

La Cimicifuga Racemosa nel trattamento della sindrome climaterica

G. BONACCORSI

FERRARA , 20 MARZO 2015
HOTEL CARLTON

**I NUTRACEUTICI AL FEMMINILE.
RAZIONALE PER UNA UTILE
SUPPLEMENTAZIONE NELLA VITA DELLA
DONNA**



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



UNIVERSITÀ
DEGLI STUDI
DI FERRARA
- EX LABORE FRUCTUS -

La **CIMICIFUGA RACEMOSA** (Black Cohosh)

una pianta appartenente al genere delle ranunculacee, nativa del Nord America con una estesa distribuzione dal sud del Canada alla Georgia. È diffusa in Europa soprattutto come pianta ornamentale da giardino.



Usata tradizionalmente presso le popolazioni indiane del Nord America, sin dagli inizi del 1800 per l'utilità del rizoma-radici della pianta nel trattamento del dolore mestruale e di svariati sintomi climaterici



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 alcolico della Cimicifuga racemosa è in genere ben tollerato alla dose raccomandata di 40 mg/die di estratto secco.

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

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.

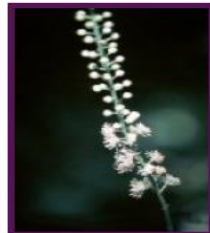
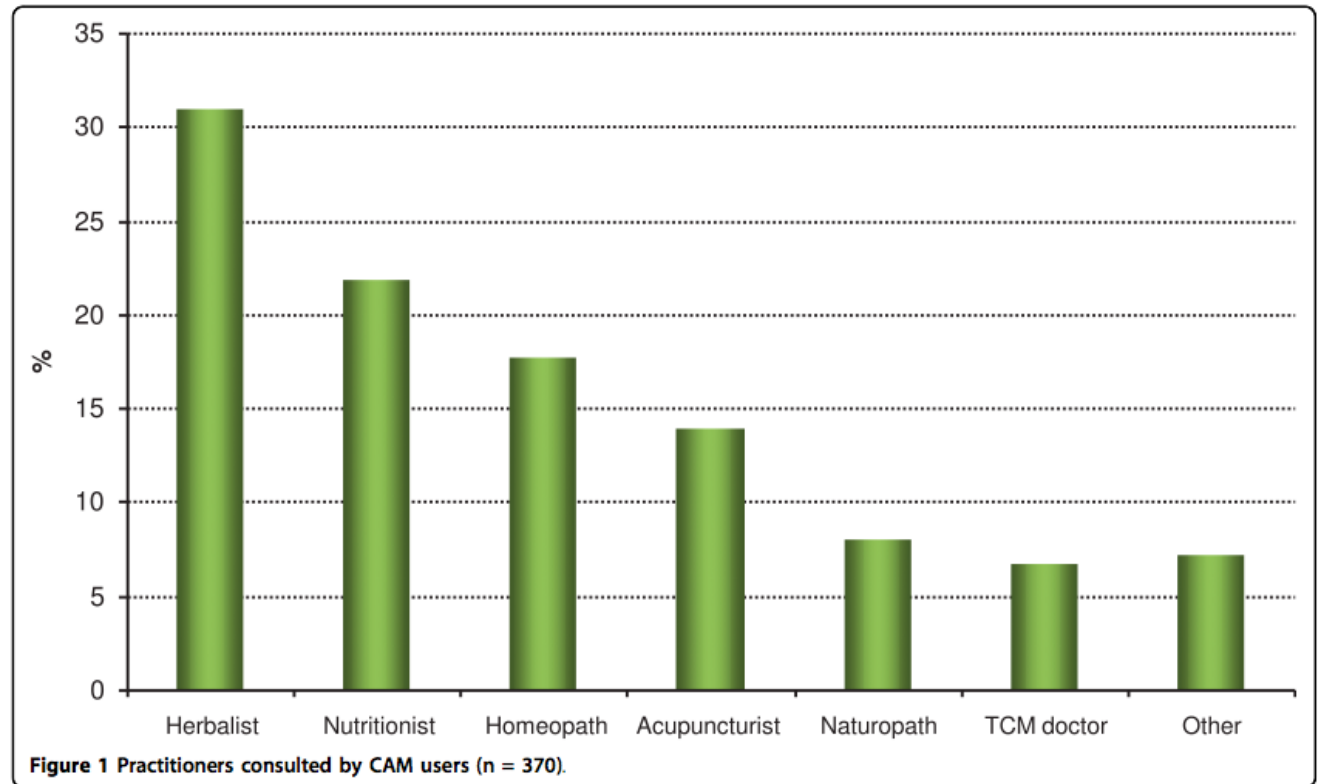
Methods: Women, aged 45-65 years attending Family Planning and Women's Health clinics or Menopause Centres in Bologna were invited to complete a voluntary, anonymous, self administered questionnaire, which was used in a previous study in Sydney. The questionnaire was translated and adapted for use amongst 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.

- Use of CAM and HRT for menopausal symptoms
- The majority of women (56.2%) reported they had not used any treatment for menopausal complaints during the previous 12 months.
- Of women who had used remedies to alleviate symptoms:
 - 10.3% had used HRT alone,
 - 26.7% had used CAM exclusively,
 - while 6.8% had used CAM in conjunction with HRT.
- Overall, 33.5% had used CAM during the twelve months before questionnaire completion.



Cimicifuga R.

Costituenti chimici

- ❖ La Cimicifuga possiede diversi costituenti chimici: (alcaloidi azotati, composti fenolici della categoria degli isoflavoni come la formononetina, acidi organici come l'ac. isoferulico, triterpenoidi, e altri composti e sostanze volatili)
- ❖ **La formononetina e i triterpenoidi sono le 2 componenti bioattive più importanti.**
- ❖ **L'estratto alcolico isopropilico utilizzato in fitoterapia risulta privo della componente fitoestrogenica fenolica della formononetina .**
- ❖ **I glucosidi triterpenici costituiscono la principale componente bioattiva presente nell'estratto alcolico responsabili degli effetti terapeutici.**

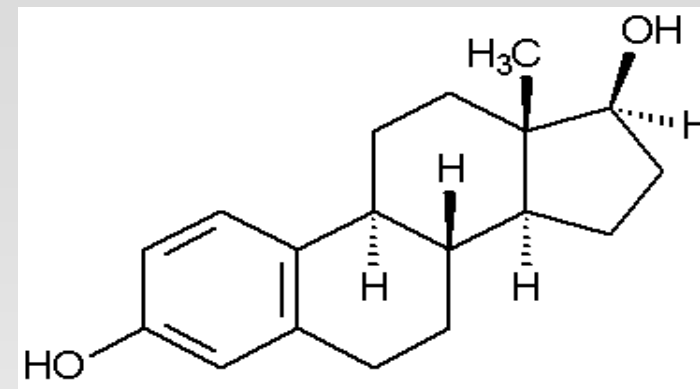
I principali componenti triterpenoidi sono:

- acteina
- cimigenolo
- gli esteri dell'acido cinnamico
- la 27-deossiacteina

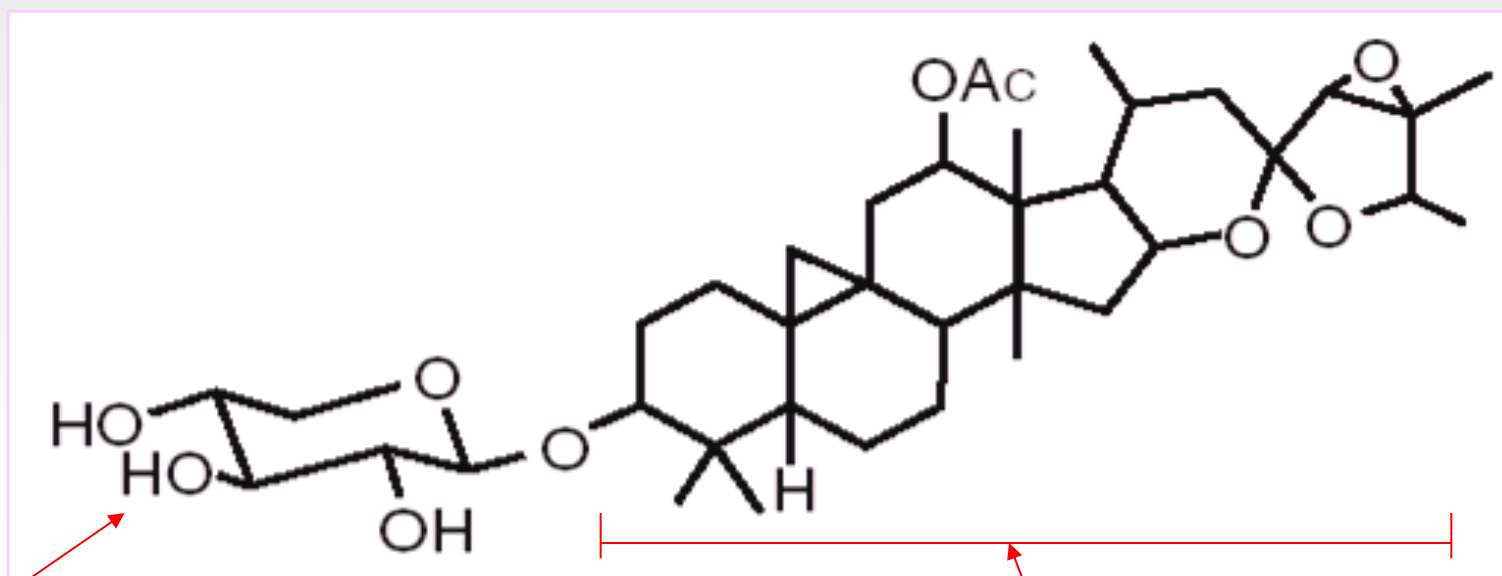


I glicosidi sono molecole costituite da **due parti unite tra loro: lo zucchero xilosio e il triterpene** del tipo cicloartenolo avente struttura steroidea.

Struttura, simile a quella degli estrogeni che permette l'interazione con i recettori ormonali: la particolare conformazione stereochimica potrebbe determinare quel legame selettivo tipico del meccanismo d'azione di questo estratto

17- β -ESTRADIOLO

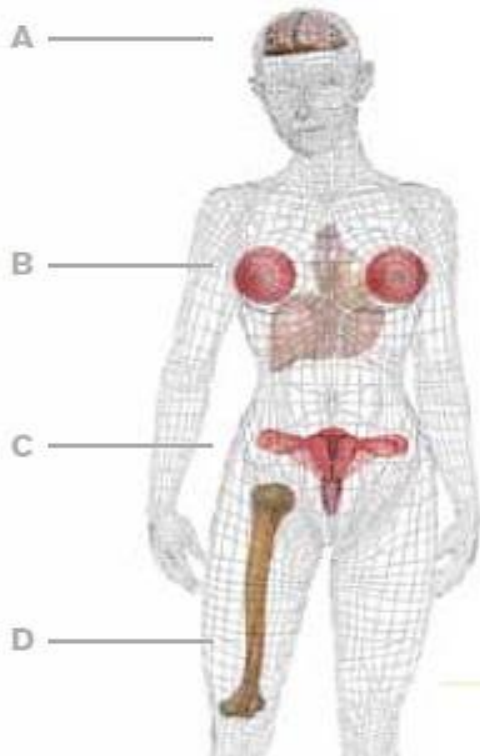
GLICOSIDE TRITERPENICO



ZUCCHERO: XILOSIO

AGLICONE: TRITERPENE CICLOARTEOLO

MECCANISMO D' AZIONE

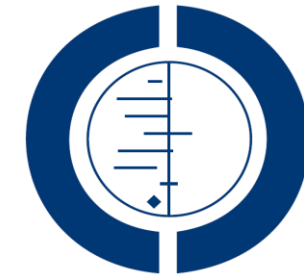


- Ⓐ Agonista a livello del **Sistema Nervoso Centrale***
- Ⓑ Antagonista a livello delle **ghiandole mammarie**
- Ⓒ Assenza di agonismo a livello di **utero e vagina**
- Ⓓ Agonista a livello dell'**osso**

* Agonista parziale dei recettori μ degli oppioidi e del recettore della serotonina^{1,2}

¹ Rhyu MR et al. Black cohosh (*Actaea racemosa*, *Cimicifuga racemosa*) behaves as a mixed competitive ligand and partial agonist at the human μ opiate receptor. *J Agric Food Chem.* 2006 Dec 27;54(26):9852-7.

² Burdette JE et al. Black cohosh acts as a mixed competitive ligand and partial agonist of the serotonin receptor. *J Agric Food Chem.* 2003 Sep 10;51(19):5661-70.



Objectives

To evaluate the clinical effectiveness and safety of black cohosh (*Cimicifuga racemosa* or *Actaea racemosa*) for treating menopausal symptoms in perimenopausal and postmenopausal women.

Search methods

Relevant studies were identified through AARP Ageline, AMED, AMI, BioMed Central gateway, CAM on PubMed, CINAHL, CENTRAL, EMBASE, Health Source Nursing/Academic edition, International Pharmaceutical Abstracts, MEDLINE, Natural medicines comprehensive database, PsycINFO, TRIP database, clinical trial registers and the reference lists of included trials; up to March 2012. Content experts and manufacturers of black cohosh extracts were also contacted.

Selection criteria

All randomised controlled trials comparing orally administered monopreparations of black cohosh to placebo or active medication in perimenopausal and postmenopausal women.

Main results

Sixteen randomised controlled trials, recruiting a total of 2027 perimenopausal or postmenopausal women, were identified. All studies used oral monopreparations of black cohosh at a median daily dose of 40 mg, for a mean duration of 23 weeks. Comparator interventions included placebo, hormone therapy, red clover and fluoxetine. Reported outcomes included vasomotor symptoms, vulvovaginal symptoms, menopausal symptom scores and adverse effects. There was no significant difference between black cohosh and placebo in the frequency of hot flushes (mean difference (MD) 0.07 flushes per day; 95% confidence interval (CI) -0.43 to 0.56 flushes per day;

Authors' conclusions

There is currently insufficient evidence to support the use of black cohosh for menopausal symptoms. However, there is adequate justification for conducting further studies in this area. The uncertain quality of identified trials highlights the need for improved reporting of study methods, particularly with regards to allocation concealment and the handling of incomplete outcome data. The effect of black cohosh on other important outcomes, such as health-related quality of life, sexuality, bone health, night sweats and cost-effectiveness also warrants further investigation.



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

Editorial

News about Black cohosh



Black cohosh preparations are not all the same

- **Many different Cimicifuga species exist.**
- These include three North American species, *C. racemosa*, *C. americana*, *C. rubifolia*, and seven Asian species, *C. acerina*, *C. biternat*, *C. dahurica*, *C. heracleifolia*, *C. japonica*, *C. foetida*, and *C. simplex*.
- A large number of American preparations contain Cimicifuga species grown in Asia instead of Cimicifuga racemosa.
- **Their chemical composition is quite different**
- For the products containing only Black cohosh, there was significant product-to-product variability in the amounts of the selected triterpene glycosides and phenolic constituents.
- Secondly and probably more important is the **dosage** used in the various studies.

Review Article

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

A.-M. Beer¹ and A. Neff²



- ❖ 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, and indication.*** Accordingly, Oxford Levels of Evidence (LOE) and Grades of Recommendation (GR) were determined.
- ❖ *CR extracts demonstrated a good to very good safety in general, on estrogen-sensitive organs and the liver.*
- ❖ ***However, only registered CR medicinal products were able to prove their efficacy.***

Figura 4: dati di sicurezza sulla Cimicifuga racemosa 2000-2012

n: pazienti trattati con Cimicifuga racemosa negli studi clinici e monitorati per gli effetti collaterali

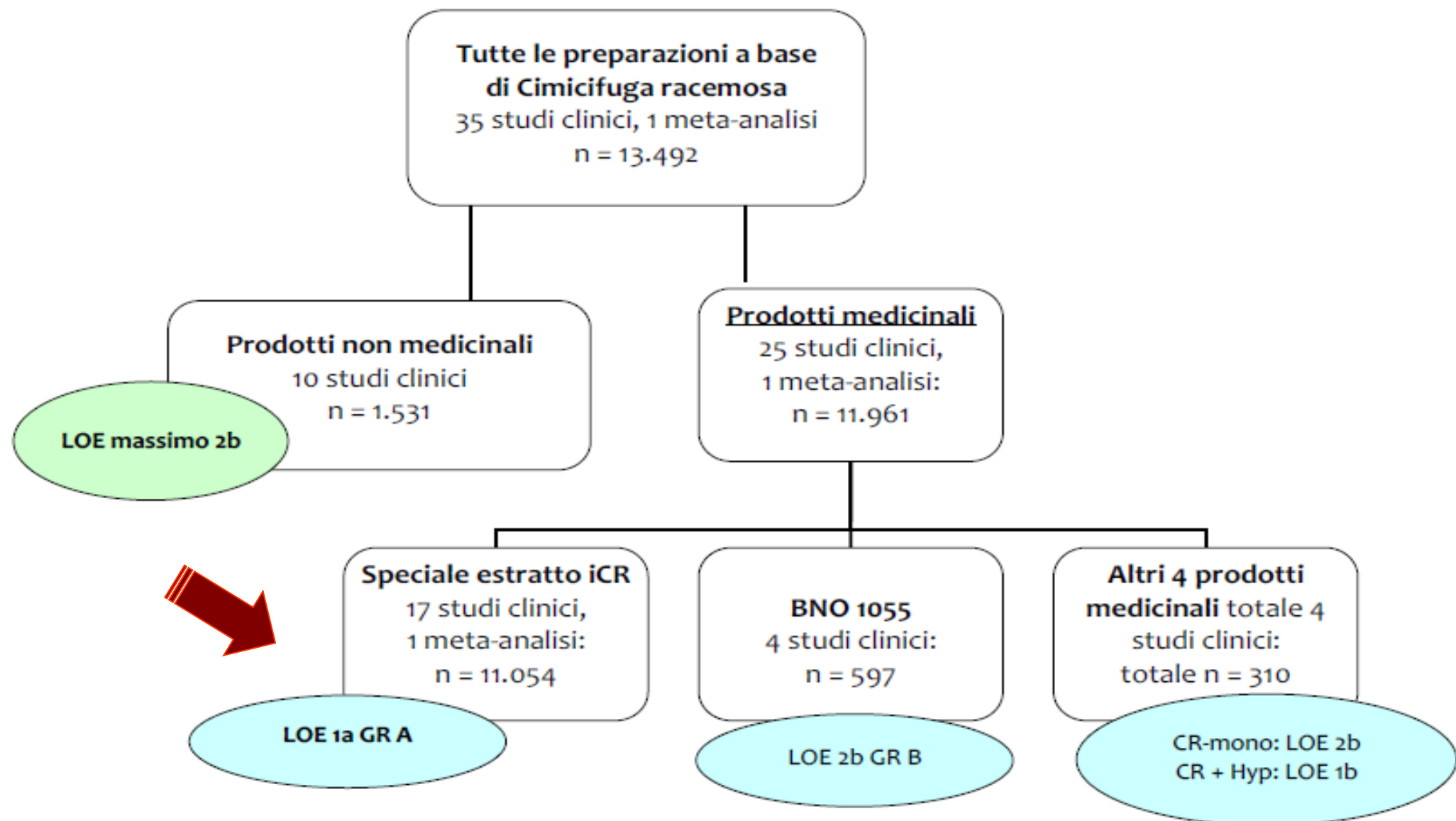
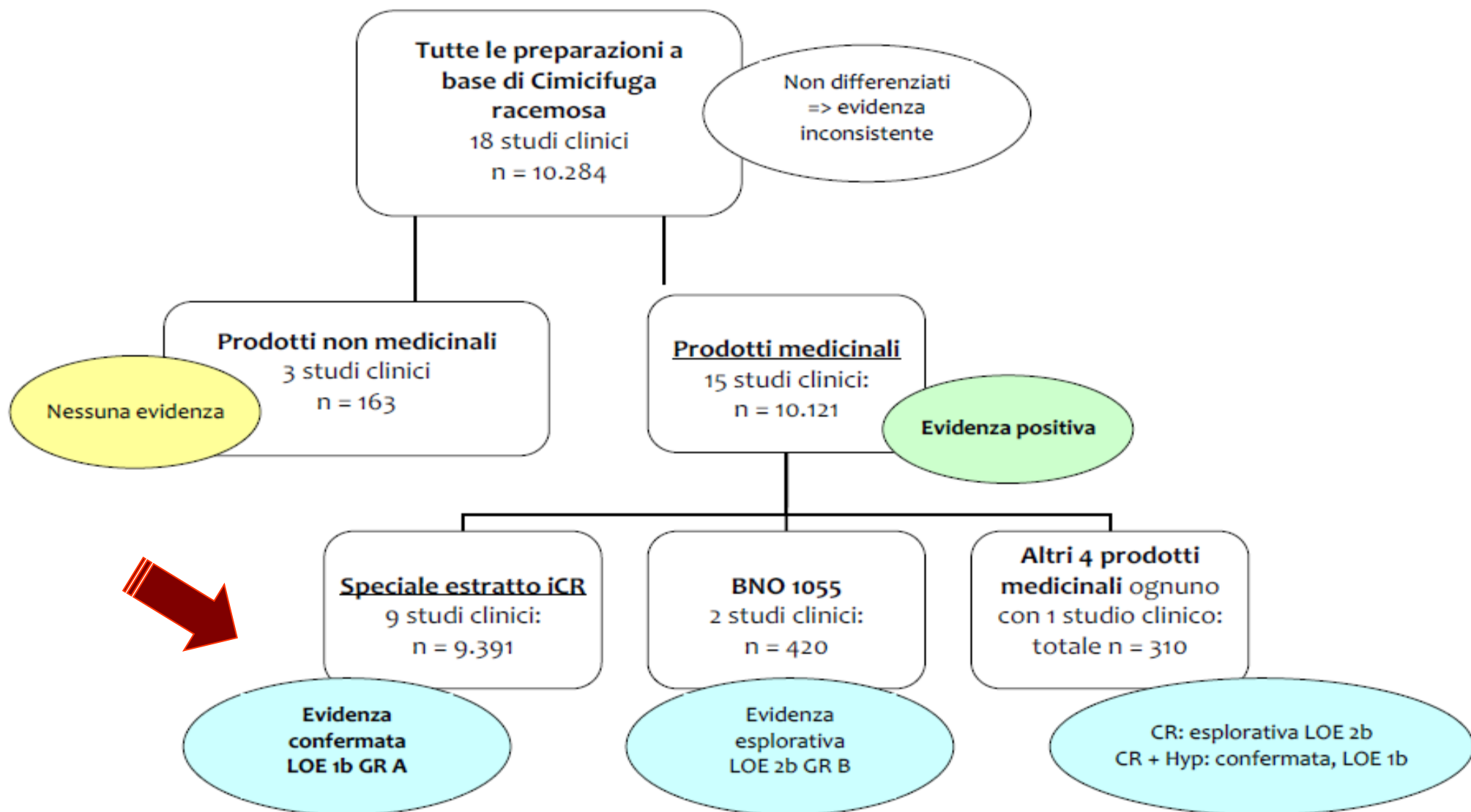


Figura 3: dati di efficacia sulla *Cimicifuga racemosa* 2000-2012

n: pazienti esaminati, trattati con *Cimicifuga racemosa*





Review

The non-estrogenic alternative for the treatment of climacteric complaints:
Black cohosh (*Cimicifuga* or *Actaea racemosa*)

Wolfgang Wuttke^{a,*}, Hubertus Jarry^b, Jutta Haunschild^c, Guenter Stecher^c,
Markus Schuh^c, Dana Seidlova-Wuttke^a

^a Hormone and Obesity Center Goettingen, Bahnhofsallee 1d, 37081 Göttingen, Germany

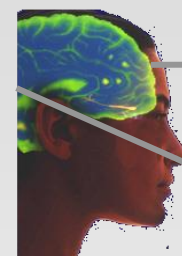
^b University Medical Center, Göttingen, Germany

^c Bionorica SE, Neumarkt 92318, Germany

EFFICACY?

SAFETY?

**EVIDENZE DA
STUDI IN VITRO E IN VIVO SULL'ANIMALE
STUDI CLINICI**



Cervello

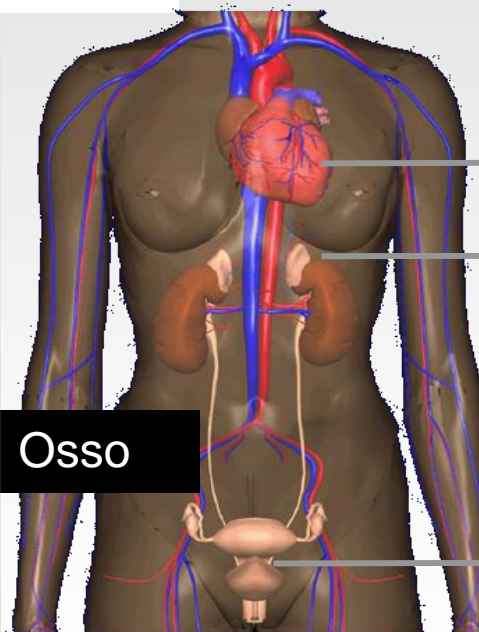
Neurovegetativo

Cuore

Mammella

Osso

Urogenitale



THE EFFECTS OF REMIFEMIN ON SUBJECTIVE SYMPTOMS OF MENOPAUSE

Gabor V. et al. *Advances in Therapy* Volume 22 No.2 March/April 2005

Effetti di Remifemin* sui sintomi della menopausa Gabor V. et al. *Advances in Therapy* Volume 22 No.2 March/April 2005

2.016 DONNE, TRA I 40 E I 65 ANNI

Terapia: Remifemin 2 cpr/die per 12 settimane.

Valutato indice di Menopausa di Kupperman ogni 4 settimane.

Dopo **12** sett la diminuzione totale

- è stata di:
- ▶ **29%** alla 4° settimana
 - ▶ **27.9%** all' 8° settimana
 - ▶ **27.6%** alla 12° settimana.
 - ▶ Il **49.4%** delle pz ha avuto una diminuzione superiore ai 18 punti.

La media è stata di **17.64** punti ($p < 0.01$)

Remifemin si è dimostrato efficace nell'alleviare i sintomi neurovegetativi e psichici legati alla menopausa.

SINTOMI →	inizio	4° sett	8° sett	12° sett
Vampate	9.65	6.95	4.90	3.33
Sudorazioni	4.29	2.99	2.12	1.43
Insonnia	3.72	2.65	1.92	1.45
Ansia	3.53	2.57	1.92	1.53
Depressione	1.20	0.84	0.63	0.48
Vertigini	0.85	0.57	0.41	0.30
Perdita di concentrazione	1.02	0.76	0.58	0.47
Dolori artrosici	1.29	1.05	0.91	0.82
Mal di testa	1.17	0.84	0.62	0.48
Palpitazioni	1.31	0.87	0.63	0.47
Totale	28.00	19.88	14.32	10.36

*estratto secco isopropanolico (iCR) di Cimicifuga racemosa rizoma (20 mg per compressa), standardizzato in glicosidi triterpenici (2-3,5%).

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: Remifemin (CR) 2 cpr/die per 3 mesi

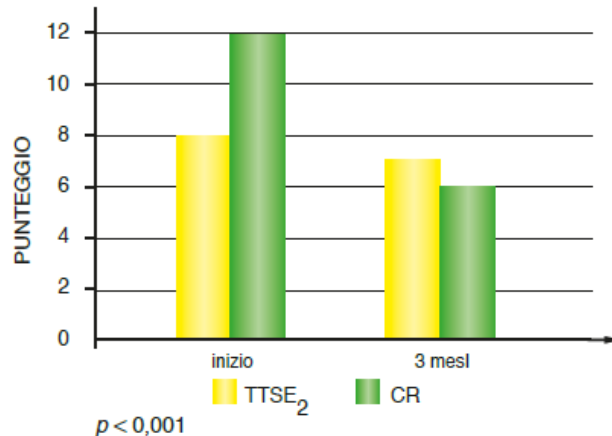
Valutati: sintomi vasomotori, neurovegetativi, parametri ormonali, profilo lipidico e spessore endometriale.

remifemin® e TTSE2 hanno ridotto significativamente i sintomi vasomotori già dopo 1 mese di trattamento

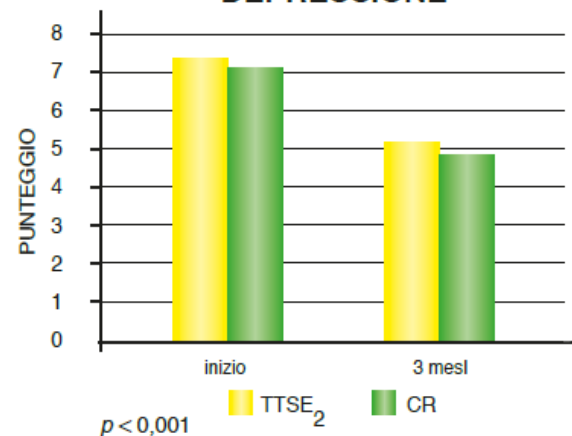
SINTOMI VASOMOTORI



ANSIA



DEPRESSIONE



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

Valutazione parametro	Inizio	dopo 3 mesi	p value
Colesterolo totale mg/dl	228.8 ± 33.1	221.8 ± 30.0	0,03
HDL mg/dl	51.6 ± 1.8	53.1 ± 1.7	NS
LDL mg/dl	153.8 ± 39.0	146.1 ± 34.1	0,002
Trigliceridi mg/dl	115.5 ± 50.5	112.5 ± 42.3	NS
GOT U/l	14.6 ± 3.4	14.5 ± 3.8	NS
GPT U/l	20.9 ± 4.6	20.8 ± 5.1	NS
FSH IU/l	57.4 ± 13.9	59.6 ± 17.1	NS
LH IU/l	28.8 ± 8.9	30.8 ± 10.8	NS
17-B-E ₂ pg/ml	19.0 ± 5.6	18.7 ± 5.0	0,001
PRL ng/ml	10.9 ± 3.5	10.4 ± 3.4	0,005
Spessore	3.8 ± 0.2	3.6 ± 0.2	NS

remifemin[®] non ha alterato:

- ▶ i livelli di ormoni nel sangue
- ▶ gli enzimi epatici
- ▶ il profilo lipidico
- ▶ lo spessore endometriale

Nappi RE, Malavasi B, Brundu B, Facchinetti F. Efficacy of Cimicifuga racemosa on climacteric complaints: a randomized study versus low-dose transdermal estradiol. Gynecol Endocrinol. 2005 Jan;20(1):30-5

C. RACEMOSA EXTRACTS HAVE NO ESTROGENIC EFFECTS IN THE ENDOMETRIUM AND THEREFORE, BARE NO RISKS FOR THE UTERUS.

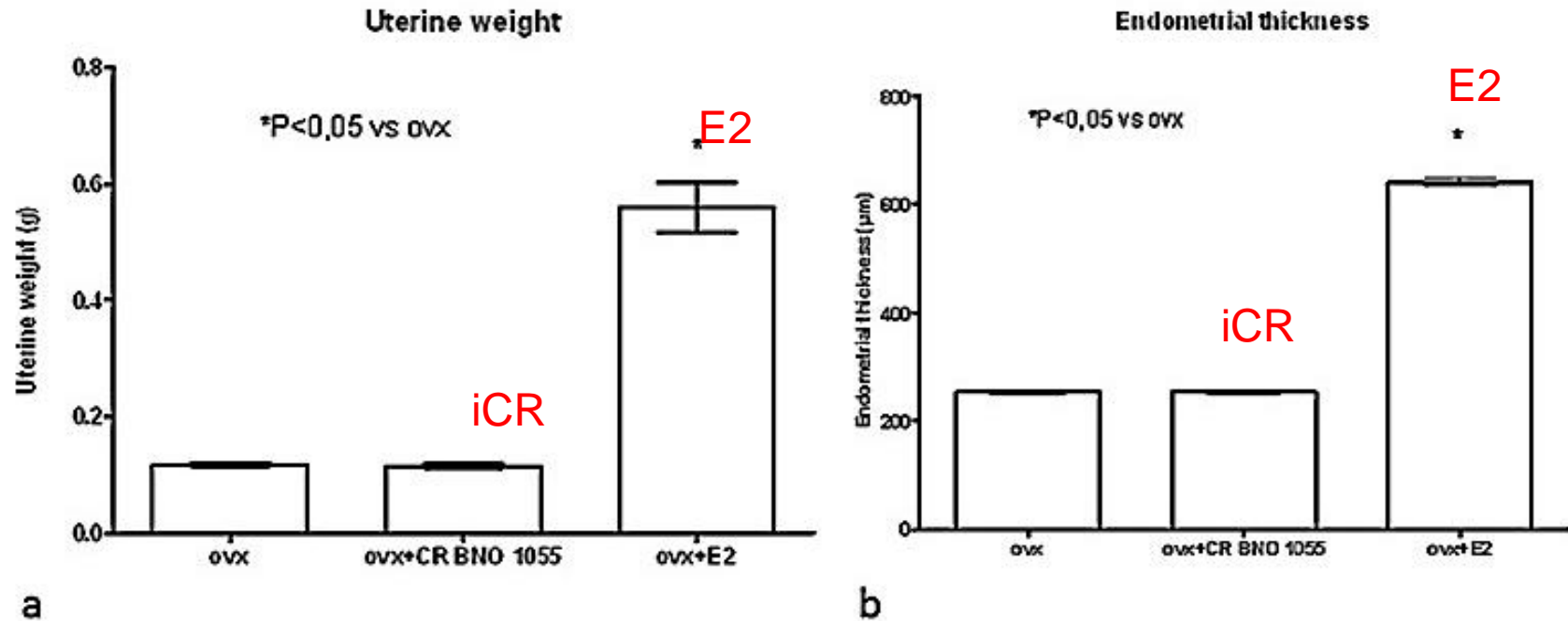


Fig. 4. Effects of estradiol (E2) and CR BNO 1055 in the uterus. Quantitative evaluation of (a) uterine weight and (b) endometrial thickness in ovx controls, ovx rats treated for 3 months with estradiol or CR BNO 1055. Note lack of stimulation of both parameters in the CR BNO 1055 treated animals. This confirms the absence of estrogenic activities in the black cohosh extract.

D. Seidlova-Wuttke, et al , Maturitas (2003)

G. Kretzschmar, et al T. Journal of Steroid Biochemistry and Molecular Biology (2005) .

Effect of Isopropanolic *Cimicifuga racemosa* Extract on Uterine Fibroids in Comparison with Tibolone among Patients of a Recent Randomized, Double Blind, Parallel-Controlled Study in Chinese Women with Menopausal Symptoms

Sisi Xi,¹ Eckehard Liske,² Shuyu Wang,³ Jianli Liu,⁴ Zhonglan Zhang,⁴ Li Geng,⁵ Lina Hu,⁶ Chunfeng Jiao,⁷ Shurong Zheng,¹ Hans-Heinrich Henneicke-von Zepelin,^{8,*} and Wenpei Bai^{1,*}

[Author information](#) ► [Article notes](#) ► [Copyright and License information](#) ►

iCR induce riduzioni significative del volume dei miomi vs Tibolone

Abstract

Go to:

Objective. Effect of isopropanolic *Cimicifuga racemosa* extract (iCR) on uterine fibroid size compared with tibolone. **Method.** The randomized, double-blind, controlled study in China enrolled 244 patients aged 40–60 years with menopausal symptoms (Kupperman Menopause Index ≥ 15). The participants were treated with either iCR of 40 mg crude drug/day ($N = 122$) or tibolone 2.5 mg/day ($N = 122$) orally for 3 months in 2004. Now, we investigated the subset of all women ($N = 62$) with at least one uterine fibroid at onset of treatment for the effect of iCR ($N = 34$) on fibroid size compared with tibolone ($N = 28$) by transvaginal ultrasonography. **Results.** The median myoma volume decreased upon iCR by as much as -30% ($P = 0.016$) but increased upon tibolone by $+4.7\%$. The percentage of volume change, mean diameter change and geometric mean diameter change of the iCR group compared to tibolone were statistically significant ($P = 0.016, 0.021, 0.016$ respectively). **Conclusion.** Our results suggest that iCR (Remifemin) is a valid herbal medicinal product in patients with uterine myomas as it provides adequate relief from menopausal symptoms and inhibits growth of the myomas in contrast to tibolone.

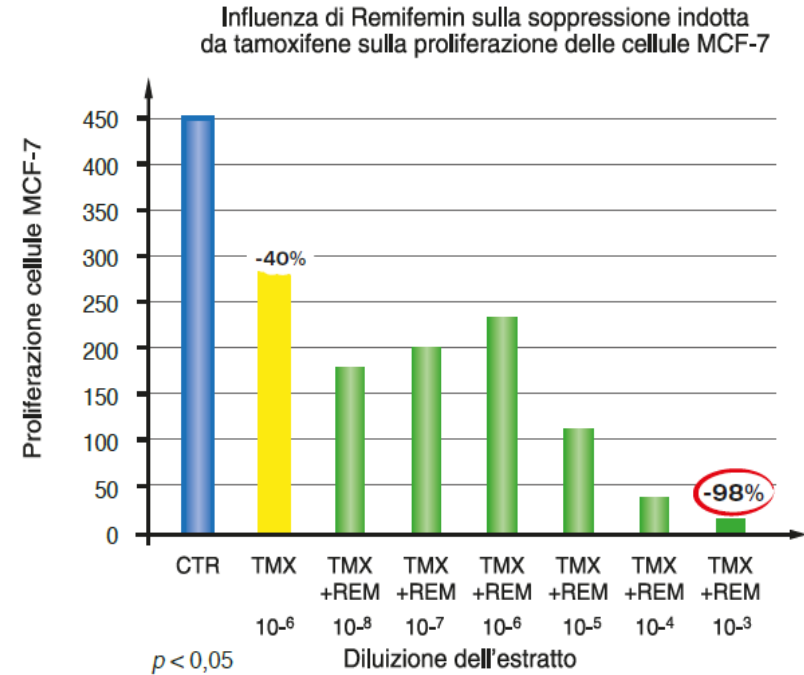
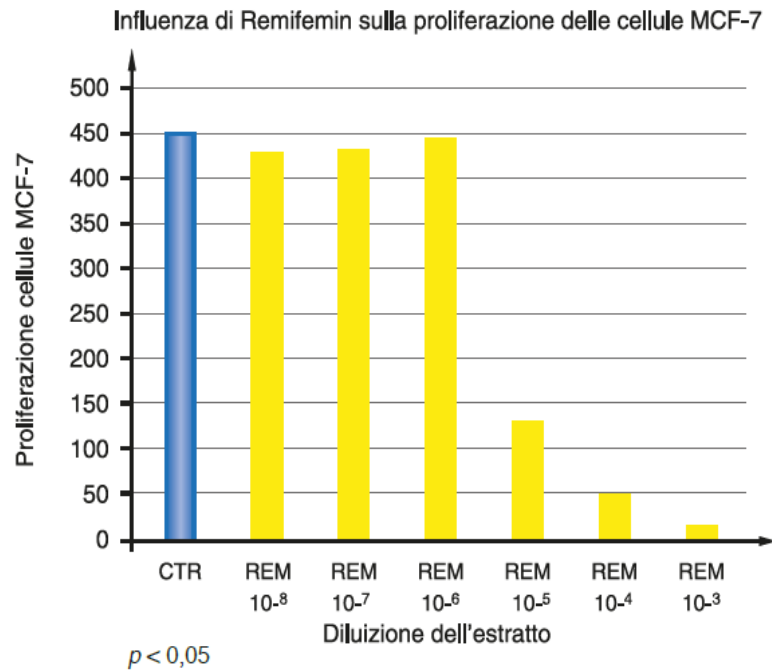
STUDIO IN VITRO SU LINEE CELLULARI MCF-7

di adenocarcinoma mammario umano MCF-7 estrogeno-dipendente

Valutazione: influenza di **Remifemin** (REM) su tumore al seno estrogeno-dipendente anche in associazione a tamoxifene (TMX)

Remifemin **inibisce** la proliferazione delle cellule di tumore al seno MCF-7

Remifemin **aumenta** l'effetto inibitorio del tamoxifene sulle cellule MCF-7 fino al 98%



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.

Dati recenti condotti “in vivo” su pazienti dimostrano che la somministrazione per 6 mesi di estratto alcolico di Cimicifuga racemosa **non modifica la densità mammografica** e, nelle cellule di aspirato mammario, la produzione dell’antigene Ki-67 (un marker di proliferazione cellulare) non risulta modificata dopo terapia


▼ Studio di sicurezza, prospettico, aperto, non controllato, con osservatori in cieco

75 DONNE IN POST-MENOPAUSA

Terapia: Remifemin 2 cpr/die per 6 mesi

Valutati: spessore endometrio, densità del seno, proliferazione cellule del seno, colesterolo tot, trigliceridi, SHBG

- Dopo 6 mesi:**
- ▶ **Nessun aumento della densità del seno**
 - ▶ **Nessuna proliferazione delle cellule del seno**
 - ▶ Nessuna alterazione dell'endometrio
 - ▶ Nessuna variazione dei lipidi nel sangue
 - ▶ Nessuna variazione di SHBG.



	Inizio	6 mesi
Spessore endometrio	2.1 ± 0.9 mm	2.1 ± 0.9 mm
Colesterolo totale	5.9 ± 0.8 µg/l	5.8 ± 0.9 µg/l
Trigliceridi	1.4 ± 0.9 µg/l	1.3 ± 0.9 µg/l
SHBG	52.1 ± 17.9 µg/l	50.4 ± 16.6 µg/l

Hirschberg AL et al. An isopropanolic extract of black cohosh does not increase mammographic breast density or breast cell proliferation in postmenopausal women. Menopause. 2007 Jan-Feb;14(1):89-96.

ISOPROPANOLIC BLACK COHOSH EXTRACT AND RECURRENCE-FREE SURVIVAL AFTER BREAST CANCER

Henneicke-von Zepelin H.H. *et al. International Journal of Clinical Pharmacology and Therapeutics. Vol 45, No. 3/2007 (143-154)*

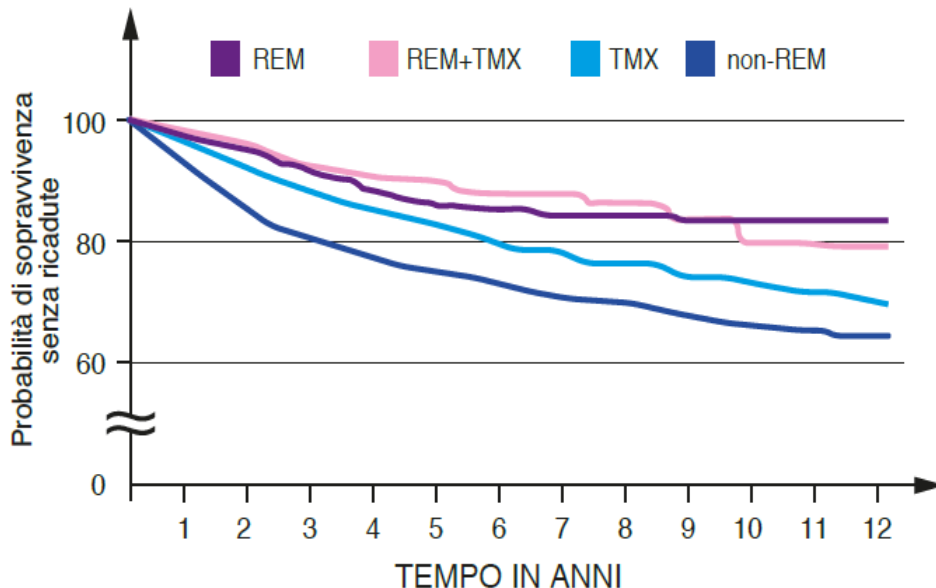
18.861 PAZIENTI DI CUI 1.102 HANNO ASSUNTO REMIFEMIN

► Studio retrospettivo, farmacoepidemiologico, osservazionale

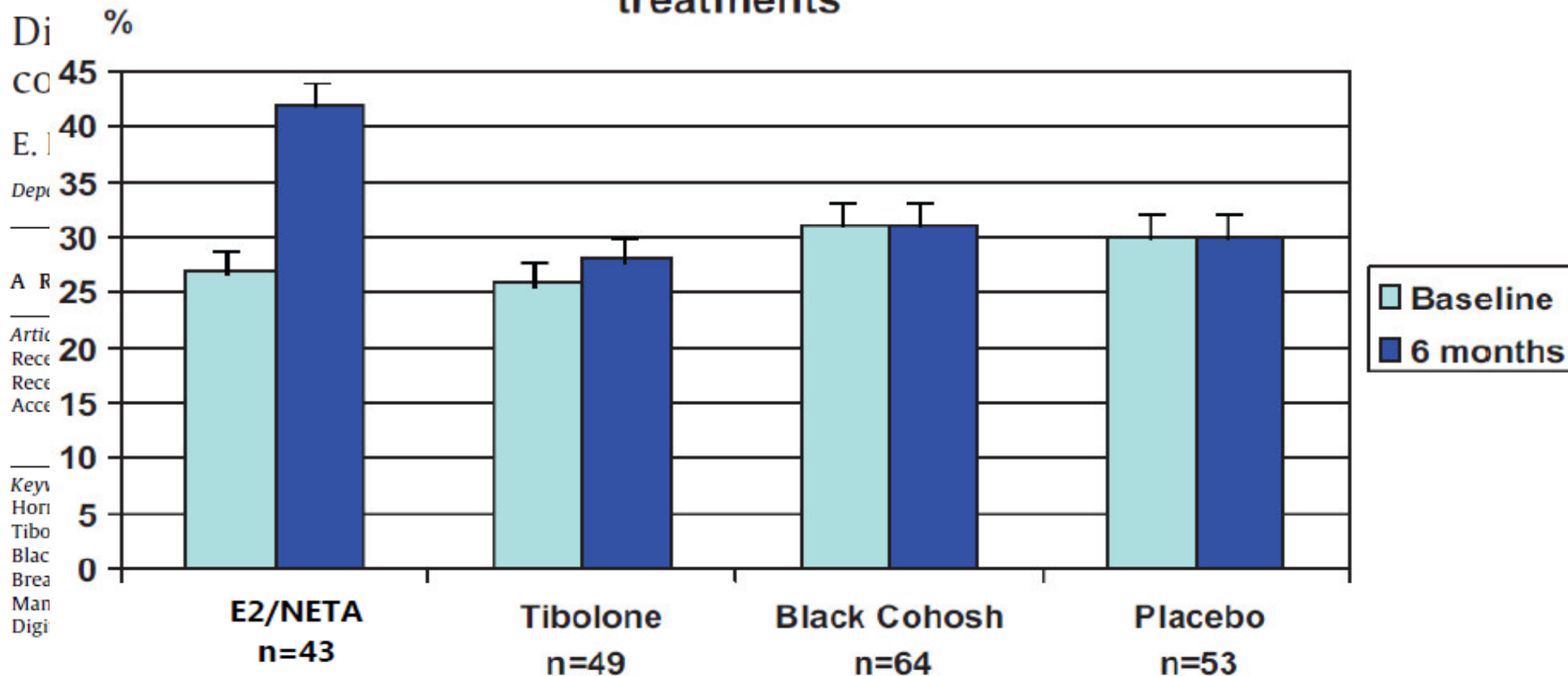
Il **35,8%** del gruppo **REM** e il **24%** del gruppo **non-REM** ha assunto tamoxifene (TMX) nel periodo della diagnosi.

Valutazione: sopravvivenza senza ricadute dopo tumore al seno

Risultati: dopo 2 anni il 14% del gruppo non-REM ha avuto una ricaduta. Il gruppo REM ha raggiunto la stessa % dopo 6,5 anni.



Change in density during different treatments



E2/NETA on the one hand and tibolone, black cohosh and placebo on the other was highly significant ($p < 0.0001$).

Conclusions: Digitized mammographic breast density is a highly sensitive method confirming significant increase in density by standard E2/NETA treatment and to a lesser extent by tibolone, whereas black cohosh does not influence mammographic breast density during six months treatment. Digitized assessment also yields data on individual variation and small increases left undetectable by visual classification.

remifemin® è efficace sui sintomi climaterici in donne con tumore al seno e in trattamento con tamoxifene

50 DONNE, ETÀ MEDIA 56 ANNI

► Studio prospettico osservazionale

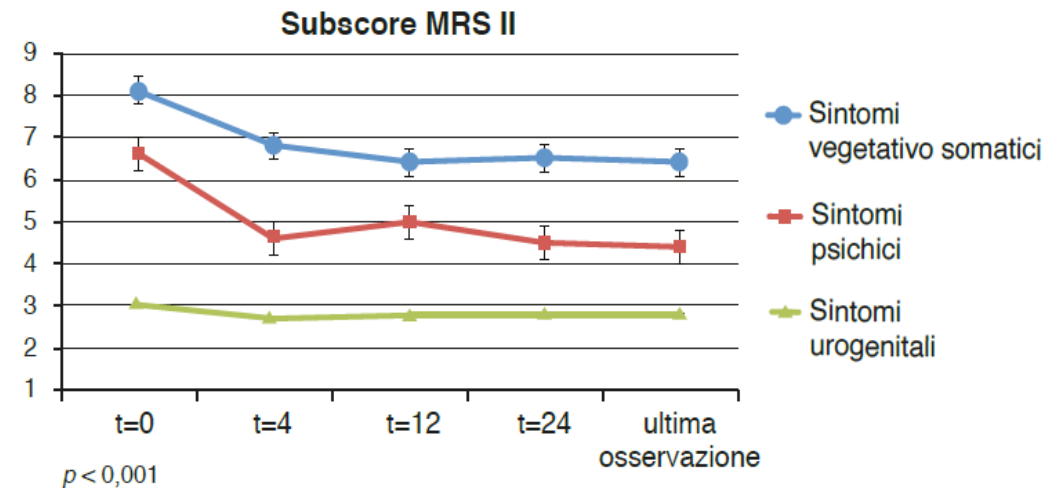
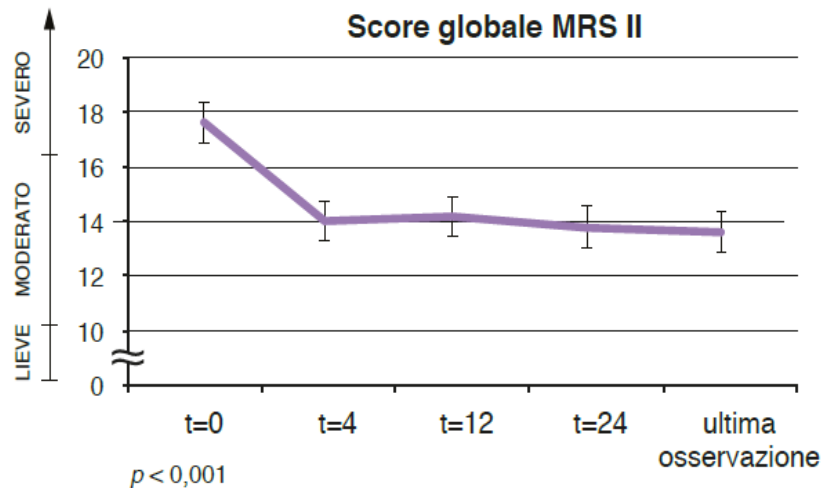
operate di tumore al seno in trattamento con tamoxifene (da 10 a 40 mg/die) e con sintomatologia climaterica

Terapia: Remifemin 1-4 cpr/die per 6 mesi

Valutazione: Menopause Rating Scale II (MRSII)

Risultati: significativo miglioramento dei sintomi

Non è stata riportata
nessuna ricaduta del tumore durante
il periodo di osservazione



REMIFEMIN E OSSO

Remifemin: effetti su cross-links urinari ed altri parametri di qualità delle ossa in un modello di osteoporosi in ratto ovariectomizzato Neisslein T, Freudenstein J. Journal of Bone Mineral Metabolism (2003) 21:370-376 World Congress on Osteoporosis 2000 Chicago, Illinois, USA

STUDIO IN VIVO RANDOMIZZATO

Studiato l'effetto di Remifemin, a confronto con raloxifene, sulla massa ossea di ratti ovariectomizzati.

30 ratti alimentati con dieta priva di soia per 12 settimane.

Terapia 1° gruppo controllo: dieta n=10 CTR

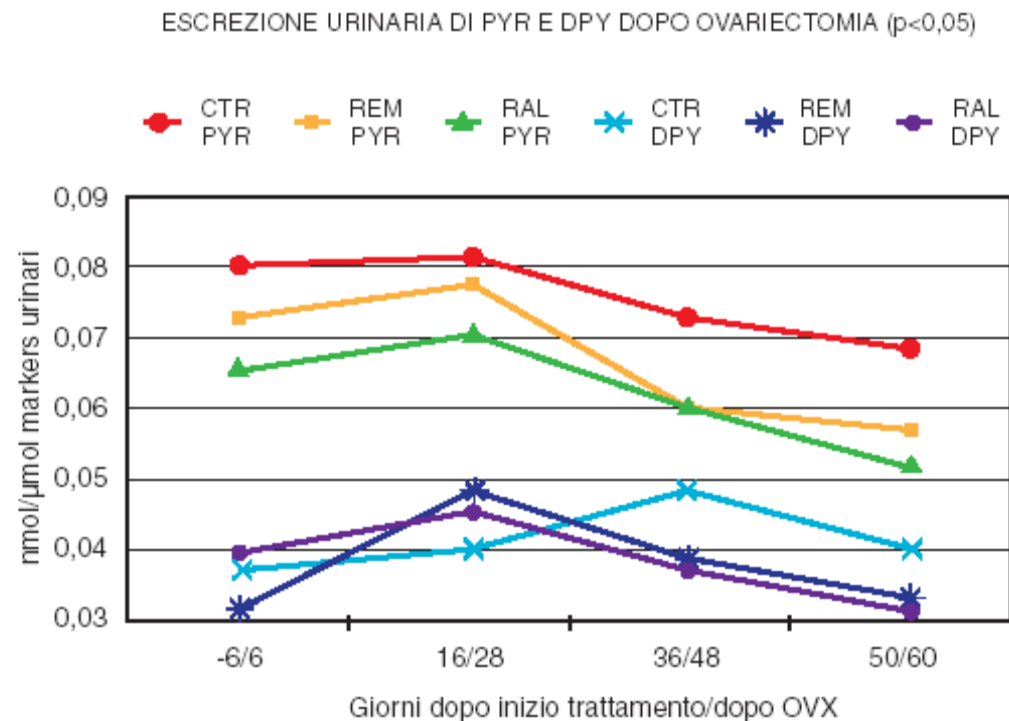
Terapia 2° gruppo: dieta+raloxifene 3mg/kg intragastrico n=10 RAL

Terapia 3° gruppo: dieta+4500µg/die di glicosidi triterpenici n=10 REM

Valutati: escrezione urinaria di piridinolina PYR e desossipiridinolina DPY, in quanto markers specifici della perdita di massa ossea, misurati all'inizio ed a successivi intervalli settimanali

Il Remifemin ha diminuito significativamente il contenuto urinario di PYR e DPY.

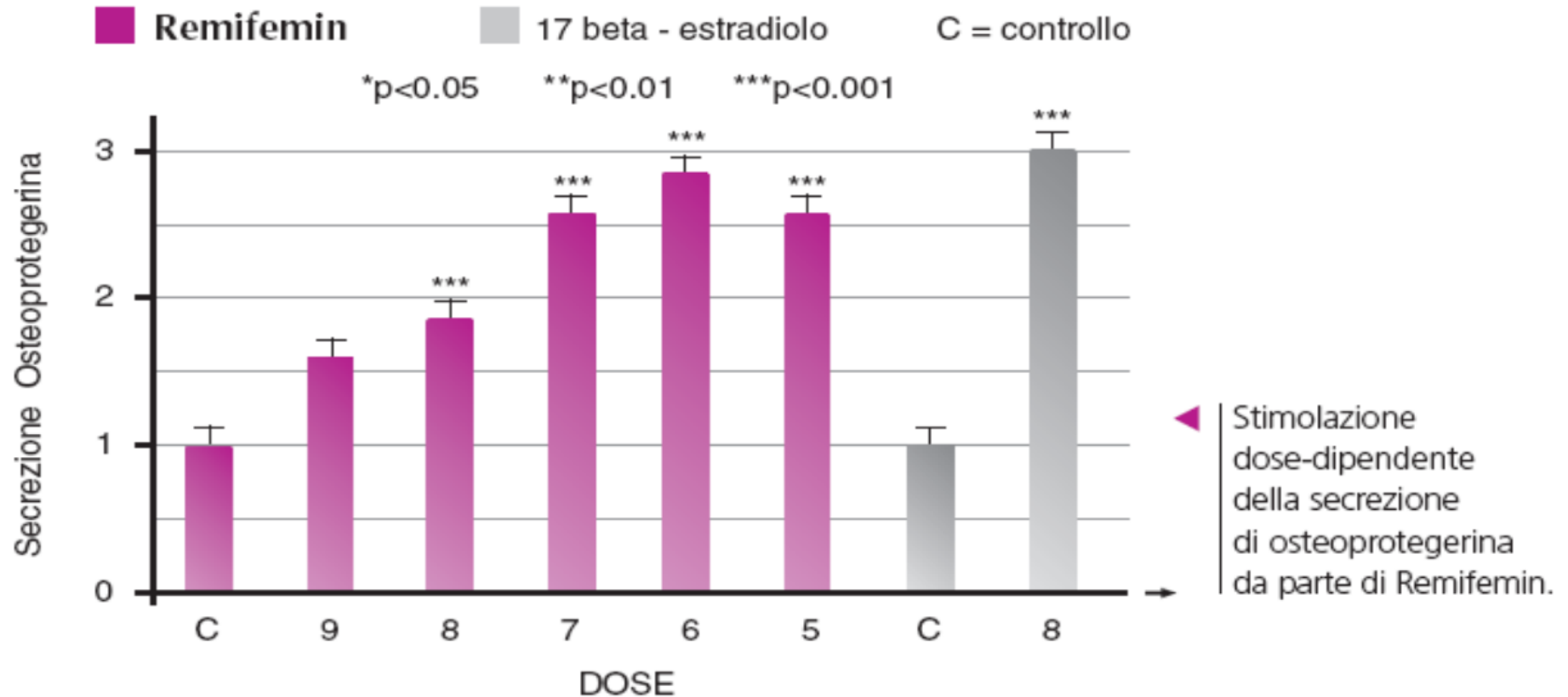
L'inversione degli effetti dell'ovariectomia sulla perdita della massa ossea è iniziata dopo 2-5 settimane dall'inizio della terapia.



Isopropanolic Extract of Black Cohosh Stimulates Osteoprotegerin Production by Human Osteoblasts

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ABSTRACT: An isopropanolic extract (iCR) from the rhizomes of *Cimicifuga racemosa* (black cohosh) is used as an alternative in the treatment of menopausal symptoms, and animal studies suggest positive skeletal effects. iCR stimulated osteoblastic OPG protein secretion by 3- to 5-fold as early as 12 h without affecting RANKL expression. The iCR effect, abrogated by the pure estrogen receptor antagonist ICI 182,780, also enhanced ALP activity (4-fold) and osteocalcin expression (3-fold), possibly contributing to the skeletal effects of black cohosh.



STUDIO IN VIVO SU 120 RATTI

► Randomizzato su ratti Sprague-Dawley ovariectomizzati

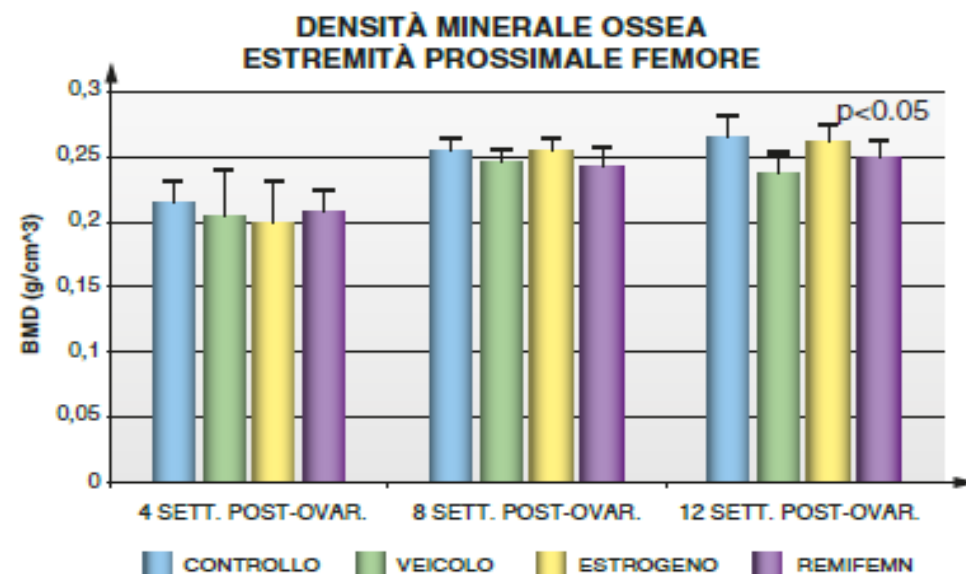
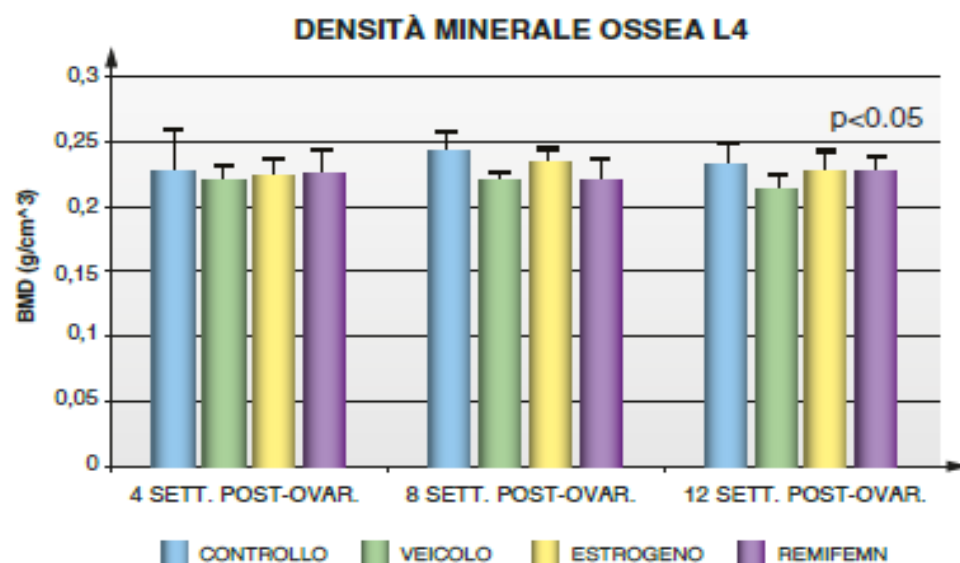
Valutato l'effetto di **Remifemin** ed Estradiolo valerato su

- densità minerale ossea
- struttura trabecolare
- parametri biomeccanici

del femore e delle vertebre lombari per 12 settimane dopo ovariectomia

Suddivisione ratti

- 1° gruppo:** no ovariectomia
- 2° gruppo:** ovariectomia + veicolo
- 3° gruppo:** ovariectomia + estrogeno
- 4° gruppo:** ovariectomia + **Remifemin**



Osservazioni sulla epatotossicità della Cimicifuga racemosa

- ❖ Sulla base di osservazioni emerse su una possibile connessione causale tra uso della Cimicifuga ed epatotossicità, nel luglio del 2006 fu raccomandato dall'EMA (Agenzia Europea per i Medicinali) la sospensione dell'uso della pianta a fini terapeutici in attesa di maggiori approfondimenti
- ❖ La rianalisi delle 42 osservazioni descritte in letteratura sulla presunta connessione tra uso della Cimicifuga e danni epatici permetteva all'EMA di riammettere nel novembre 2006 la pianta alla commercializzazione
- ❖ Dalla rianalisi dei dati effettuata dall'EMA è infatti emerso che dei 42 casi osservati e descritti di possibile epatotossicità solo 16 casi risultavano avere sufficiente documentazione da poter essere rianalizzati. In nessuno dei 4 casi identificati in cui la correlazione era stata definita come “possibile” o “probabile” è risultato essere stato utilizzato l'estratto alcolico di Cimicifuga racemosa .

Suspected black cohosh hepatotoxicity: no evidence by meta-analysis of randomized controlled clinical trials for isopropanolic black cohosh extract

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Abstract

Objective: Black cohosh, a popular herbal treatment for menopausal symptoms, has been implicated in a number of hepatotoxicity case reports. The purpose of this investigation was to analyze data gained from clinical trials on the effect of black cohosh on liver function.

Methods: A meta-analysis of randomized, double-blind, and controlled clinical trials was conducted. These studies primarily evaluated the efficacy and safety of the isopropanolic black cohosh extract (iCR) in perimenopausal and postmenopausal women. Raw data on liver function values of aspartate aminotransferase, alanine aminotransferase, and γ -glutamyltranspeptidase were considered in this analysis, if these data at baseline and after 3 to 6 months were available.

Results: Five randomized, double-blind, and controlled clinical trials were included in the meta-analysis. The overall analysis showed no significant effect of iCR on liver function. The nonsignificant effects concerned the overall analyses of all included studies as well as the proportion of placebo-controlled studies.

Conclusions: The results of this meta-analysis of five randomized, double-blind, and controlled clinical trials showed no evidence that iCR has any adverse effect on liver function.

Key Words: Black cohosh – Black cohosh hepatotoxicity – Liver function – Meta-analysis.

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