Effect of red ginseng (홍삼) and pomegranate (석류) on menopausal symptoms and cardiovascular risk factors

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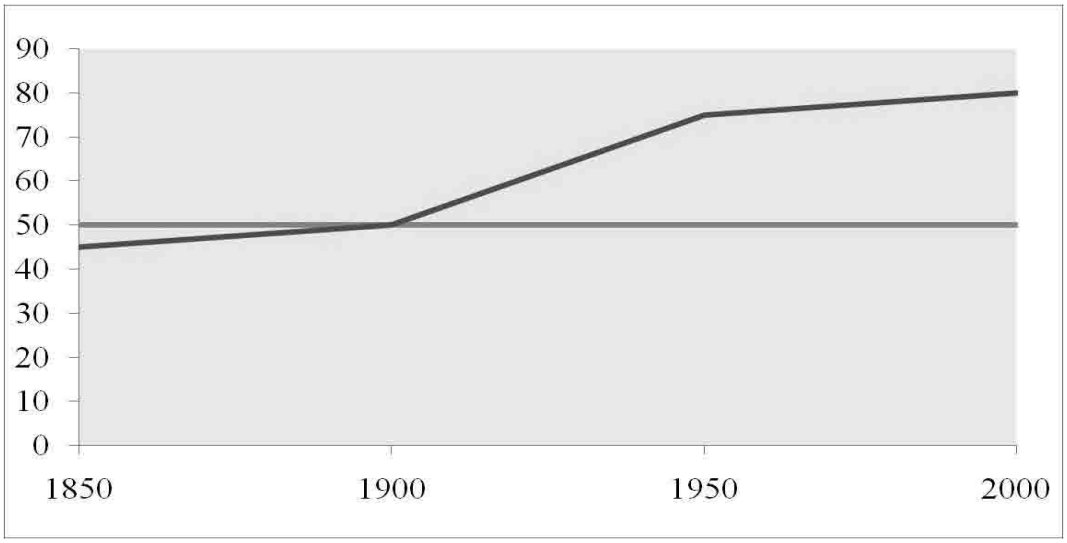
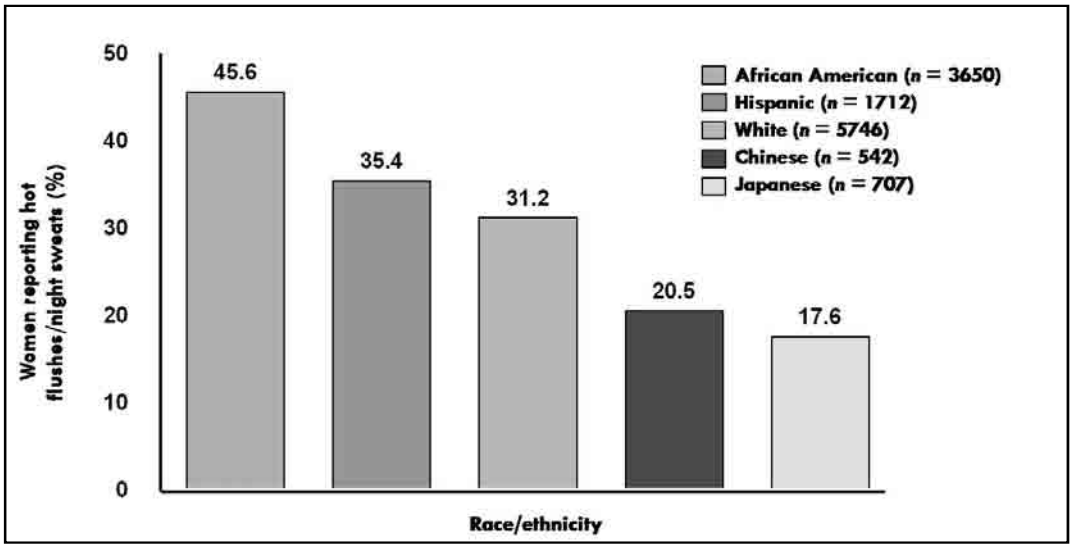
Introduction

Life expectancy and age of menopause



Prevalence of vasomotor symptoms in perimenopausal women



Gold EB. Am J Epidemiol 2000;152:463–73.

Menopause: The Journal of The North American Menopause Society
Vol. 16, No. 5, pp. 870-876
DOI: 10.1097/gme.0b013e31819d88da

Do Japanese American women really have fewer hot flashes than European Americans? The Hilo Women's Health Study

- In Asia, for example, the incidence of hot flashes was reported to be less than a third of that for women in the United States
- Experts at the time attributed this disparity to possible ethnic differences in sweating mechanisms, endogenous estrogen concentrations, or dietary practices, citing the higher intake of soy in the Asian diet across the lifespan.
- The common finding of fewer reported HFs in people of Japanese ancestry may be a consequence of reporting bias: JAs report fewer symptoms of many conditions compared with people from other ethnic groups. This is probably due to cultural conceptions of what is appropriate to report.

Menopausal hot flashes: How long do they really last?

In Europe and North America, hot flashes are the commonest symptoms of menopause, affecting around 70% of women and persisting for an average of 2 to 5 years, although some 20% of women continue to flash into their 70s and 80s

Kronenberg F. Ann NY Acad Sci 1990;592:52-86.

Complementary and alternative medicine (CAM)

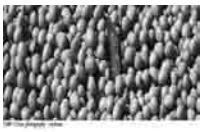
1. **Alternative medical systems**
   - Traditional Chinese Medicine, Homeopathy, Ayurvedic Medicine, Naturopathic Medicine
2. **Mind-body intervention**
   - Biofeedback, Meditation, Cognitive-Behavioral therapy Stress Management, Art Therapy, Music Therapy, Relaxation Techniques, Breathing Exercises, Hypnosis, Tai Chi, Yoga
3. **Biologically based therapies**
   - Phytotherapy, Western Herb, Clinical nutrition, Dietary supplement, Diet based therapy, Orthomolecular medicine, Vitamin C therapy, Enzyme therapy, Chelation, Cell therapy, Oxygen therapy, Detoxification
4. **Manipulative and body-based methods**
   - Chiropractic, Osteopathy, Acupressure, Applied kinesiology, Prololotherapy, Intra Muscular Stimulation, Neural Therapy, Hydrotherapy, Therapeutic massage, Reflexoogy, Shiatsu, Taping therapy
5. **Energy therapies**
   - Gi gong, Magnetic field therapy, Light therapy

Why should providers care about CAM therapies?

- 25-36% of patients are using CAM
- Only 45-56% will tell their provider about their use
- 68% of patients in one study felt the herbs improved their symptoms
- Use of CAM is common among many ethnicities
  - ➢ 50% Hispanic, 50% Asian, 41% White, 22% African American

Botanicals for menopausal symptoms

- Soy



- Red clover

- Wild yam (야생참마)

- Black cohosh

- St John's Wort

- Evening primrose
- Don Quai (당귀)

Ginseng

Ginseng

- *Panax ginseng* (Asian ginseng) and *Panax quinquefolius* (American ginseng) have been traditionally used as tonics.
- 2 studies (American ginseng) conducted showed no significant change in hot flashes. ***(Wiklund,1999; Tode,1999)***
- But both studies showed improved sense of wellbeing, depression, mood and sleep consistent with its traditional use as a tonic (invigoration or fortification).
- Although ginseng is generally well tolerated, reported side effects have included nervousness, insomnia, dizziness and hypertension.

Ginsenosides

- The major pharmacologically active components of ginseng
  - Steroidal saponins comprising 3-6 % of ginseng
- Two ginsenosides with estrogenic activity
  - Rb 1 and Rh1
- Ginsenoside-Rb 1
  - Activates estrogen- responsive genes in the presence of either ERα or ER β

Effects of a standardized ginseng extract on quality of life and physiological parameters in symptomatic postmenopausal women: a double-blind, placebo-controlled trial. Swedish Alternative Medicine Group *(Wiklund et al,1999)*

- **A randomized, multicenter, double-blind, parallel group study**
  - 193 women treated with ginseng & 191 treated with placebo
- **QoL**
  - Psychological General Well-Being (PGWB) index, Women's Health Questionnaire (WHQ),Visual Analogue (VA) scales
- **Physiological parameters**
  - FSH, estradiol levels, endometrial thickness, maturity index, vaginal pH

- Exploratory analysis of PGWB subsets reported p-values < 0.05 for **depression**, **well-being** and **health subscales** in favor of ginseng compared with placebo.
- No statistically significant effects were seen for the WHQ and the VA scales or the physiological parameters, including vasomotor symptoms (hot flushes).

Effect of Korean red ginseng on psychological functions in patients with severe climacteric syndromes *(Tode,1999)*

- 12 postmenopausal women with climacteric syndromes or 8 postmenopausal women without any climacteric syndrome
- **Treatment with daily oral administration of 6 g RG**
- **Psychological tests**
  - Cornell Medical Index (CMI) and the State-Trait Anxiety Inventory (STAI)
- **Blood test**
  - ACTH, cortisol and DHEA-S

- Improvement of CMI and STAI scores in postmenopausal women suffering climacteric syndromes, particularly **fatigue**, **insomnia** and **depression**, by RG seemed to be brought about in part by effects of RG on stress-related hormones as shown by a decrease in cortisol/DHEA-S ratio.

Menopause: The Journal of The North American Menopause Society
Vol. 19, No. 4, pp. 461-466
DOI: 10.1097/gme.0b013e3182325a4b
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Effects of red ginseng supplementation on menopausal symptoms and cardiovascular risk factors in postmenopausal women: a double-blind randomized controlled trial

Objective: The aim of this study was to evaluate the effects of red ginseng (RG) on menopausal symptoms and cardiovascular risk factors in postmenopausal women.

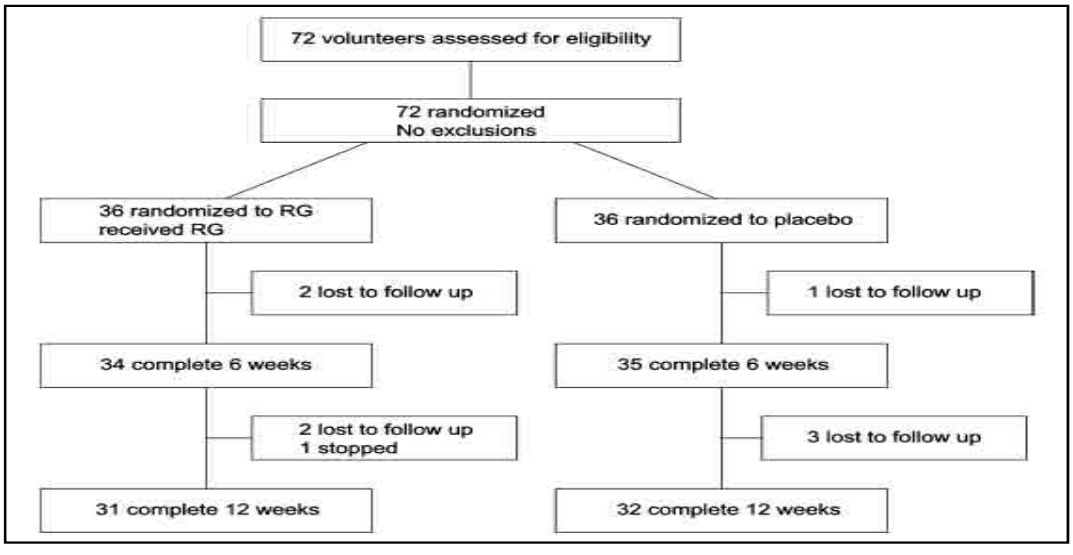
Methods: A randomized, placebo-controlled, double-blind clinical trial was conducted with postmenopausal women between the ages of 45 and 60 years. A total of 72 women were randomly assigned to either an RG group (supplemented with 3 g of RG, including 60 mg of ginsenosides, per day) or a placebo group for 12 weeks. We analyzed changes in menopausal symptoms (the Kupperman index and the menopause rating scale), cardiovascular risk factors (lipid profiles, high-sensitivity C-reactive protein, and carotid intima-media thickness), and serum estradiol levels from baseline to 12 weeks.

Results: Significant improvements in the Kupperman index (P = 0.032) and in the menopause rating scale (P = 0.035) scores were observed in the RG group compared with the placebo group. Total cholesterol (P = 0.009) and low-density lipoprotein cholesterol (P = 0.015) significantly decreased in the group receiving RG. The RG group also showed a significant decrease in carotid intima-media thickness (P = 0.049). Serum estradiol levels were not influenced by RG supplementation.

Conclusions: RG could be an attractive herbal dietary supplement for relieving menopausal symptoms and conferring favorable effects on markers of cardiovascular disease in postmenopausal women.

Menopause 2012;19:461-466.

Study design



Menopause 2012;19:461-466.

Red ginseng supplementation

- **Study group**
  - Korean red ginseng
    - Obtained by steaming and drying naturally dried and unpeeled 6-year-old raw white ginseng
  - RG - 3g/day for 12 weeks
    - Ginsenosides - 60mg/day for 12 weeks
- **Control group**
  - Placebo for 12 weeks

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Assessment of menopausal symptoms & cardiovascular risk factors

Assessment of menopausal symptoms

- Kupperman's index
- Menopause rating scale

Laboratory test

- Lipid profile
  - Total cholesterol, LDL-cholesterol, HDL-cholesterol, Triglyceride
- C-reactive protein (CRP)
- Carotid intima-media thickness (CIMT)
- Estradiol (E2)

Menopause 2012;19:461-466.

Baseline characteristics of the study participants

	RG group	Placebo group	P
Age (y)	52.98 ± 3.04	55.01 ± 3.67	0.101
Age at menopause (y)	50.37 ± 3.73	51.32 ± 2.47	0.412
BMI (kg/m^2)	22.35± 2.36	22.03 ± 2.42	0.731
Systolic BP (mmHg)	118.53 ± 14.59	121.29 ± 12.56	0.785
Diastolic BP (mmHg)	74.86 ± 9.25	72.89 ± 10.75	0.610
Total cholesteol (mg/dL)	138.11 ± 43.78	128.52 ± 39.24	0.082
LDL-cholesterol (mg/dL)	78.12 ± 27.53	73.09 ± 27.85	0.472
HDL-cholesterol (mg/dL)	38.02 ± 12.37	36.64 ± 12.32	0.783
Triglyceride (mg/dL)	104.75 ± 46.77	102.90 ± 50.34	0.764
hs-CRP (mg/L)	0.39 ± 0.48	0.29 ± 0.31	0.335

Menopause 2012;19:461-466.

Changes in menopausal symptoms by group

	RG group	P[a]	Placebo group	P[a]	P[b]
KI	18.93 ± 11.28 13.32 ± 10.15	0.021	15.21 ± 12.08 15.10 ± 11.73	0.898	0.032
MRS	12.45 ± 8.79 8.32 ± 6.75	0.027	10.23 ± 7.30 9.26 ± 7.51	0.512	0.035
Hot flash of KI	5.25 ± 3.59 3.51 ± 2.36	0.032	5.37 ± 3.79 4.87 ± 2.94	0.651	0.046
Hot flash of MRS	1.85 ± 1.15 1.10 ± 0.79	0.096	1.86 ± 1.22 1.63 ± 0.86	0.715	0.121

RG, red ginseng; KI, Kupperman index; MRS, Menopause Rating Scale.
[a]Paired t-test comparing mean at baseline with mean at week 12 by group.
[b]Independent t-test comparing supplementation effects between two groups.

Menopause 2012;19:461-466.

Changes in lipid profiles from baseline to week 12 by group

	RG group	P[a]	Placebo group	P[a]	P[b]
TC (mg/dL)	138.11 ± 43.78 108.82 ± 46.79	0.001	128.52 ± 39.24 128.03 ± 40.19	0.962	0.009
LDL-C (mg/dL)	78.12 ± 28.53 60.02 ± 25.56	0.001	73.09 ± 27.85 71.24 ± 30.41	0.555	0.015
HDL-C (mg/dL)	38.02 ± 12.37 34.23 ± 13.42	0.061	36.64 ± 12.32 35.20 ± 14.01	0.299	0.312
TG (mg/dL)	104.75 ± 46.77 95.28 ± 41.51	0.052	102.90 ± 50.34 103.98 ± 46.82	0.228	0.063

RG, red ginseng; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.
[a]Paired t test comparing mean at baseline with mean at week 12 by group.
[b]Independent t test comparing supplementation effects between two groups.

Menopause 2012;19:461-466.

Change in mean serum levels of hs-CRP and E2 from baseline to week 12 by group

	RG group	P[a]	Placebo group	P[a]	P[b]
Hs-CRP (mg/L)	0.39 ± 0.48 0.29 ± 0.36	0.030	0.29 ± 0.31 0.28 ± 0.29	0.393	0.298
Estradiol (pg/dL)	38.52 ± 23.37 36.72 ± 20.19	0.513	39.09 ± 29.52 37.81 ± 26.44	0.728	0.631

E2, estradiol; RG, red ginseng; hs-CRP, high-sensitivity C-reactive protein.
[a]Paired t test comparing mean at baseline with at week 12 by group.
[b]Independent t test comparing supplementation effects between two groups.

Menopause 2012;19:461-466.

Changes in CIMT from baseline to week 12 by group

	RG group	P[a]	Placebo group	P[a]	P[b]
CIMT (mm)	0.735 ± 0.069 0.705 ± 0.066	0.001	0.734 ± 0.070 0.733 ± 0.062	0.178	0.049

RG, red ginseng; CIMT, carotid intima-media thickness.
[a]Paired t test comparing mean at baseline with at week 12 by group.
[b]Independent t test comparing supplementation effects between two groups.

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Pomegranate

Pomegranate

- Pomegranate seed oil is a very rich source of phytoestrogens.
- Its main constituents are linolenic acid,punicic acid, and ellagic acid.
- Its main phytosterols are Asitosterol, campesterol, and stigmasterol.
- Pomegranate seed oil influences estrogen receptors such as the selective estrogen receptor modulators.
- In animal studies, pomegranate seed oil shows an effect on blood pressure; cardiovascular disease; obesity; insulin resistance; and the prevention of prostate, colon, lung, and breast cancers.

Menopause: The Journal of The North American Menopause Society
Vol. 19, No. 4, pp. 426-432
DOI: 10.1097/gme.0b013e3182345b2f

Pomegranate seed oil in women with menopausal symptoms: a prospective randomized, placebo-controlled, double-blinded trial

Objective: The aim of this study was to investigate the potential effects of pomegranate seed oil (PGS) on menopausal symptoms.

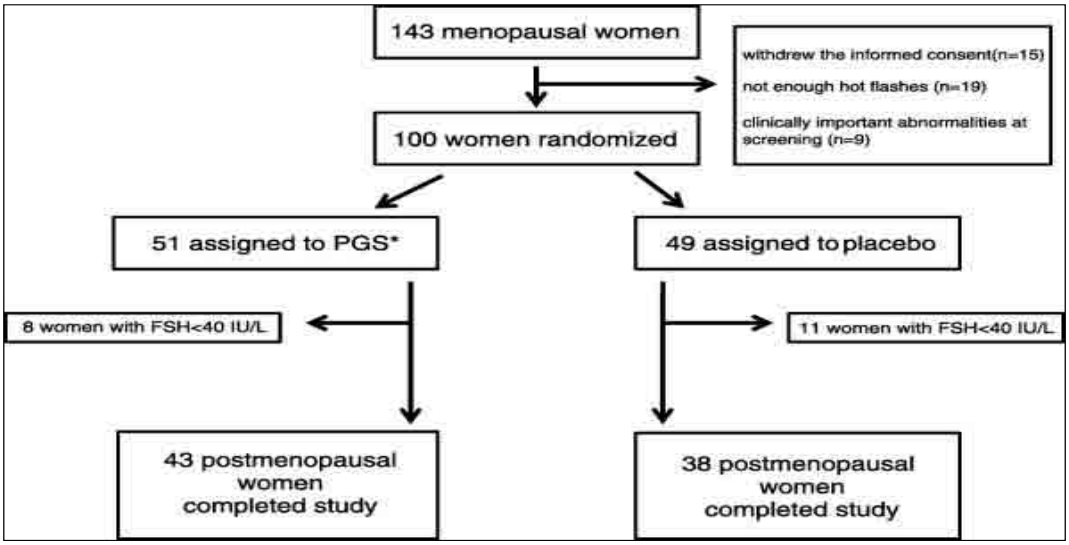
Methods: The prospective randomized, placebo-controlled, double-blinded trial was completed by 81 postmenopausal women, who received two daily doses of either 30 mg PGS containing 127 Kg of steroidal phytoestrogens per dose or a placebo for 12 weeks. The participants reported their number of hot flashes and completed the Menopause Rating Scale II at baseline and at weeks 4, 8, 12, and 24. At baseline and after 12 weeks, hormonal status was determined.

Results: After 12 weeks of treatment, PGS reduced the number of hot flashes per day by 4.3 (38.7%), whereas placebo reduced it by 2.5 (25.6%). Both groups were significant compared with baseline, but the treated group was not significant compared with the placebo group (P = 0.17). After 24 weeks, the treated group showed a mean of 7.1 (interquartile range, 4.0) hot flashes per day compared with the placebo group with a mean of 8.8 (interquartile range, 5.0; P = 0.02). Although the overall sum score of the Menopause Rating Scale II parameters at week 12 decreased in the treated group from 16.0 to 9.0 at week 12 and in the placebo group from 18.0 to 14.5 (P = 0.08), the sum score of the vegetative somatic symptoms subgroup decreased strongly versus placebo (P G 0.03), attributable mainly to an improvement in sleeping disorders. PGS did not affect the hormone status, and no adverse effects were reported.

Conclusions: In postmenopausal women, PGS does not significantly reduce hot flashes within a 12-week observation period, but further studies are needed to investigate the long-term effect.

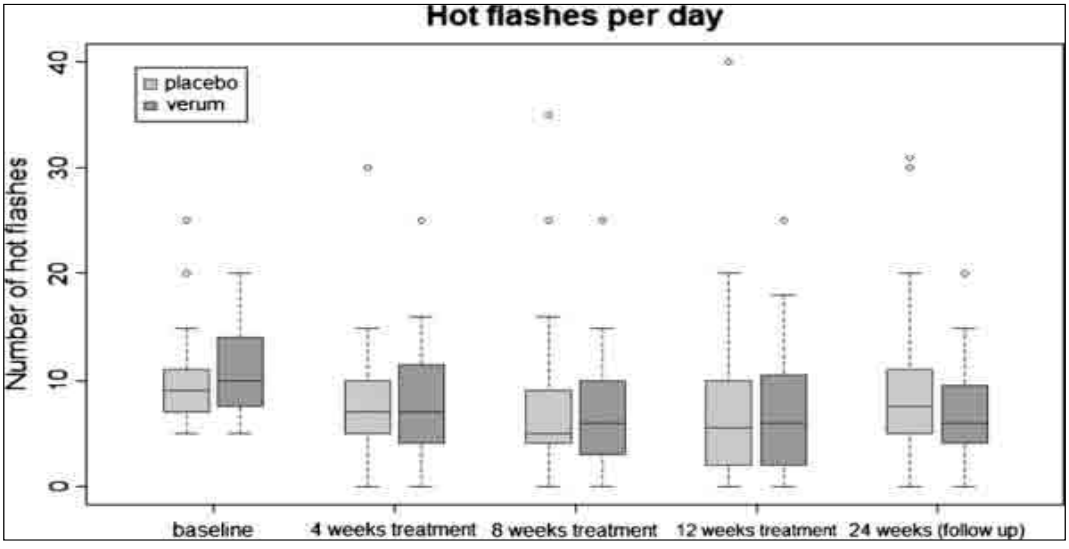
Menopause 2012;19:426-432.

Study design



Menopause 2012;19:426-432.

Number of hot flashes recorded in the treated and placebo group at the initial visit; after 4, 8, and 12 weeks of treatment; and after a 12-week follow-up



Menopause 2012;19:426-432.

Menopause Rating Scale, all parameters and subgroups

Sum score		Baseline	*P*	Week 4	*P*	Week 8	*P*	Week 12	*P*	Week 24	*P*
ALL	T P	16.0 (9.5) 18.0 (7.7)	0.15	12.0 (10.0) 16.0 (9.5)	0.07	9.0 (10.5) 16.0 (11.7)	0.06	9.0 (11.5) 14.5 (11.7)	0.08	10.0 (10.5) 11.0 (8.5)	0.71
Mental Symptoms	T P	4.0 (5.0) 6.0 (4.0)	0.05	3.0 (5.5) 5.0 (5.5)	0.15	2.0 (5.0) 4.0 (6.7)	0.06	2.0 (5.0) 4.5 (5.0)	0.11	3.0 (4.5) 3.5 (4.7)	0.68
Urogenital symptoms	T P	3.0 (3.5) 3.0 (3.7)	0.57	1.0 (4.0) 2.0 (3.0)	0.53	1.0 (2.0) 2.0 (4.0)	0.67	2.0 (2.5) 2.0 (3.0)	0.90	2.0 (2.5) 2.0 (2.0)	0.66
Vegetative smatic symptoms	T P	8.0 (3.0) 10.0 (4.0)	0.19	6.0 (5.0) 8.0 (4.0)	0.07	6.0 (5.5) 7.0 (3.0)	0.09	4.0 (5.5) 7.0 (4.0)	0.03	5.0 (3.5) 8.0 (3.5)	0.34

Data are expressed as median (interquartile range); P value.
Rating system is from 0 (symptom free) to 4 (severe).
Sum score of all parameters: from a maximum of 44 to a minimum of 0.
[a]P < 0.05

Conclusion

Conclusion

- CAM seems to constitute a popular treatment option among menopausal women.
- Dietary herbal supplements have demonstrated mixed and inconclusive results in placebo-controlled trials.
- Healthcare providers should prepare to inform menopausal women about all treatment options, including CAM, and should be aware of the possible adverse effects of CAM and potential interactions between CAM and conventional medicine among women in menopause who are under their care.