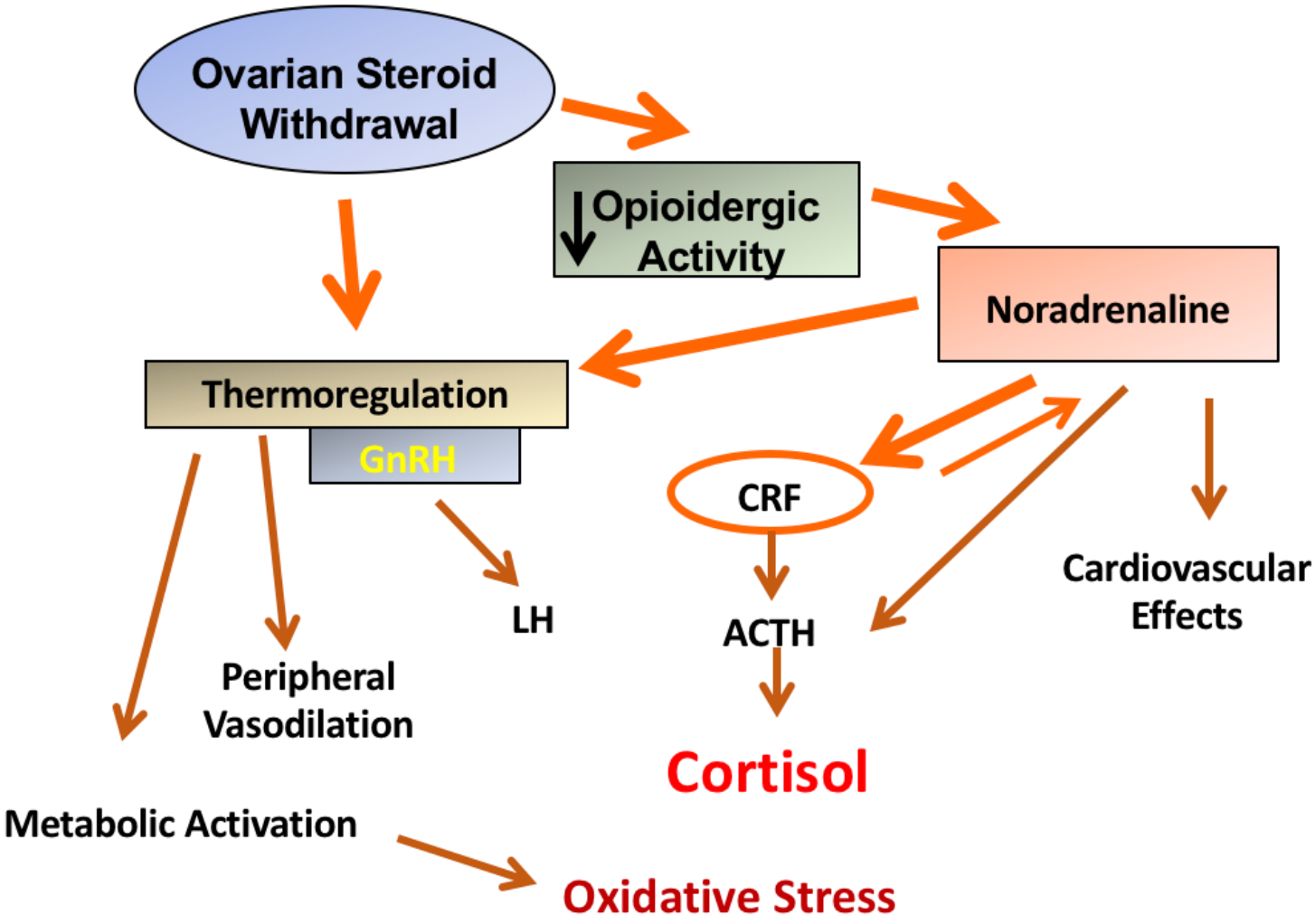
Low-dose dietary genistein negates the therapeutic effect of tamoxifen in athymic nude mice

Mengyuan Du[1,2,†], Xujuan Yang[2,†], James A.Hartman[2], Paul S.Cooke[3], Daniel R.Doerge[4], Young H.Ju[5] and William G.Helferich[1,2,*]

- The low doses of dietary genistein abrogated the inhibitory effect of tamoxifen potentially by acting on the tumor cell proliferation/apoptosis ratio and the messenger RNA (mRNA) expression of cyclin D1 in addition to regulating the mRNA expression of progesterone receptor.
- **Data from the current study suggest that caution is warranted regarding the consumption of dietary genistein by breast cancer patients while on tamoxifen therapy.**



PATOGENESI DELLE VAMPATE



Casper and Yen, 1985

CIMICIFUGA RACEMOSA

Pianta non alimentare: rizoma e radici vengono utilizzate fresche o in forma essiccata.

La Cimicifuga possiede diversi costituenti chimici:

- I ***glucosidi triterpenici*** costituiscono la principale componente bioattiva presente nell'estratto alcolico responsabili degli effetti terapeutici;
- L'estratto isopropilico utilizzato in fitoterapia risulta **privo della componente fitoestrogenica fenolica della formononetina.**

È commercializzato in Italia con autorizzazione ministeriale come **Integratore alimentare.**

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

Risposta differenziata in base al tipo di estratto: **efficacia e sicurezza dimostrati per estratto isopropilico ed estratto alcolico, titolati e standardizzati.**

Meccanismi d'azione:

- **antagonista competitivo degli estrogeni** a livello dei recettori estrogenici **(agonista su SNC e osso, antagonista su mammella, assenza di agonismo su utero e vagina);**

- **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).

Beer et al.,Evid Based Complement Alternat Med. 2013

Available online at www.sciencedirect.com
ScienceDirect
Maturitas 58 (2007) 31–41
MATURITAS
THE EUROPEAN MENOPAUSE JOURNAL
www.elsevier.com/locate/maturitas

Clinical trial paper

Efficacy and tolerability of a medicinal product containing an isopropanolic black cohosh extract in Chinese women with menopausal symptoms: A randomized, double blind, parallel-controlled study versus tibolone

Wenpei Bai [a], Hans-Heinrich Henneicke-von Zepelin [b,*], Shuyu Wang [c], Shurong Zheng [a], Jianli Liu [d], Zhonglan Zhang [d], Li Geng [e], Lina Hu [f], Chunfeng Jiao [g], Eckehard Liske [b,1]

Cimicifuga vs Tibolone

244 menopausal patients with a Kupperman Menopause Index (KMI)≥15.

RTC:

iCR corresponding to 40 mg crude drug/day (N= 122)
vs
tibolone 2.5 mg/day (N= 122) orally.

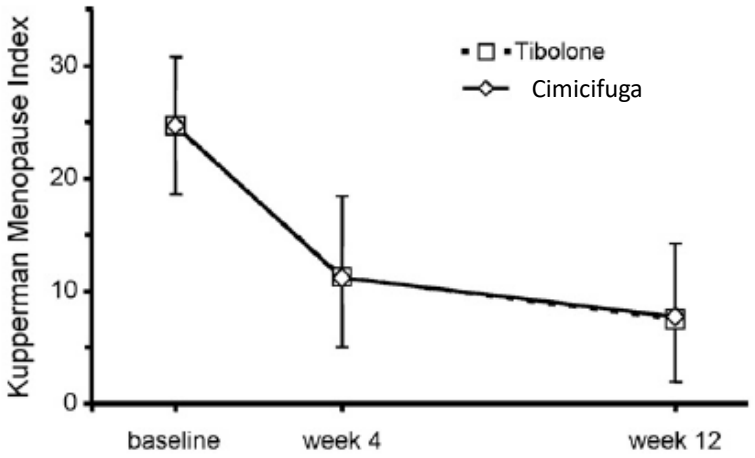


Fig. 1. Time course of the Kupperman Index in the full analysis set, baseline-adjusted data. Mean ± S.D. are shown.

The efficacy of iCR (medicinal product Remifemin®) is as good as tibolone for the treatment of climacteric complaints, even for moderate to severe symptoms, whereby iCR is clearly superior regarding the safety profile.

Gynecol Endocrinol. 2005 Jan;20(1):30-5.

Efficacy of Cimicifuga racemosa on climacteric complaints: a randomized study versus low-dose transdermal estradiol.

Nappi RE[1], Malavasi B, Brundu B, Facchinetti F.

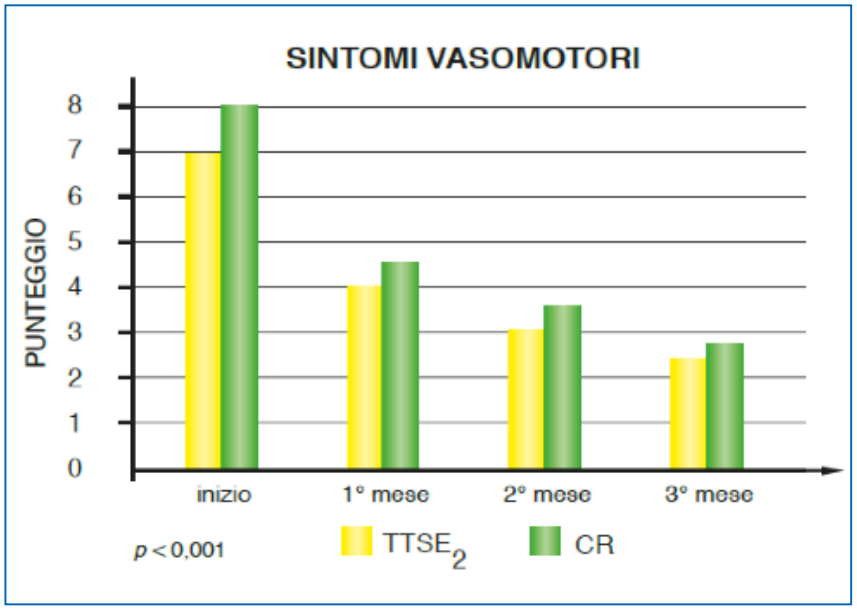
▼ Studio prospettivo multicentrico randomizzato

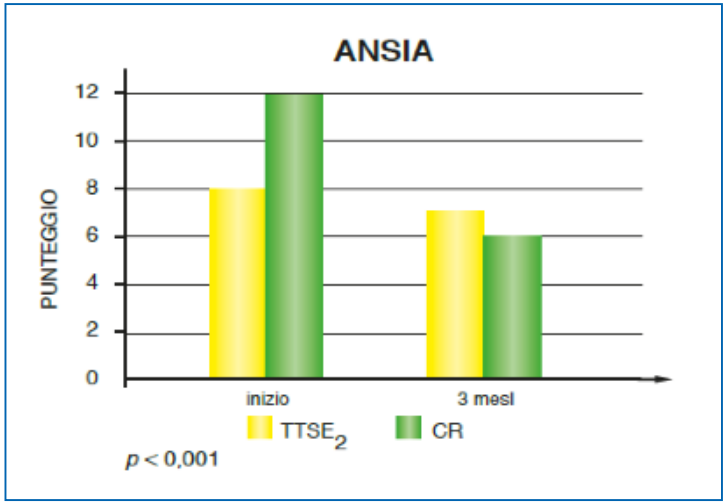
64 DONNE IN POSTMENOPAUSA

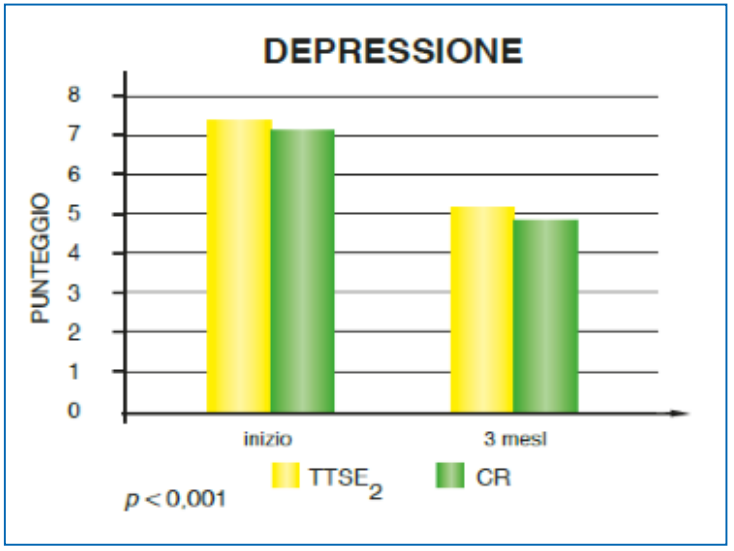
Terapia 1° gruppo: 25 µg estradiolo per via transdermica (TTSE2) per 3 mesi.

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

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





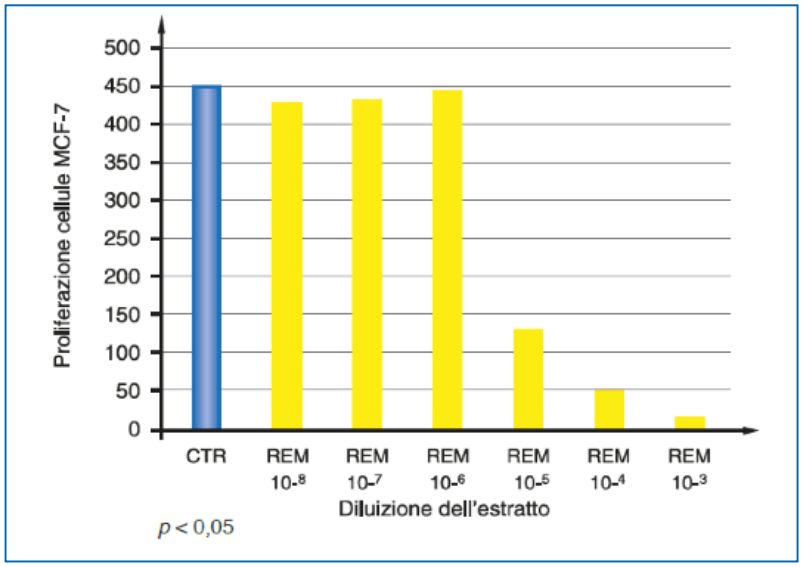


Breast Cancer Res Treat. 2002 Nov;76(1):1-10.

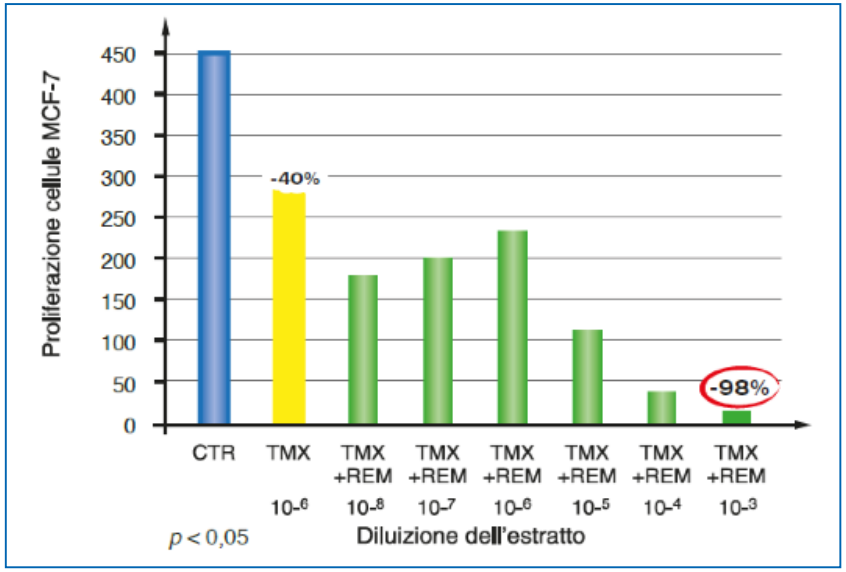
Influence of Cimicifuga racemosa on the proliferation of estrogen receptor-positive human breast cancer cells.

Bodinet C[1], Freudenstein J.

iCR inibisce in vitro la proliferazione di cellule di k seno MCF-7



iCR aumenta effetto inibitorio del Tamoxifene su MCF-7 fino al 98%



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 (a differenza degli SSRI)**

ESTRATTO DI POLLINE PURIFICATO

phytoSSRI

Menopause: The Journal of The North American Menopause Society
Vol. 19, No. 7, pp. 825-829
DOI: 10.1097/gme.0b013e31824017bc

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]

Concentrazioni di isoflavoni in estratto di polline

TABLE 1. *Concentration of common isoflavonoid phytoestrogens in the pollen extracts PI 82 and GC FEM*

	Isoflavonoid concentration in the extracts, ng/mg extract					
Extract and batch	Daidzin	Genistin	Daidzein	Genistein	Formononetin	Biochanin A
PI 82						
570005101	94	9	22	nd	nd	nd
570008101	79	15	nd	nd	nd	nd
570009101	48	9	nd	nd	nd	nd
GC FEM						
578907103	59	nd	14	nd	nd	nd
578908101	50	13	11	nd	nd	nd
578909101	28	nd	10	nd	nd	nd

nd, not detected.

Effetto uterotropico dell'estratto di polline

TABLE 2. *Uterotropic effect of the pollen extracts in Femal, PI 82 and GC FEM, and its vehicle, and of the positive control ethinylestradiol and its vehicle*

	Treatment[b]					
Uterus weight, mg[a]	Corn oil	Ethinylestradiol 0.3 μg kg^{-1} d^{-1}	Ethinylestradiol 1 μg kg^{-1} d^{-1}	CMC 0.5%	PI 82,GC FEM 5 mg kg^{-1} d^{-1}	PI 82,GC FEM 500 mg kg^{-1} d^{-1}
With luminal fluid	36 ± 4	41 ± 5	64 ± 9[c]	42 ± 9	36 ± 5	38 ± 6
Without luminal fluid	28 ± 3	33 ± 4	52 ± 8[c]	32 ± 6	28 ± 4	29 ± 6

CMC, carboxymethylcellulose.
[a]Mean ± SD (n = 10).
[b]By gavage once daily for 3 days.
[c]$P < 0.01$ when compared with the uterine weight of the corn oil vehicle group.

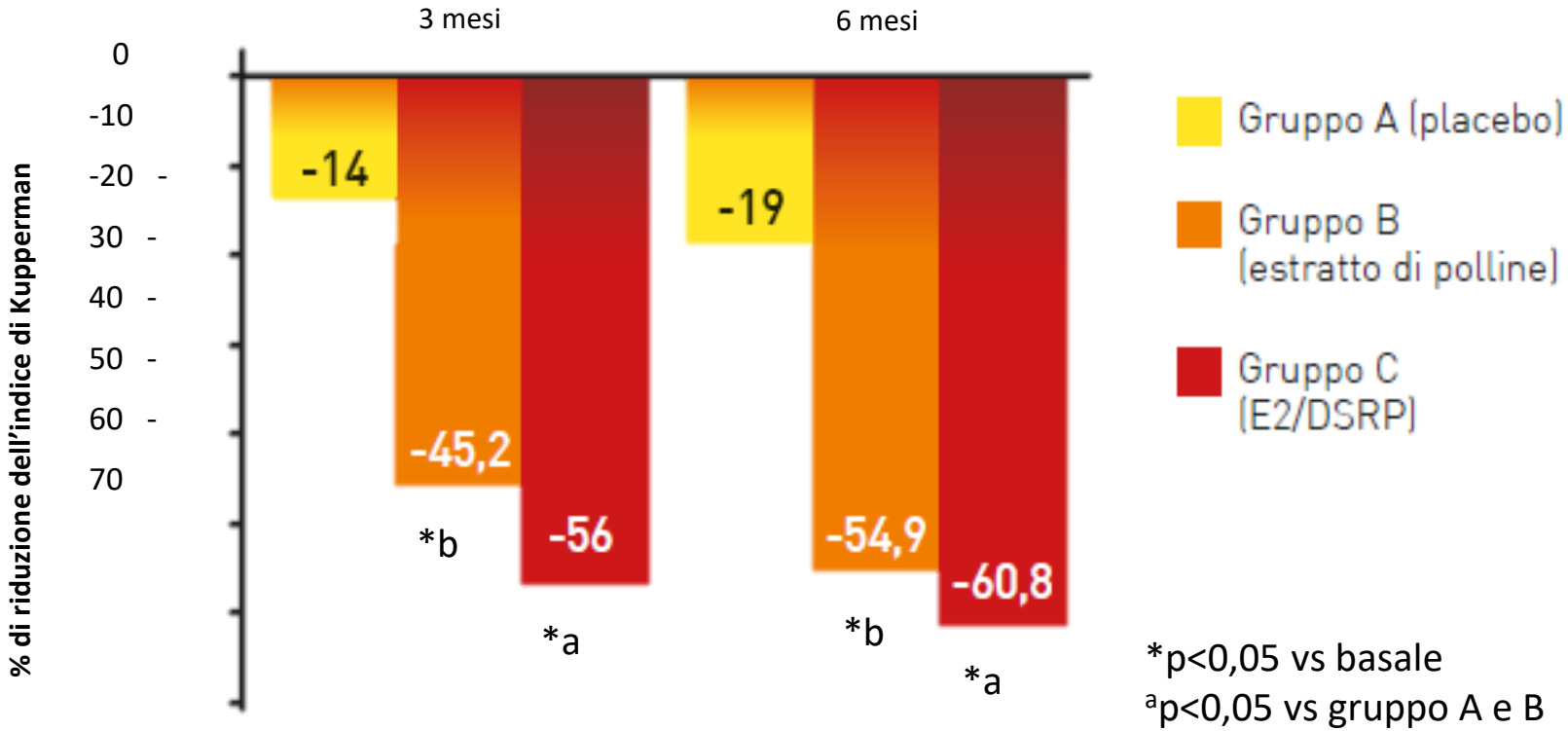
Results: **The pollen extracts were found to contain low, subeffective concentrations of daidzin, daidzein, and genistin.** Genistein, formononetin, and biochanin A could not be detected. Pollen extract in the high dose of 500 mg kg^{-1} day^{-1} did not cause **any uterine growth in immature female rats**.

Conclusions: The results show that the **pollen extract in Femal does not give the preparation any estrogenic effect**. Thus, Femal, which has proven clinical efficacy, is a nonestrogenic alternative to hormone therapy in women with menopausal symptoms.

“GC Fem, PI 82, vitamin E” in menopause treatment: benefits for peri- and postmenopausal neurovegetative symptoms

Efficacia polline su sintomi neurovegetativi vs HRT (gold standard)

Popolazione: 47 donne in postmenopausa (51-54 anni)
Misurazione : Indice di Kupperman (baseline, 3 e 6 mesi)



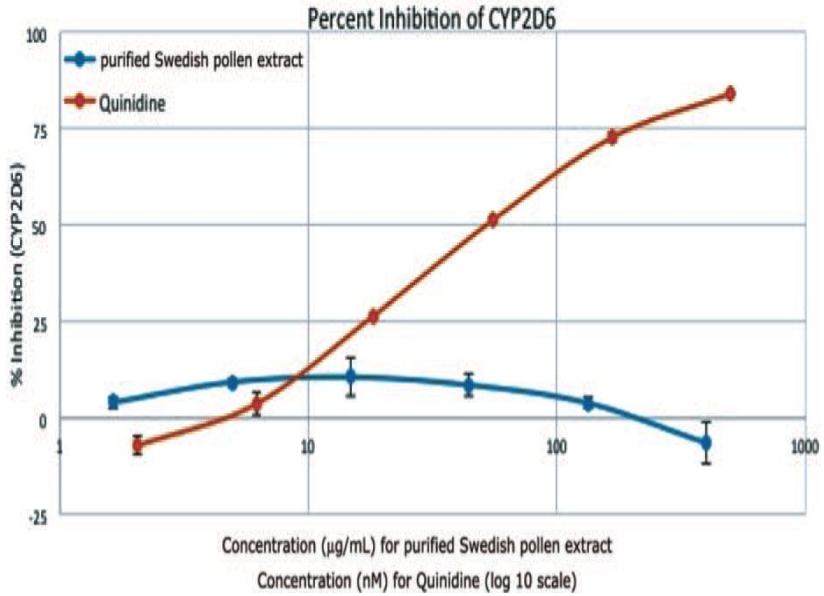
*p<0,05 vs basale
[a]p<0,05 vs gruppo A e B
[b]p<0,05 vs placebo

D’Alterio et al. MJWH 2015;4

Menopause: The Journal of The North American Menopause Society
Vol. 22, No. 11, pp. 1212-1214
DOI: 10.1097/GME.0000000000000535

Does purified Swedish pollen extract, a nonhormonal treatment for vasomotor symptoms, inhibit the CYP2D6 enzyme system?

Steven R. Goldstein, MD,[1] Marc Espié,[2] and René Druckmann[3]



Membrane-initiated effects of Serelys® on proliferation and apoptosis of human breast cancer cells

Harald Seeger[a], Xiangyan Ruan[a,b], Hans Neubauer[c], Sara Brucker[a] and Alfred O Mueck[a,b]

[a]Department of Women's Health, Women's Health Research Institute, Tuebingen, Germany; [b]Beijing Obstetrics and Gynecology Hospital, Capital Medical University, Beijing, China; [c]Department of Obstetrics and Gynecology, University Hospital and Medical Faculty of the Heinrich-Heine University Duesseldorf, Dsseldorf, Germany

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

"Non stimola la proliferazione delle cellule di carcinoma mammario"

L'estratto di polline non inibisce il complesso enzimatico che metabolizza il tamoxifene (CYP2D6 enzyme), a differenza di SSRI (paroxetina,fluoxetina).

Sicurezza della somministrazione dell'estratto di polline in pazienti in tp con tamoxifene per k mammilla.

ALTRI FITOTERAPICI PER LA MENOPAUSA

A review of effective herbal medicines in controlling menopausal symptoms

Table 1. Notable medicinal plants used in controlling menopause syndrome

References	Type of study	Mechanisms	Effects	Common name / Scientific name
16, 38	Clinical Trial	Bind to GABA complex/benzodiazepine Receptors in the brain, anti-perspiration feature, phytoestrogens	Treatment of flashes, sweats reduction, positive effects on the nervous system including improved memory	Sage herb/ Saliva Officinalis
17, 39	Clinical Trial, Animal Study	Lemon balm aroma affects the nervous system	Treatment of sleep disorders, nervousness, gastrointestinal problems in menopause	Lemon balm/ Melissa Officinalis
18,19,40	Clinical Trial, Clinical Trial, Cell Study	Increase of GABA in the synaptic cleft	Treatment of hot flashes in menopause	Valerian/ Valerian Officinalis
21		No permanent effect on estrogen receptors	Treatment of menopause symptoms such as night sweat, hot flash, insomnia, irritability, palpitations and headache	Cimicifugaracemose/ Black Cohosh
22,23	Clinical Trial-A systematic review	Inhibit the excess activity of testosterone	Treatment of vasomotor symptoms in menopause	Fenugreek/ Trigonella Foenum
24	Clinical Trial	Visceral body fat reduction	Treatment of metabolic syndrome in menopause	The Black Seeds/ Nigella sativa
25, 42	Clinical Trial, Randomized Trial	Stimulate the expression of genes related to progesterone receptors as well as its ability to eliminate defects in the synthesis of progesterone in luteal phase	Treatment of hot flashes	Hayfork/ Vitex Agnuscastus
26, 42	Clinical Trial, Clinical Trial	Retard excessive production of testosterone	Treatment of menopausal symptoms and vaginal atrophy	Fennel/ FoeniculumVulgare

Rahele Kargozaret al., Electronic Physician, 2017

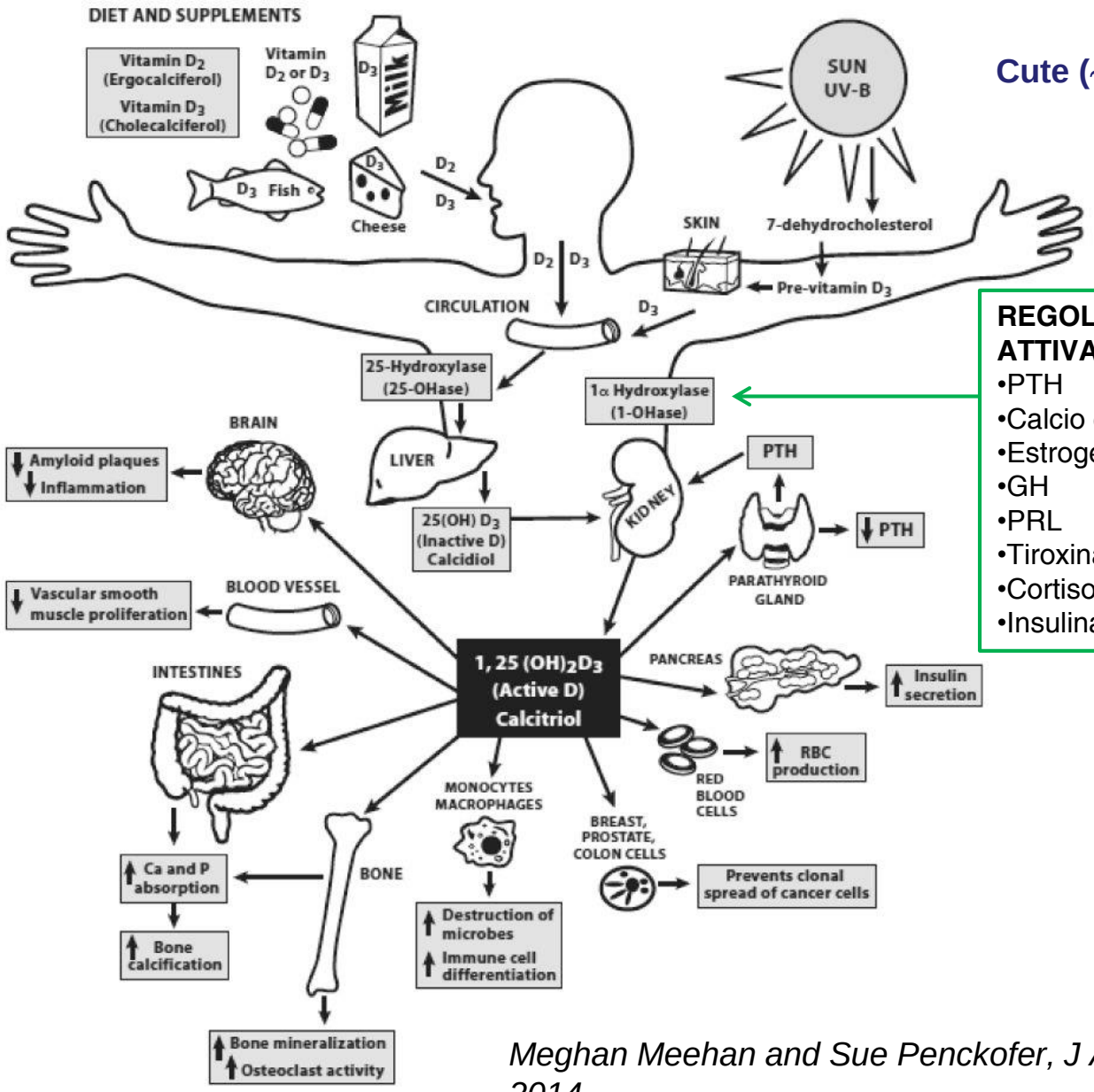
A review of effective herbal medicines in controlling menopausal symptoms

27	Clinical Trial	Antioxidant activities, contains prostaglandin E_1	Treatment of vasomotor symptoms	Oenotherabiennis/ Evening Prim Rose
28	Clinical Trial	Antioxidant and vasodilator activities	Treatment of attention disorders, memory impairment in postmenopausal women	Ginkgo/ Ginkgo Biloba
29	Clinical Trial	Estrogenic effects	Treatment of hot flashes	Alfalfa/ Medicago Sativa
30	a randomized pilot trial,	Benzodiazepine receptor activation	Treatment of hot flashes	Hypericum (Hvfaryqvn)/ Hypericume Perforatum
31	a randomized pilot trial	Estrogenic effects	Treatment of sleep disorders, fatigue, menopausal symptoms	Ginseng/ Panax Ginseng
32	Clinical Trial	Estrogenic effects	Treatment of hot flashes	Anise/ Pinpinella Aanisune
33	Clinical Trial	Estrogenic effects	Treatment of hot flashes	Glycyrrhiza Glabra/ Licoric
34, 44	Clinical Trial, Animal Study	Activation of $GABA_A$ receptor	Treatment of menopausal symptoms and hot flashes and neurological disorders	Passion fruit/ Passiflora Incarnata
35	Clinical Trial	Inhibit angiogenesis and provide protection agonist oxidative damage, anti-oxidant, estrogenic effect	Ability to reduce menopausal symptoms and support the maintenance of bone density and protect the cardiovascular and immune system	Red clover/ Trifolium Pretense
36	Clinical Trial	Estrogenic effects	Ability to reduce menopausal symptoms, support the maintenance of bone density, protects the immune system	Soya/ Glycine soja

Rahele Kargozaret al., Electronic Physician, 2017

VITAMINA D: Fisiologiapatologia

Dieta (~20%)
Vitamina D_3
Vitamina D_2



Cute (~80%)

REGOLATORI dell' ATTIVAZIONE:
- PTH
- Calcio e fosfato
- Estrogeni e androgeni
- GH
- PRL
- Tiroxina
- Cortisolo
- Insulina

Meghan Meehan and Sue Penckofer, J Aging Gerontol. 2014

IpoVitaminosi D e complicanze correlate

Cognitive Decline
• Associated with cognitive decline • Associated with ↑ risk for dementia • Associated with ↑ risk for Alzheimer disease • Mechanisms may include inflammation and formation of amyloid plaque in the brain
Depression
• Associated with major depression • Associated with ↑ depressive symptoms • Mechanisms may include neuroimmunomodulation and regulation of neurotrophic factors in the brain
Osteoporosis
• Evidence for ↑ risk for low trauma fracture • Associated with ↑ risk for falls • Mechanisms include ↑ PTH and bone turnover

Meghan Meehan and Sue Penckofer, J Aging Gerontol. 2014

- ✓ ***Per decenni la vitamina D considerata una vitamina, ma ad'oggi è riconosciuta come un ormone attivo che esercita la sua azione come fattore di trascrizione che regola l'espressione di numerosi geni.***
- ✓ ***Le prove accumulate hanno dimostrato che circa il 3% del genoma umano potrebbe essere regolato dalla VitD e ciò vuol dire che la deficienza di VitD è associata a conseguenze cliniche significative.***

Matyjaszek-Matuszek B, et al. Prz Menopauzalny. 2015

Cardiovascular Disease
• Associated with ↑ risk for cardiovascular morbidity and mortality • Associated with ↑ stroke in women • Mechanisms may include smooth muscle proliferation and inflammatory processes
Hypertension
• Associated with ↑ risk for hypertension • Mechanisms may include alterations in the regulation of the renin-angiotensin system
Type 2 Diabetes
• Associated with higher fasting glucose levels • Associated with ↑ risk for insulin resistance • Potential mechanisms may include insulin sensitivity and secretion
Cancer
• Associated with ↑ risk for colorectal cancer, more specifically rectal cancer • Associated with ↑ risk for metastatic prostate cancer • Potential mechanisms may include alterations in the autoimmune response and cellular proliferation

MENOPAUSA

% di donne in peri- e postmenopausa con Vit D <30 ng/ml: 43-90%[1,2]
Dato Italiano:76-80%[3,4]

IPOESTROGENISMO

AUMENTO DEL GRASSO VISCERALE

RIDOTTA ESPOSIZIONE SOLARE

RIDOTTO ASSORBIMENTO INTESTINALE

DEFICIT FUNZIONALE DI 25 OH asi e 1αOHasi

AUMENTO ETà

↓ VITAMINA D

SINTOMI VASOMOTORI / DISTURBI UMORE E DEL SONNO

GSM

CANCRO

OSTEOPOROSI (↓ BMD)

SARCOPENIA (↑ CADUTE)

MORTALITà TOTALE

↑ FRATTURE

1. *Cauley JA,et al. J Clin Endocrinol Metab. 2014*
2. *Hilger J, et al. British Journal of Nutrition. 2014*
3. *Iolascon G, et al. Europian Journal of Physical and Rehabilitation Medicine. 2017*
4. *Isaia G, et al. Osteoporos Int. 2003*

Vitamina D e Sintomi climaterici

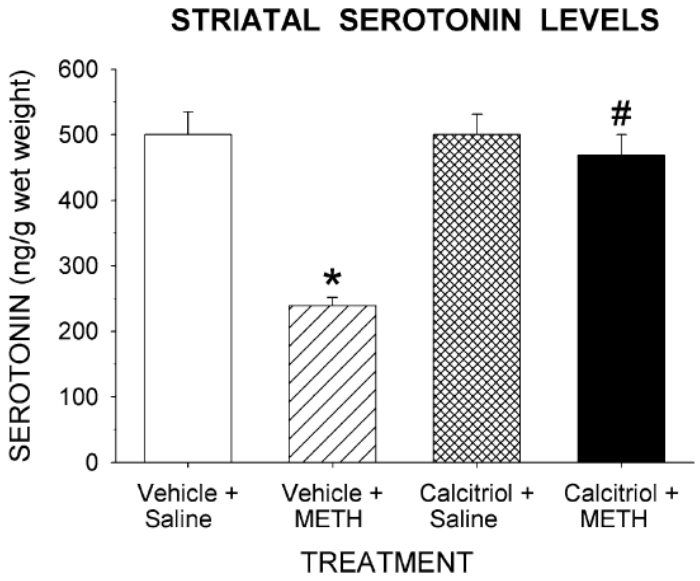
Calcitriol Protects against the Dopamine- and Serotonin-Depleting Effects of Neurotoxic Doses of Methamphetamine

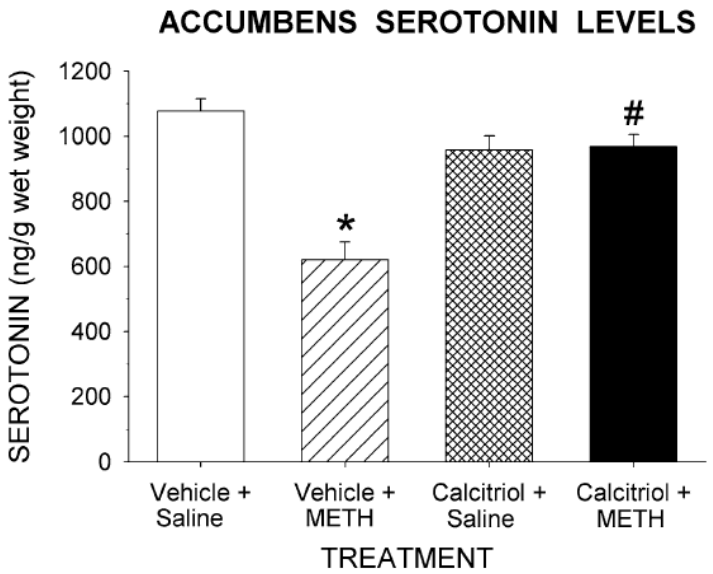
WAYNE A. CASS, MICHAEL P. SMITH, AND LAURA E. PETERS

Department of Anatomy and Neurobiology, University of Kentucky College of Medicine, Lexington, Kentucky 40536-0298, USA

- ✓ La vitamina D, proteggendo contro la deplezione sperimentale di serotonina nei ratti, potrebbe intervenire sul deficit di serotonina in menopausa.
- ✓ La serotonina è un neurotrasmettitore che, avendo effetti noti sulla termoregolazione, contribuisce alle vampate di calore.

Ann N Y Acad Sci. ***2006***





* p <0,05 rispetto al gruppo veicolo + soluz salina

\# p <0,05 rispetto al gruppo veicolo + METH

Breast Cancer Res Treat. 2010 Jan;119(1):111-8. doi: 10.1007/s10549-009-0495-x. Epub 2009 Aug 5.

Effect of vitamin D supplementation on serum 25-hydroxy vitamin D levels, joint pain, and fatigue in women starting adjuvant letrozole treatment for breast cancer.

Khan QJ[1], Reddy PS, Kimler BF, Sharma P, Baxa SE, O'Dea AP, Klemp JR, Fabian CJ.

42 donne in pre-menopausa in tp con AI x k mammella a 16 sett di tp con 50000 UI di VitD3 settimanali

2010

Assessment	Serum 25OHD level at 16 weeks <66 ng/ml *N* = 21	Serum 25OHD level at 16 weeks >66 ng/ml *N* = 21	Comparison *P*-value*
HAQII			
Score, median (range)	0.6 (0–2.3)	0.0 (0–1.2)	**0.008**
Number with scores = 0 (%)	4 (19%)	11 (52%)	0.026
Number with scores <0.25 (%)	6 (29%)	12 (57%)	0.059
BFI			
Score, median (range)	2.9 (0–8.0)	1.4 (0–7.2)	0.096
MEN-QOL			
Summary, median (range)	3.2 (0.2–5.4)	2.2 (0.5–3.8)	0.035
Vasomotor, median (range)	3.0 (0–5.0)	1.8 (0–5.0)	0.032
Psychosocial, median (range)	2.5 (0–6.0)	1.9 (0–4.1)	0.19
Physical, median (range)	3.5 (0.2–5.4)	2.2 (0–4.1)	0.028
Sexual, median (range)	0 (0–6.0)	0 (0–5.0)	0.75
Lack of subjective joint pain, number (%)	5 (24%)	10 (48%)	0.099
Lack of subjective muscle pain, number (%)	10 (50%)	11 (52%)	0.92

Sintomi muscolo-scheletrici

Affaticamento

Sintomi climaterici

Maturitas 74 (2013) 172–178

Contents lists available at SciVerse ScienceDirect

Maturitas

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

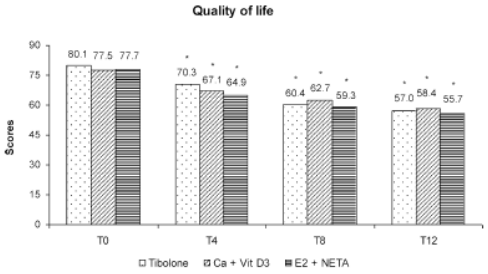
Effects of a continuous-combined regimen of low-dose hormone therapy (oestradiol and norethindrone acetate) and tibolone on the quality of life in symptomatic postmenopausal women: A double-blind, randomised study☆

Alvaro Fernando Polisseni[a,*], Amaury Teixeira Leite Andrade[b], Luiz Claudio Ribeiro[c], Isabela Queirós Castro[c], Marcos Brandão[d], Fernanda Polisseni[a], Martha de Oliveira Guerra[b]

Comparisons between groups in the domains of the WHQ that exhibited significant differences in *p*-values by the Kruskal–Wallis test at the end of treatment (T12).

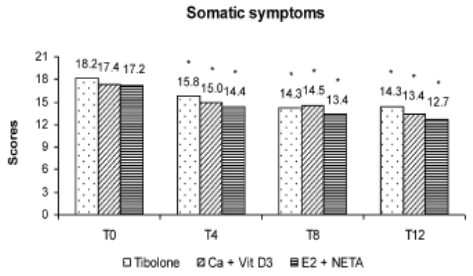
Groups	Mean ± std. deviation	*p* value
Vasomotor symptoms		
Tibolone × Ca + Vit D3	4.0 ± 1.8 × 4.3 ± 2.0	0.531
Tibolone × E2 + NETA	4.0 ± 1.8 × 3.2 ± 1.5	0.036
Ca + Vit D3 × E2 + NETA	4.3 ± 2.0 × 3.2 ± 1.5	0.007
Sexual behaviour		
Tibolone × Ca + Vit D3	4.2 ± 2.6 × 5.4 ± 2.8	0.034
Tibolone × E2 + NETA	4.2 ± 2.6 × 5.6 ± 2.8	0.018
Ca + Vit D3 × E2 + NETA	5.4 ± 2.8 × 5.6 ± 2.8	0.987

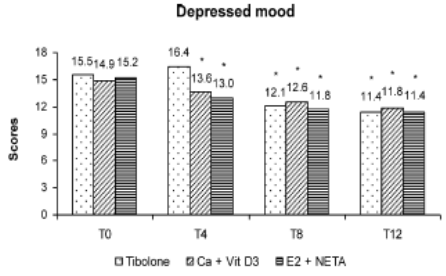
Ca + Vit D3: calcium carbonate/vitamin D3; E2 + NETA: oestradiol/norethindrone acetate.

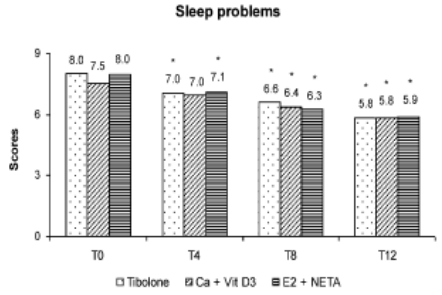


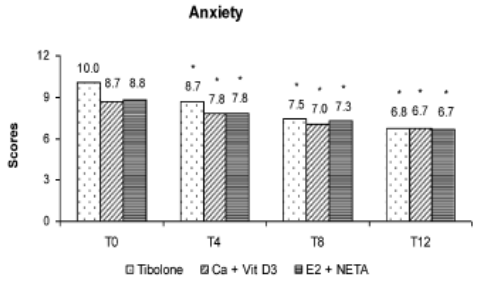
*** p<0.05 vs basale**

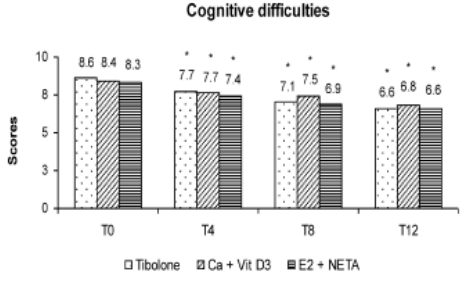
2013

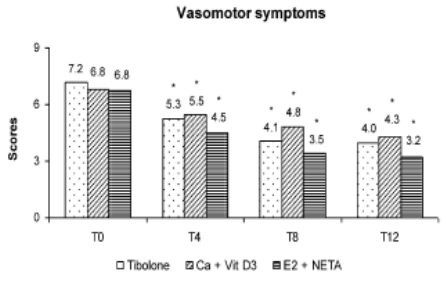


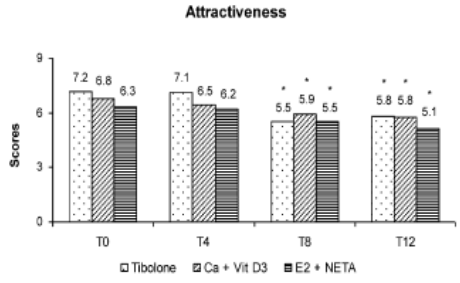


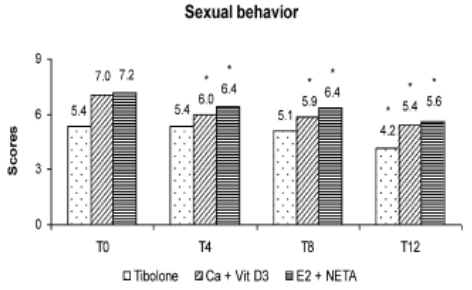












Menopause. 2014 Nov;21(11):1197-203. doi: 10.1097/GME.0000000000000238.

Vitamin D levels and menopause-related symptoms.

LeBlanc ES[1], Desai M, Perrin N, Wactawski-Wende J, Manson JE, Cauley JA, Michael YL, Tang J, Womack C, Song Y, Johnson KC, O'Sullivan MJ, Woods N, Stefanick ML.

Adjusted[a] composite symptom scores according to 25(OH)D clinical cut-off categories (≥75 nmol/L as referent[b])

Menopause-related symptom	25(OH)D level <25 nmol/L[b]	25(OH)D level ≥25 to <50 nmol/L	25(OH)D level ≥50 to <75 nmol/L	25(OH)D level ≥75 nmol/L	P value
Symptom Total[c]	0.84 (-1.02, 2.70)	0.85 (-0.7, 2.39)	0.32 (-1.27, 1.91)	Ref	0.06
Sleep disturbance construct[d]	0.23 (-2.35, 2.80)	1.04 (-1.10, 3.18)	0.14 (-2.06, 2.34)	Ref	0.25
Emotional well being[e]	-5.11 (-9.78, -0.45)	-2.87 (-6.18, 0.44)	-1.10 (-4.50, 2.31)	Ref	0.11
Energy/fatigue[e]	-1.29 (-11.96, 9.38)	-3.32 (-12.19, 5.54)	1.33 (-7.78, 10.44)	Ref	0.39

[a] Results are adjusted for age, years since menopause, ethnicity, education, BMI category, smoking status, UV exposure, HT use at screening, trial arm (HT or DM), calcium (dietary and supplement), and vitamin D (dietary and supplement).

[b] Adjusted coefficients from linear models (with 95 % CI) for difference between symptom scores in each vitamin D category relative to highest vitamin D level ≥75 nmol/L

[c] Higher total symptom score indicates more symptoms

[d] Higher sleep score indicates greater sleep disturbance

[e] Higher score indicates better health

2014

WHI calcium and vitamin D trial (CaD trial)

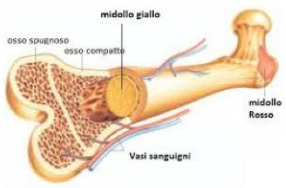
Odds Ratio[a](95% Confidence Interval) for individual menopause-related symptoms according to 25(OH)D clinical cut-off categories

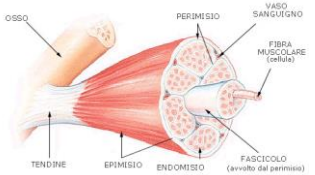
Menopause-related symptom[b]	25(OH)D level <25 nmol/L	25(OH)D level ≥25 to <50 nmol/L	25(OH)D level ≥50 to <75 nmol/L	25(OH)D level ≥75 nmol/L	P value	P value adjusted or multiple comparisons
Hot flashes	1.89 (0.64, 5.59)	1.23 (0.55, 2.75)	1.34 (0.61,2.93)	Ref	0.68	0.85
Night sweats	1.53 (0.61, 3.83)	0.84 (0.43, 1.66)	1.08 (0.56, 2.08)	Ref	0.46	0.63
Dizziness	2.51 (0.96, 6.56)	1.35 (0.64, 2.84)	1.55 (0.75, 3.23)	Ref	0.25	0.63
Heart racing	1.91 (0.71, 5.12)	1.26 (0.61, 2.58)	1.94 (0.97, 3.90)	Ref	0.18	0.41
Tremors	1.61 (0.29, 9.02)	1.12 (0.33, 3.82)	0.33 (0.07, 1.53)	Ref	0.32	0.58
Restless	1.71 (0.76, 3.84)	1.02 (0.58, 1.81)	0.67 (0.37, 1.19)	Ref	0.08	0.71
Feeling tired	1.73 (0.54, 5.49)	1.07 (0.50, 2.29)	1.21 (0.57, 2.59)	Ref	0.78	0.58
Difficulty concentrating	2.14 (0.91, 5.03)	2.40 (1.30, 4.44)	1.60 (0.87, 2.97)	Ref	0.04	0.82
Forgetfulness	1.41 (0.64, 3.10)	1.44 (0.83, 2.48)	1.00 (0.59, 1.70)	Ref	0.38	0.24
Mood swings	1.38 (0.60, 3.20)	1.49 (0.83, 2.67)	1.10 (0.61, 1.97)	Ref	0.51	0.24
Vaginal dryness	1.43 (0.59, 3.49)	1.26 (0.67, 2.35)	1.15 (0.62, 2.15)	Ref	0.87	0.24
Breast tenderness	2.50 (0.98, 6.37)	1.19 (0.59, 2.40)	1.75 (0.89, 3.43)	Ref	0.11	0.92
Headache	0.98 (0.44, 2.18)	1.40 (0.81, 2.44)	1.25 (0.72, 2.16)	Ref	0.53	0.58
Wake at night	2.11 (0.96, 4.68)	2.24 (1.27, 3.94)	1.42 (0.81, 2.49)	Ref	0.03	0.92
Waking earlier than planned	2.82 (0.74, 10.7)	1.51 (0.53, 4.28)	0.99 (0.33, 2.96)	Ref	0.32	0.24
Trouble going back to sleep	2.68 (0.92, 7.77)	1.75 (0.78, 3.92)	1.62 (0.72, 3.67)	Ref	0.34	0.41
Quality of sleep	0.74 (0.33, 1.64)	0.70 (0.41, 1.21)	0.99 (0.58, 1.67)	Ref	0.43	0.58
Restless sleep	1.70 (0.67, 4.31)	1.37 (0.69, 2.73)	1.33 (0.67, 2.64	Ref	0.72	0.78
Energy	0.94 (0.40, 2.21)	0.84 (0.45, 1.57)	0.91 (0.49, 1.70)	Ref	0.95	0.94

[a] Odds ratios are adjusted for age, years since menopause, ethnicity, education, BMI category, smoking status, UV exposure, HT use at screening, trial arm (HT or DM), calcium (dietary and supplement), and vitamin D (dietary and supplement).

[b] Higher values indicate more bothersome symptoms or more frequent occurrence

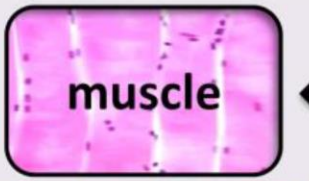
Vitamina D e Rischio di frattura



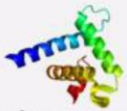


Menopause

↓ Sex hormones ↓ Anabolic hormones



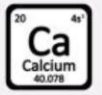
↑ Resistance (and aerobic) training



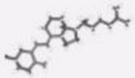
↑ Dietary protein

↑ Intramuscular fat
↓ Type I and II fibers
↓ Vitamin D receptor
↓ 1-alpha hydroxylase
↓ Protein synthesis
↓ Estrogen receptor
↓ Calcium release

↑ Calcium release
↓ Vitamin D
↓ Vitamin D receptor
↓ Estrogen



Calcium ↑



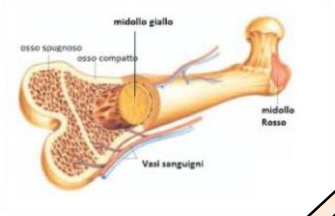
Vitamin D ↑

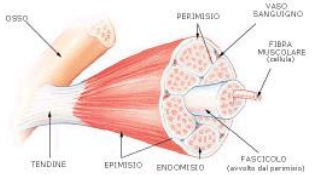
sarcopenia

osteoporosis

Lifestyle changes

Agostini D, et al. Nutrients 2018





Carenza di vitamina D

↓ assorbimento intestinale di calcio

↓ calcemia

↑ PTH

↑ turnover osseo con prevalenza dell'attività di riassorbimento

Osteoporosi

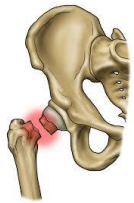
↑ Fratture

Se severa e prolungata

Osteomalacia

Miopatia prossimale / Sarcopenia

↑ Rischio di cadute



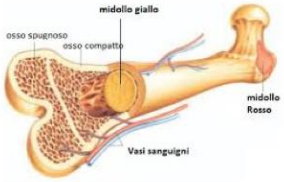
Osteoporosis International
https://doi.org/10.1007/s00198-018-4395-y

ORIGINAL ARTICLE

CrossMark

Effect of isolated vitamin D supplementation on bone turnover markers in younger postmenopausal women: a randomized, double-blind, placebo-controlled trial

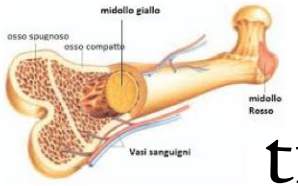
J. Nahas-Neto[1] · L. M. Cangussu[1] · C. L . Orsatti[1] · F. N. Bueloni-Dias[1] · P. F. Poloni[1] · E. B. Schmitt[1] · E. A. P. Nahas[1]



Vit D vs PLB: effetto su markers di turnover osseo

2018

Parameter/time points	Group		*p* value*
	80 pz Vitamin D	Placebo 80 pz	
s-CTX (ng/mL)			
Basal	0.33 (0.16)	0.29 (0.17)	0.136
9 months	0.25 (0.13)	0.27 (0.13)	0.913
p value**	<0.0001	0.092	
P1NP (ng/mL)			
Basal	54.9 (23.9)	52.1 (25.7)	0.487
9 months	47.5 (21.1)	51.8 (24.4)	0.254
p value**	0.003	0.918	



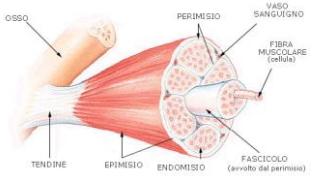
Δ BMD femorale (%): trattamenti anti-osteoporosi vs placebo

placebo
terapia

ΔBMD (%)

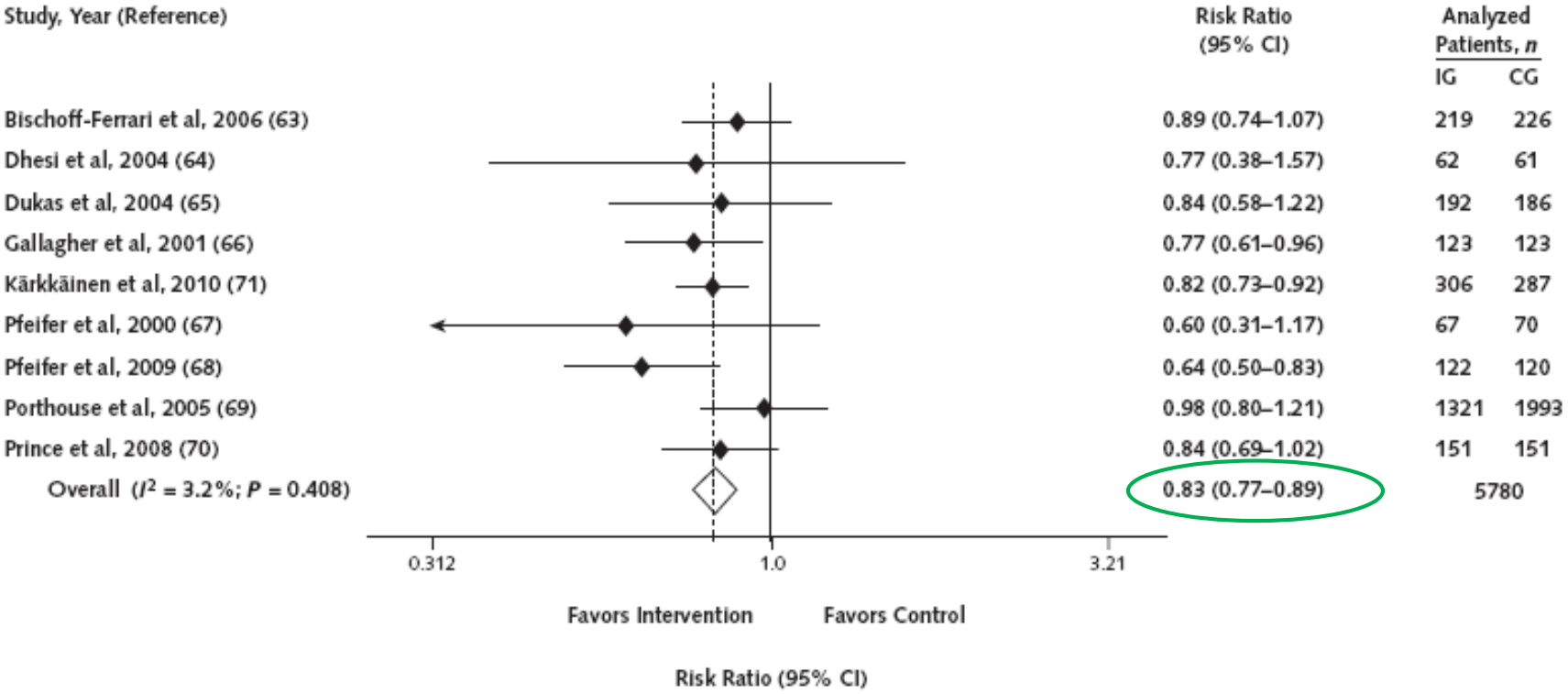
6
5
4
3
2
1
0
-1
-2
-3
-4
-5

	Ca+VitD	TOS	ALN	BZX	RLX	CT	RIS	IBN	RS	TERIP	DEN	ZLN
	+0,59%	+1,6%	+5,8%	+1,1%	+2,1%	NS	+2,8%	+4,1%	+8,3%	+3,5%	+6%	+6%
Età media	62	63	64	66	67	68	69	69	69	69	72	73



Rischio di caduta dopo correzione dell'ipovitaminosi D

2010



CG = control group; IG = intervention group.

Michael YL, Ann Intern Med, 2010

J Clin Endocrinol Metab. 2015 May;100(5):2046-54. doi: 10.1210/jc.2014-4367. Epub 2015 Feb 26.

Serum 25 hydroxyvitamin D, bone mineral density and fracture risk across the menopause.

SWAN, 2015

Cauley JA[1], Greendale GA, Ruppert K, Lian Y, Randolph JF Jr, Lo JC, Burnett-Bowie SA, Finkelstein JS.

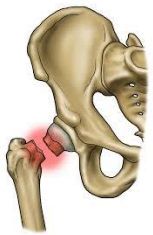
Livelli di 25(OH)D, fratture traumatiche e non traumatiche in transizione menopausale

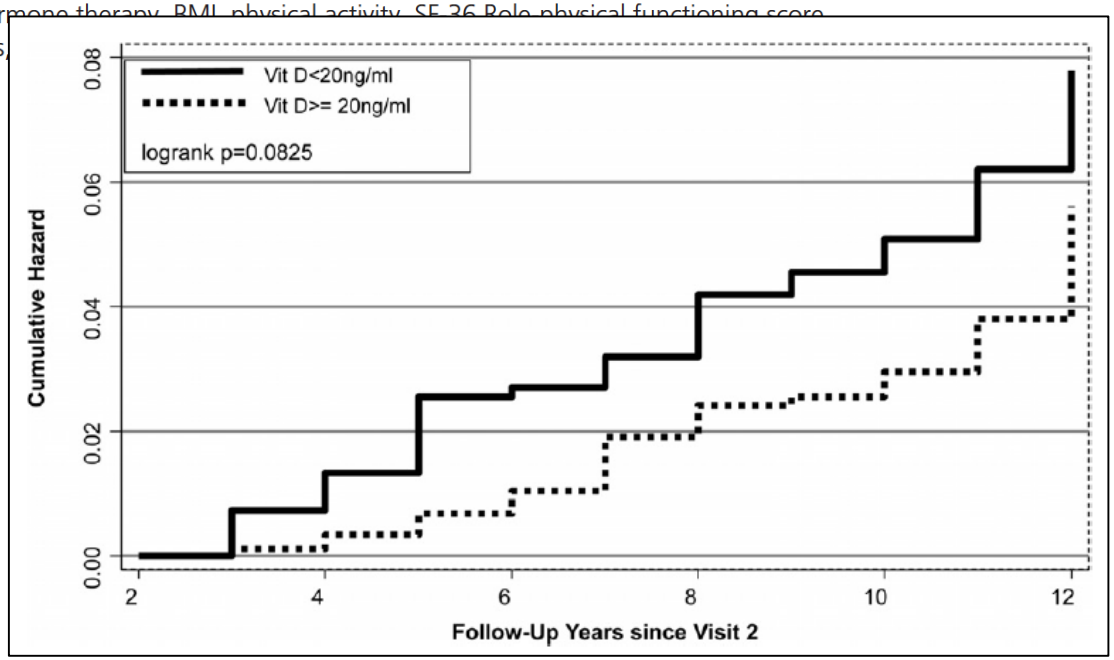
	Base Model[1]	Multivariate Model[2]
	HR (95% CI)	**HR (95% CI)**
Traumatic Fractures		
Per 10 ng/mL increase	1.14 (0.94, 1.37)	1.02 (0.80, 1.28)
≥20 *vs.* < 20 ng/mL	1.24 (0.83, 1.87)	1.11 (0.70, 1.77)
Non-traumatic Fractures		
Per 10 ng/mL increase	0.75 (0.58, 0.96)	0.72 (0.54, 0.96)
≥20 *vs.* < 20 ng/mL	0.55 (0.35, 0.86)	0.54 (0.32, 0.89)

[1] Adjusted for age, site, race.

[2] Base model + fracture history, prior and current menopausal hormone therapy, BMI, physical activity, SF-36 Role physical functioning score, education, lumbar spine BMD, calcium and vitamin D supplements.

Livelli di 25(OH)D (<20 ng/mL vs ≥20 ng/mL) e rischio fratture non traumatiche





Efficacia anti-frattura femorale

	Ca+ VitD	TOS	BZX	RLX	CT	IBN	TERIP	ALN	DEN	ZLN	RS	RIS
STUDIO	WHI	WHI°	Silverman 2008	MORE	PROOF	BONE	Neer 2001	FIT 1	FREEDOM	HORIZON	TROPOS	HIP
Età media	62	63	66	67	68	70	70	71	72	73	77	79
Pazienti In studio	36282	16608	4216	1539	1255	2946	1637	1946	7808	7765	1997	9331
RRR a 3 aa	-	-	-	-	-	NS	-	51%**	41%	40%	36% ***	30%
RRR a 5 aa	29% *	EP: 33% E: 39%	-	-	-	-	-	-	-	-	43% ***	-

°donne a basso rischio di fratture osteoporotiche e ad alto rischio cardiovascolare
*pz altamente complianti, che hanno assunto la terapia per l'intero periodo in studio
**T-score del collo del femore ≤-2,5
***≥74 anni+T-score del collo del femore ≤-2,5

Vitamina D e Malattia cardiovascolare

MENOPAUSA ,VARIAZIONI CORPOREE E CVR

COMPOSIZIONE CORPOREA	METABOLISMO GLUCIDICO	METABOLISMO LIPIDICO	PRESSIONE	ALTRO
↓ MASSA MAGRA	↓ TOLLERANZA AL GLUCOSIO	↑ COLESTEROLO TOT	RIDUZIONE DELLA COMPLIANCE VASCOLARE	↑ OMOCISTEINA
↑ MASSA GRASSA	↑ INSULINO RESISTENZA	↑ COLESTEROLO LDL	⇩	↑ STRESS OSSIDATIVO
↓ GRASSO GINOIDE	↑ RISCHIO PER DIABETE DI TIPO II	↑ TRIGLICERIDI	↑ PRESSIONE ARTERIOSA	↑ MARKERS D' INFIAMMAZIONE
↑ GRASSO ANDROIDE		↓ COLESTEROLO HDL		

Review

Levels of vitamin D and cardiometabolic disorders: Systematic review and meta-analysis

Johanna Parker[a], Omar Hashmi[a], David Dutton[b], Angelique Mavrodaris[a], Saverio Stra
Ngianga-Bakwin Kandala[b], Aileen Clarke[a], Oscar H. Franco[a,*,1]

[a] Health Sciences Research Institute, Warwick Medical School, University of Warwick, Coventry CV4 7AL, United Kingdom
[b] Clinical Sciences Research Institute, Clifford Bridge Road, Coventry CV2 2DX, United Kingdom

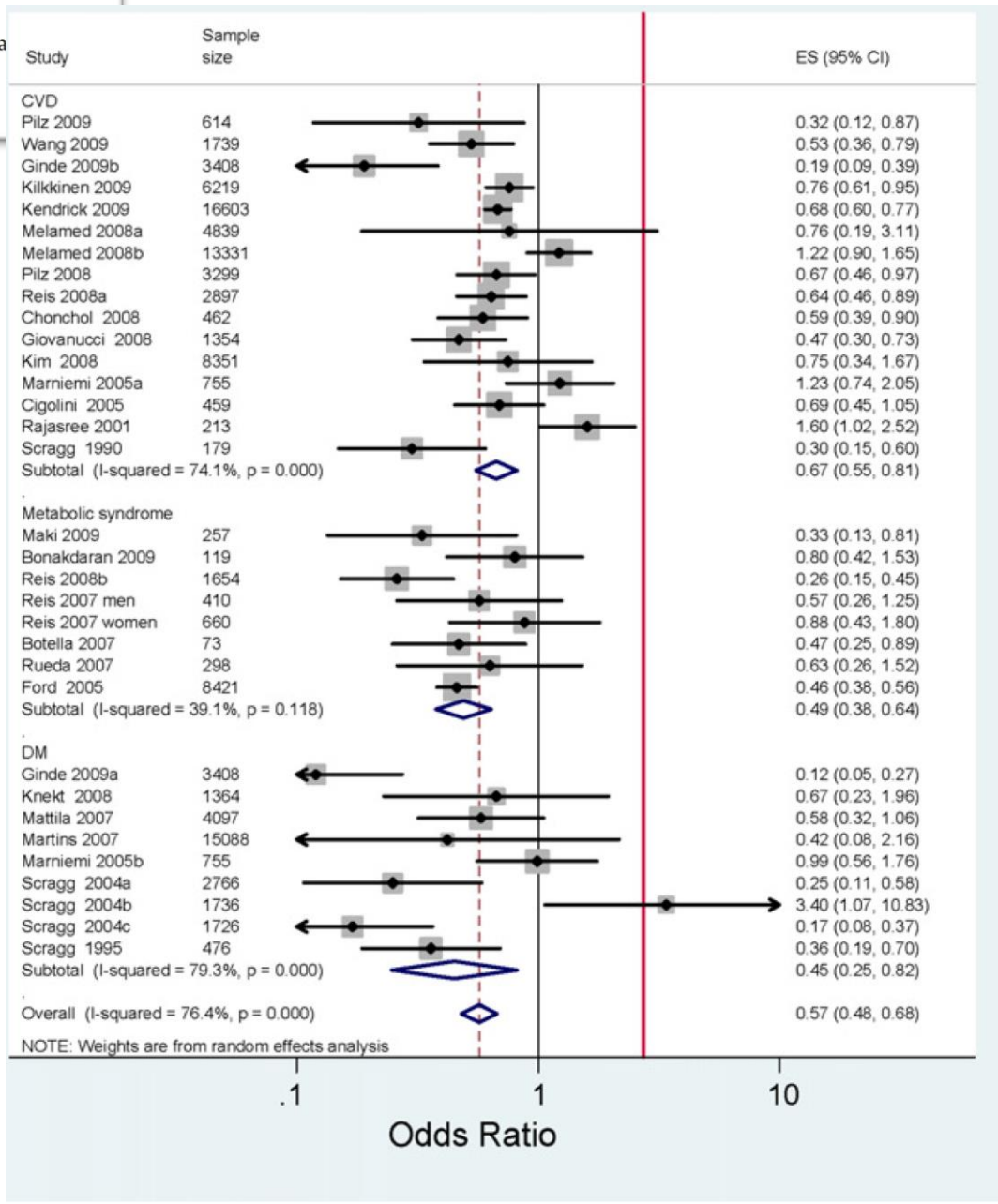
2010

Malattie cardiovascolari

Sindrome metabolica

Diabete Mellito di tipo 2

Alti livelli di vitamina D tra le popolazioni di mezza età e anziane sono associati ad una sostanziale diminuzione delle malattie cardiovascolari, diabete di tipo 2 e sindrome metabolica.



J. Parker, et al. Maturitas 2010

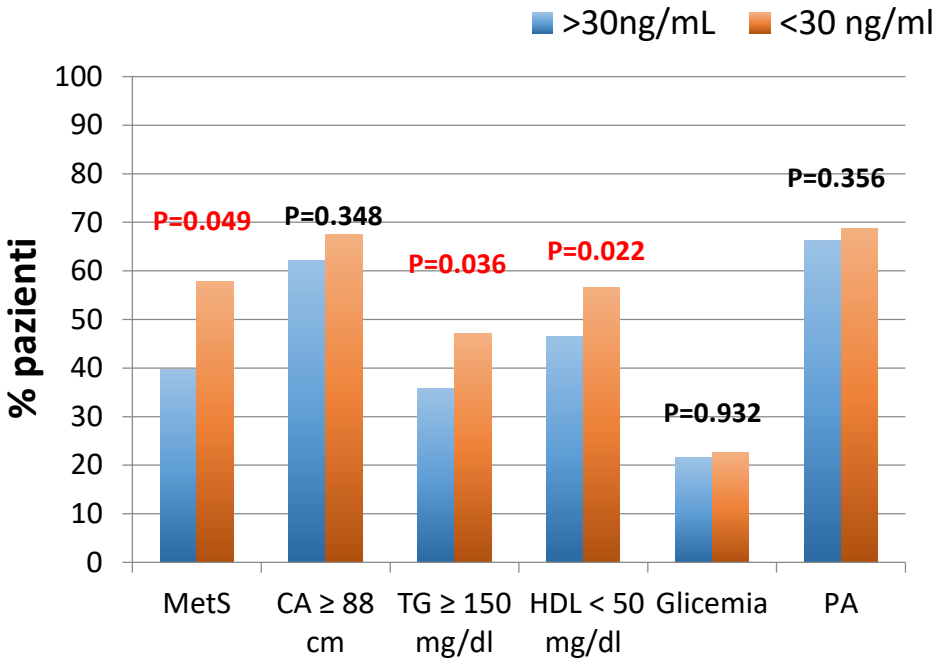
Vitamin D deficiency is associated with metabolic syndrome in postmenopausal women

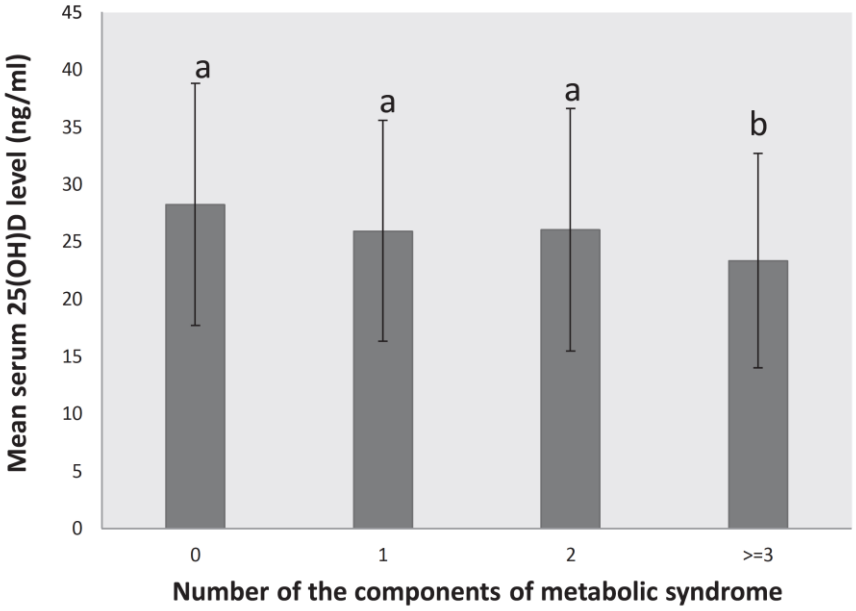
Eneida Boteon Schmitt, Jorge Nahas-Neto, Flavia Bueloni-Dias, Priscila Ferreira Poloni, Claudio Lera Orsatti, Eliana Aguiar Petri Nahas*

Department of Gynecology and Obstetrics, Botucatu Medical School, Sao Paulo State University – UNESP, Sao Paulo, Brazil

2018

Studio osservazionale, 463 donne brasiliane, 45-75 anni, in post-menopausa





Conclusions: VitD deficiency in postmenopausal women was associated with a higher prevalence of Metabolic Syndrome (MetS).

Women with VitD deficiency had a higher risk of MetS, hypertriglyceridemia and low HDL than those with adequate levels.

Vitamina D e Cancro

TABLE 1. Mechanisms of Calcitriol Anticancer Effects

Proliferation	Increase in p21 and p27 expression[116]
	Decrease in CDKs, cyclins, MYC and RB expression[117]
Apoptosis	Increase in BAX[118]
	Decrease in BCL-2[119]
	Increased sensitivity to radiation and chemotherapy[120]
Differentiation	Myeloid leukemia cells differentiate into monocytes[121]
	Increased expression of differentiation factors such as casein, lipids, PSA, E-cadherin[82,83]
Inflammation	Inhibition of expression of COX2, PG receptors, stress kinase, and NF-κB signaling[12,122]
	Increased TIMP 1 and E-cadherin response[123]
Invasion and metastasis	Decreased expression of MMP9, α6 integrin, ·4 integrin, plasminogen activator[123]
Angiogenesis	Decreased HIF1 α, VEGF, IL-8, tenascin C, PGE2 levels[124]

CDK indicates cyclin-dependent kinase; COX2, cyclooxygenase 2; HIF1 α, hypoxia inducible factor 1alpha; IL-8, interleukin 8; MAPKP5, mitogen activated protein kinase phosphatase 5; MMP9, metalloproteinase 9 ; NF-κB, nuclear factor κB; PG, prostaglandin; 15-PGDH, 15-hydroxyprostaglandin dehydrogenase; PGE, prostaglandin E; POL II, polymerase II; PSA, prostate-specific antigen; TIMP1, tissue inhibitor of metalloproteinase 1; VEGF, vascular endothelial growth factor.
Adapted from Feldman D, Krishnan AV, Swami S, et al. The role of vitamin D in reducing cancer risk and progression. *Nat Rev Cancer.* 2014;14(5):342-357.

Vitamina D e cancro: evidenze epidemiologiche

Conclusioni del rapporto IARC su Vitamin D and Cancer (2008)

- Forti evidenze di un'inversa associazione tra vitamina D e cancro colon-retto,anche se:
  - Le prove di un nesso causale sono limitate
  - RCT non conclusive

- Evidenze deboli su associazione inversa con cancro al seno

- Scarse evidenze per un'associazione con il cancro alla prostata

- Studi insufficienti per altri tumori

- La supplementazione di vitamina D può ridurre tutte le cause di mortalità

IARC. Vitamin D and Cancer. IARC Working Group Reports Vol.5, International Agency for research on Cancer, Lyon, 25 November 2008

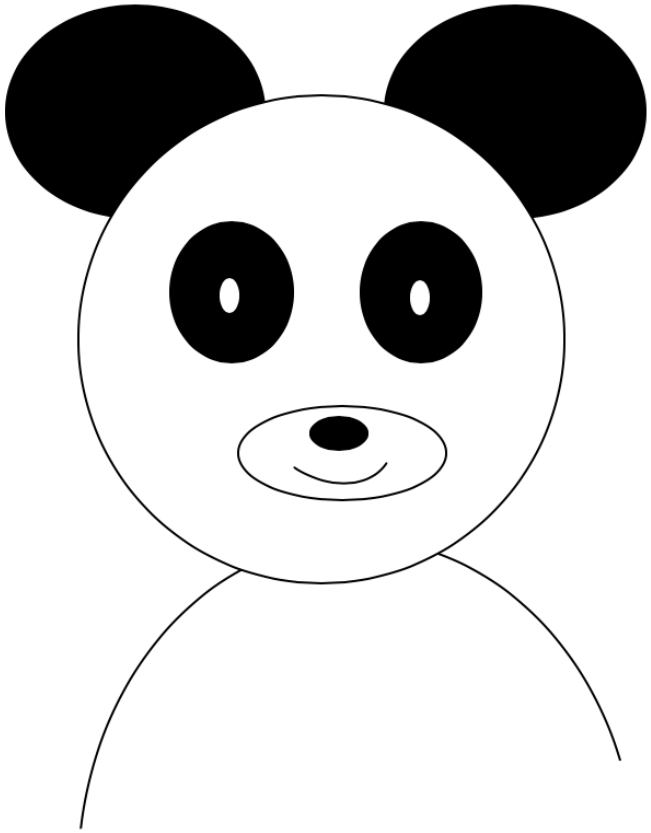
CONCLUSIONI

Di integratori alimentari per la menopausa ne abbiamo tanti, ma con alcuni limiti:

- *Dati i **risultati contrastanti**, non è possibile al momento concludere che i **fitoestrogeni** siano meglio del placebo sui sintomi vasomotori.*
- *Dimostrati **effetti anti-riassorbitivi sull'osso**, **ma mancano studi** clinici adeguati (studi **sull'**outcome più importante: **rischio di frattura**).*
- *Possibili **effetti protettivi sul cardiovascolare**.*
- ***Sicurezza su endometrio e mammella**, purchè non ci sia un' evidenza di rischio antecedente.*
- *Nelle **pazienti ad elevato rischio per K mammella o in tp con tamoxifene per k mammella** valide alternative sono **Cimicifuga Racemosa ed estratto di polline purificato**.*
- *In tutti i casi da ricordare che l'**efficacia** degli integratori si manifesta dopo **almeno 3-6 mesi di trattamento**.*

Inoltre:

- *In peri- e postmenopausa la supplementazione con **Vitamina D** deve essere parte integrante del percorso diagnostico-terapeutico perché **sembrerebbe poter trattare i sintomi e prevenire le complicanze correlate**.*



Grazie per l'attenzione!