What is the Evidence for Supplement Use for Menopausal Symptoms?

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Global Health Challenge: Ageing

- By 2025 >800 m >65 yrs
- Two-thirds in developing countries
- Population ageing has immense health consequences for all countries, including the USA
- Healthcare goals:
  - Prevent and postpone disease and disability
  - Maintain the health, independence and mobility of our ageing population

Gender and Ageing

- Women make up the majority of the older populations in all countries
- Average age 80 yrs old
- Live an average of eight extra years
  - Generally have more health problems than men
  - Increase in chronic diseases after menopause
  - After the age of 55, 1 in 5 live in disability

Menopause

- Y2000-80 million women entering menopause
  - 1990 467 million postmenopause
  - 2030 1.2 billion postmenopause
  - 55-75% of women experience vasomotor symptoms or a # of other sequelae
  - depression, mood, sleep disorders, vaginal dryness, joint pain
- 25% of women seek treatment from their provider

Increase in Chronic Disease Postmenopause

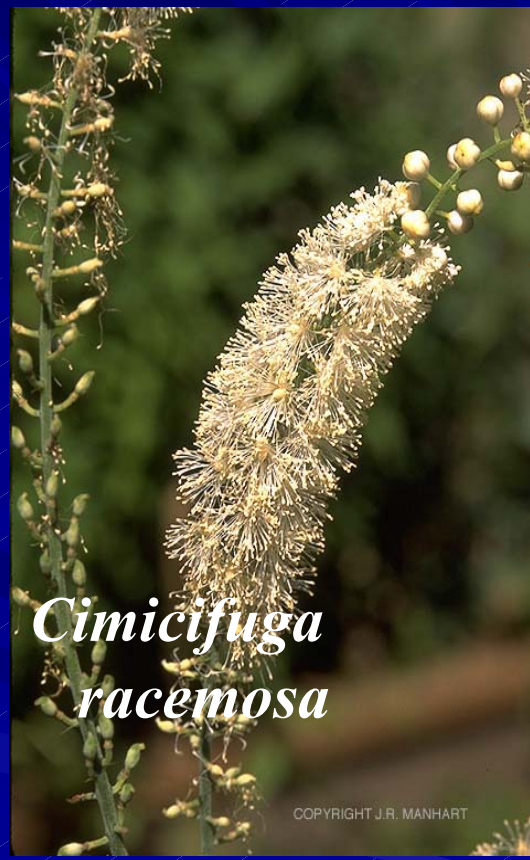
- Cardiovascular disease-CHD and stroke-60% of all adult female deaths
  - **Risk increases after menopause**
    - **1 in 50 (45-64 years)**
    - **1 in 3 (> 65 years)**
- Osteoporosis and associated fractures are major causes of death, illness and disability
  - Bone loss accelerates after menopause- 30% PM
  - 80% of hip fractures in women
- Dementia/Alzheimer's Disease
  - May be accelerated with the onset on menopause
  - Clinical studies suggest improvement in cognition with ERT as well as ERT and Tacrine combinations
- Lower urogenital dysfunction
  - Polyuria, nocturia, urgency, increased incidence of UTI's, incontinence

BDS Use in Menopausal Women

- 79% of women surveyed used one or more BDS, diverse ethnicity
- Soy, green tea, ginkgo, ginseng, echinacea
- Most women thought BDS were relatively safe and effective
- The majority of respondents were not getting their BDS information from healthcare providers
- Not informing their physician about their BDS use. (70%)-soy

Black Cohosh (*Cimicifuga racemosa*)

- Native American plant used by native American Indians-squawroot
  - Root/Rhizome
  - Distribution-Eastern U.S.
  - Ranunculaceae (Buttercup)
- Synonyms: Bugbane(to drive away bugs), Black Snakeroot, Rattleroot, Squaw-weed, *Actaea racemosa*, *Macrotys actaeoides*
- U.S.P-1820-1936, N.F. 1936
- Pinkham's Vegetable Compound



BLACK COHOSH

- Treatment of menopausal symptoms such as anxiety, depression, hot flushes, profuse sweating, insomnia and vaginal atrophy
- 11 clinical trials -7 controlled, 4 open, some double-blinded, randomized
  - 40-60% alcohol extracts of the rhizome-40-80 mg of the extract daily
  - Reduced vasomotor symptoms, Kupperman index, HAMA scale reduced, in some reduces LH levels,
    - as effective as 0.625 mg of conjugated estrogens

Jacobson JS et al., 2001

- Patients: 85(68)-breast cancer diagnosis (59 taking tamoxifen)
- Design: Randomized, Placebo-controlled, double-blind
- Efficacy Criteria: hot flashes, FSH, LH
- Dose: 40% Isopropanol extract, 40 mg daily
- Outcomes:Improvement of symptoms but not significant as compared with placebo
- Problems-

Tamoxifen versus Black cohosh

- Tamoxifen-mechanism of action not completely elucidated
  - Partial agonist/antagonist
  - down regulates ER expression
  - Brain-estrogen is a serotonin agonist up-regulates SERT and 5HTR
  - Serotonergic mechanism-LHRH secretion-LH release
  - Tamoxifen-estrogen/serotonin antagonist-SERT and 5HTR
- Black cohosh-mechanism has not been completely elucidated
  - Estrogenic effects????
  - Serotonergic mechanism of action

Liske E et al., 2001

- RCT (n=150) peri and post menopausal women
- Design: Randomized, double-blind
- Dose: 40% Isopropanol extract, Remifemin
- Compared 40 mg of BC with 127 mg/day for 24 weeks
- Efficacy Criteria: KMI symptoms, vaginal cytology, hormone levels
- Outcomes: 70% and 72%, Improvement of KMI and SDS, no estrogenic effects (NO PLACEBO)
- 40 mg/day dosing
- *J Women's Health and Gender Based Medicine, 2002, 11:163-173

Is Black Cohosh Estrogenic?

- 1985-1995-in vitro and in vivo-Jarry et al
- Formononetin-CHCL3
- Adulteration of plant material
- In vivo study
  - –ovx rats, 3wks, extract not described, uterine wt
- 1999 In vitro-ERalpha upregulation in MCF 7
  - Jarry et al.
- No formonentin
- No ER binding
- No estrogenic effects in mice
- Bodinet 2002-Breast Can Res & Treat-ER+breast cancer cell lines-inhibited proliferation
- Freudenstein 2002 Cancer Res-mammary tumor if rats, no stimulation of tumor proliferation

Competitive Binding of Extracts to Estrogen Receptors (ER) and Their Estrogenic Activity in Ishikawa Cells

Methanol Extracts	200 μg/ml (%)		20 μg/ml (%)	
	ER^{α}	ER^{β}	Estrogenic	Antiestrogenic
Angelica sinensis (Angelica)	27	30	-	-
Cimicifuga racemosa (Black cohosh)	19	16	-	-
Glycyrrhiza glabra (Licorice)	33	29	-	-
Humulus lupulus (Hops)	70	79	25	42 *
Panax ginseng (Ginseng)	0	0	-	-
Panax ginseng (White ginsneg)	8	18	-	-
Panax quinquefolius (Am. ginseng)	5	11	-	-
Trifolium pratense (Red clover)	73	74	56	-
Vitex agnus-castus (Chaste berry)	57	67	40	-

* Shows cytotoxicity at the concentration tested. J. Agric Food Chem, 2001, 49:2472-247

INDUCTION OF PS2 EXPRESSION BY PLANT EXTRACTS

Agents/Extracts	Expression of PS 2 Gene		
	S30	MCF-7	MDA-MB-231
Estrodiol (1 nM)	+++++	+++++	
DMSO (1 μL)	+	+++++	
Control		+++++	
Genistein (1 μM)	+++++	+++++	
Angelica sinensis (20 μg)		+++++	
Cimifuga racemosa (20 μg)		+++++	
Humulus lupulus (20 μg)	+++	+++++	
Trifolium repens (20 μg)	+++	+++++	
Vitex agnus castus (20 μg)	+++	+++++	
Panax ginseng (20 μg)	+++	+++++	
Panax ginseng(white) (20 μg)	++++	+++++	
Glycyrrhiza glabra (20 μg)		+++++	
Trifolium pratense (20 μg)	++	+++++	

DPPH Free Radical Scavenging Ability and Inhibition of Xanthine/Xanthine Oxidase Activity of Extracts and Fractions

EXTRACTS	DPPH (%) 200 μg/ml (IC_{50})	OXIDASE (%) 100 μg/ml
Angelica sinensis (Angelica)	36	-
Cimicifuga racemosa	79 (99)	-
Glycyrrhiza glabra (Licorice)	53	-
Humulus lupulus (Hops)	49	-
Panax ginseng	26	-
Panax quinquefolius	26	-
Trifolium pratense (Red clover)	74 (99)	-
Vitex agnus-castus (Chaste berry)	51	-

Prevention of Osteoporosis

- Increase in serum calcium and bone mineral density in ovx rats (Li, 1996 -EtOAc fraction from a methanol extract of the rhizome)

- Anti-osteoporosis effects (Li, 1995, MeOH ext.); Li 1996 (EtOAc fraction from MeOH extract)

"Each Tablet Contains:

20 mg extract

Dose: 40-80 mg/day

"One-two tablets twice a day."

Red Clover (*Trifolium pratense*)

- **Symptoms of menopause**
- **Standardized extract-200-230 mg containing 40 mg of four isoflavones (biochanin A, formononetin, daidzein and genistein 20:12:1:1)**
- **Four small RCTs**
  - **Two R, DB, PC trials -40 -160 mg/day for 3 months**
  - **no effect on menopausal symptoms(2)**
  - **R, DB, PC trial (n=30), 80 mg/d for 12 weeks- 44% decrease in hot flushes** (1)
    - Maturitas 2002:42:187

Red Clover

- One uncontrolled trial (n=46) women, 28.5 mg, 57 mg or 85.5 mg/d for 6 months
  - Increased HDL-C; increased bone mineral density with the higher doses
    - Menopause 2001, 8:259-265
- R, DB study in 66 women with hypercholersterolemia-12 week
  - 50 mg isoflavones did not affect total plasma cholesterol, LDL, HDL or triglycerides
- 80 mg/day for 10 weeks (n=17) improved arterial compliance by 28%, a risk factor for CVD (1)

Competitive Binding of Red Clover Extracts and Fractions to Estrogen Receptors (ER) and Their Estrogenic Activity in Ishikawa Cells

	200 µg/ml (%)		20 µg/ml (%)	
	ER^{α}	ER^{β}	Estrogenic(IC_{50})	Antiestrogenic
TP-MeOH	78	72	30	-
TP-MeOH/H_2O 5:5	84	99	94	-
TP-EtOH/H_2O 5:5	89	98	65	-
TP- PE	61	77	12	-
TP - $CHCl_3$	83	93	33 (2.6 ± 0.14)	70 (17 ± 2.0) *
TP – BuOH	28	34	77 (8.0 ± 1.4)	-
TP - H_2O	7	0	8	-

* Shows cytotoxicity at the concentration tested.

Estrogenic activities of Isoflavones Present in Red Clover and Their Concentration in Extracts and Fractions

EC_{50}	ER^{α} (μM)	ER^{β} (μM)	E (μM)	Concentration (% w/w) M	M/H	E/H	PE	$CHCl_3$	BuOH	H_2O
Biochanin A	8.1	2.8	5.12	0.04	0.12	0.08	2.77	5.73	-	-
Daidzein	5.5	1.0	1.24	0.16	0.05	0.02	0.27	0.62	3.21	0.82
Formononetin	104.5	59.7	8.32	0.06	0.22	0.14	0.66	10.4	-	-
Genistein	0.63	0.012	0.31	0.10	0.03	0.01	0.19	0.57	2.02	0.44

E - Estrogenic activity in Ishikawa cell test;

M - MeOH; E - EtOH; H - H_2O.

Red Clover-Estrogenic?

- Isoflavones-0-15% depends on the extract
- 9-15% extract binds to the ER
- Estrogenic effects in rodents
  - Increased uterine weights
  - Vaginal cornification
- DB, R, PC study (n=30) 50 mg/d, 3 months
  - No effect on the endometrium
  - However, may need at least 80 mg/d for pharmacological effects

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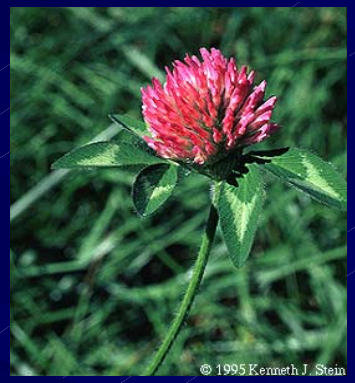
www.nccam.nih.gov

OFFICE OF DIETARY SUPPLEMENTS

Botanical Dietary Supplements for Women's Health



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