1B/2B (repeat): Spice is Nice for Women’s Health

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1:00 p.m. – 2:30 p.m.
2:45 p.m. – 4:15 p.m.
Savoring Effects of Spices on Women

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HerbalConstituents.com

Women’s Health & Spices

• Premenstrual Syndrome (PMS)
• Morning sickness of pregnancy
• Menopause

Women’s Health & Spices

• Role of plant-based medicines used to benefit patients with PMS, especially subtype C (Cravings for Carbs)
• Review limits to botanicals appropriate for morning sickness and related minor-to-moderate symptoms of pregnancy
• Review of holistic approach to menopausal symptom clusters
### PMS

- Menstruation is not a disease
- Culture, status of women determine ways we experience monthly flow of blood
- PMS & Dysmenorrhea not the same yet often occur together
- Epidemiology - worldwide prevalence of PMS 80%–90%

### PMS

- * Signs and Symptoms
- Mild Sx virtually universal
- 25% have Sx that impair daily life
- 3-5% severe Sx

### PMS

PMS - 150 recognized signs & Sx grouped under 6 headings: A, C, D, H, P, S
- PMDD reclassified in DSM V as depressive disorder
- Focus here on more common PMS & Dysmenorrhea
PMS

- Focusing on hormones “out of balance” misses the point of causes of pre-menstrual tension
- Herbs can help self-regulating mechanisms to “re-balance hormones,” reduce signs & Sx

Bad News 1st

- 2016 Cochrane Review on Dysmenorrhea & Herbs - evidence low or very low quality
- Limitations: imprecision due to very small sample sizes
- Failure to report study methods
- Inconsistency


PMS A - Anxiety

- 80% of women with PMS
  - Irritability, nervous tension, mood swings
  - Assoc’d w/ hi’er estrogen r/t low progesterone
  - ? Hi Calcium r/t low Mg
  - Drop dairy, animal food vs. pain

PMS A

1st line Tx: “cleansing the liver” using hepatic herbs between menses and ovulation

Chasteberry (Vitex agnus-castus) with hepatic herbs – see below

Calcium - not dairy – greens, nuts, millet, sesame (tahini), cashews

Chaste berry (Vitex agnus-castus)

PMS A

Vitex: Clinical Studies–PMS

Chasteberry (Vitex agnus-castus)

Dose: Tinctures = Aqueous-alcohol extract (35%) 1:5 - 45 drops/day

May be single morning dose

Powdered seed (tabs/caps)

120-240 mg/day

Up to 500 mg/day
PMS A

Vitex PMS Open Trial
- N=50 1/2 on BCP
- Tx: 20 mg ACE (Ze440) X 3 cycles
- 3 month non-Tx f/u


Results:
- 50% reduced VAS score/pain Other Rx allowed
- 20/43 Px responders: 43% decr in Sx scale (p<0.001)
- Effect decr w/ end Tx
- Benefit still present at 3 months
- No serious ADE's


PMS A

Vitex Safety: AHP Rating: 2b, 2d
- Not generally recommended in pregnancy
- Toxicity: Minor side effects
- Drug-Herb Interactions
  - Dopamine agonist
- No significant lowering normal PL (American Herbal Pharmacopoeia 2000)
### PMS C – Carb Craving

- Sudden high appetite especially for refined CHO
- Body more sensitive to insulin premenstrually

### PMS C

- Commercial chocolate increases sugar cravings
- Salt in all its disguises
- Alcohol depletes B vitamins and minerals
- Processed "convenience" foods, artificial colors, flavors, preservatives and stabilizers

### PMS C

**Nutrition**

- B6 100-300mg/dy
- Mg. 200-800 mg/dy
- Zn. 15 mg (for PG series 1)
- EFA’s, O-3 ie Evening Primrose Oil 1-3 grams daily from 5 days before PMS
- Cinnamon (C. zeylanicum, C. verum)

- Not *Cinnamomum cassia* (Wickenberg / et al, 2014)
Cinnamon

Cinnamon (true *Cinnamomum spp.*), Lauraceae
- Contains: Vitamin A, thiamin, riboflavin, ascorbic acid, essential oil with cinnamaldehyde (55 - 57%) and eugenol (5 - 18%)
- Several studies - cinnamon lowers blood glucose, cholesterol, NAFLD
- Doses studied: In adults and adolescents, 120mg - 750mg - 1.5 - 6 g daily of dried bark cinnamon

Cinnamon Mechanisms where known:
- Aqueous extracts from cinnamon increase in vitro glucose uptake & glycogen synthesis
- Isolated flavone “insulin-potentiating factor” (IPF)
PMS C

Cinnamon Mechanisms, con’t:

• Increase phosphorylation of the insulin receptor
• Likely to aid in triggering insulin cascade system
• Insulin’s role in lipid metabolism shown in vivo (Khan, 2003)
• Cinnamaldehyde - antispasmodic effect


Cinnamon & T2DM

Cinnamon RDBPC Crossover Trial
• N=60 women & men T2DM
• Tx: Groups 1, 2, and 3: 1, 3, or 6g cinnamon dy, respectively
• Groups 4, 5, and 6: placebo capsules X 40 days
• 20 dy washout


Cinnamon & T2DM

Cinnamon RDBPC Crossover, con’t:

• Results: All 3 doses cinnamon reduced:
  • mean fasting serum glucose (18–29%)
  • triglyceride (23–30%), LDL cholesterol (7–27%)
  • total cholesterol (12–26%) levels
• No significant changes w/ placebo. Changes in HDL cholesterol not significant

**Cinnamon & Dysmenorrhea**

**RDBPCT**
- N= 76 women nursing students 18-30 yo in good health, no OCP, BMI 19 - 26
- Tx: 2 capsules each 420 mg cinnamon TID (N=38) during 1st 3 dys menstrual cycle
  - Daily total 2.52 g
- Control: capsules contain starch TID (N = 38)

Jaafarpour et al, 2015

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**Cinnamon & Dysmenorrhea**

RDBPCT, con’t:
- Assessed by: VAS - severity of pain and nausea
  - To determine reliability of VAS, Cronbach’s alpha test used; determined to be 0.89.
- Pain intensity, nausea, vomiting and menstrual bleeding monitored in the groups during the first 72 hours of cycle
- Pain severity assessed in 1, 2, 3, 4, 8, 16, 24, 48 and 72 hours after the intervention

Jaafarpour et al, 2015

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**Cinnamon & Dysmenorrhea**

RDBPCT, con’t:
- Results: pain severity score in cinnamon group lower than w/ placebo (P < 0.001)
  - Mean duration of pain
  - Mean amount of menstrual bleeding
  - Mean severity of nausea

(Jaafarour, 2015)
Cinnamon & Dysmenorrhea

RDBPCT, con’t:

- Weak points of study:
  - Uncontrollable factors influencing pain intensity and other symptoms
  - Culture, genetics and nutrition


Turmeric (Curcuma longa)

- Turmeric, and its isolated flavone compound, curcumin, have been described in over 9000 papers since curcumin was isolated in 1815
- Described in various presentations this conference

PMS & Turmeric
PMS & Turmeric

- New attention on curcumin & BDNF in PMS
- Circulating serum BDNF levels correlate with PMS symptoms
- Some actions of sex hormones on brain are mediated by BDNF (Cubeddu et al., 2011)

PMS & Turmeric

- Women with PMS during late luteal phase - serum BDNF level different than women without PMS (Cubeddu et al., 2011; Oral et al., 2015)
- BDNF widely expressed in limbic system: roles in mood and behavior regulation (Autry & Monteggia, 2012)

PMS & Turmeric

- RDBPCT
- N = 63 women, (32 Tx, 31 Placebo)
- Assessed with serum BDNF
- Sx by questionnaire
  - Mood
  - Physical Sx
  - Behavior

Fanaei H et al, 2016
PMS & Turmeric

RDBPCT, con’t:

• Tx Dose: 100mg/12 h Standardized Extract: Curcumin (from turmeric, Curcuma longa)
• Results: Total score of PMS:
• Curcumin group significantly lower than placebo group

Fanaei H et al 2016

PMS & Turmeric

RDBPCT, con’t:

• Curcumin group serum BDNF levels -- first, second and third cycles after intervention -- significantly higher than placebo group.
• Authors note time was a significant factor, with more visible Tx effects over 4 consecutive Tx cycles


PMS & Turmeric

RDBPCT

• N = 70 women w/ PMS
• Tx: curcumin 7 dys prior + 3 dys after menses
• X 3 menstrual cycles
• Assessed by Daily Questionnaire

Khayat S et al, 2015
PMS & Turmeric

RDBPCT, con’t:

- Results: After 3 cycles total severity of PMS score
- In curcumin group score reduced from 102.06±39.64 to 42.47±16.37
- In placebo group changed from 106.06±44.12 to 91.60±43.56


Ginger (Zingiber spp.)

PMS P – Ginger & Dysmenorrhea

- RCT
- N=122 women w/ mild to moderate dysmenorrhea
- 2 Tx:
  1) 250 mg mefenamic acid ev 8 h (Ponstel, Ponstan – NSAIDs)
  2) 250 mg capsules ginger (Zintona®)
- Both every 6-8 h from onset of menstruation until pain relief

Shirvani MA, 2015
PMS P - Ginger

Zintona RCT, con't:
- VAS X 2 cycles
- Results:
  - 1st month -
    Pain intensity in mefenamic 39.01 ± 17.77
  - in ginger group 43.49 ± 19.99
  - 2nd month -
    33.75 ± 17.71 and 38.19 ± 20.47, respectively
    \( p > 0.05 \)

Shirvani MA, 2015

PMS P - Ginger

RCT, con't:
- Severity of dysmenorrhea, pain duration, cycle duration, and bleeding
  - Not significantly different between groups
- Ginger at this dose equivalent to mefenamic acid


Ginger & HMB

- DBRPCT - Heavy Menstrual Bleeding
- N= 92 High School girls 15-18 yo with self-reported HMB
- Exclusion criteria by Gyn exam, Hx, US

Kashefi et al, 2015
RDBPCT Ginger & HMB, con’t:

- Monitored for 6 consecutive cycles
- Assessed HMB by Pictorial Blood Assessment Chart (PBAC)
- At baseline both groups similar HMB
  - from 112 to 118mL per menstrual cycle (p>0.05 between groups)

Kashefi et al, 2015

RDBPCT Ginger & HMB, con’t:

- Tx: 250 mg ginger capsule TID
  - Starting 1 dy before + 3 dys during menses
  - (4 dys) X 3 cycles
- Placebo capsules – lactose

Kashefi et al, 2015

RDBPCT Ginger & HMB, con’t:

- Results:
  - Decrease in hemorrhage per menstrual cycle in subjects receiving ginger during intervention X 3 mo’s
  - Slight changes for hemorrhage in participants receiving placebo

Kashefi et al, 2015
Ginger & HMB

RDBPCT Ginger & HMB, con’t:
Mean Blood Loss Pre-intervention During
- Ginger Group 113.73 mL 60.67 mL
- Placebo Group 113.43 mL 110.97 mL
- % Mean Decreased
  - Ginger 46.6
  - Placebo 2.1

Kashefi et al, 2015

Ginger & HMB

RDBPCT Ginger & HMB, con’t:
- Difference between the two groups was statistically significant (p<0.001 between groups)
- AE: 3 in Ginger group, 3 in Placebo group (minor transient GI Sx)


Morning Sickness of Pregnancy

Ginger (Zingiber officinale)
- Traditional use: 19th C Eclectic physicians
- TCM - ginger used cautiously usually in combination with other herbs
- India - with care and only for nausea and vomiting
Morning Sickness

Ginger

- Contains: pungent compounds gingerols, shogaols, volatile (essential oil) sesquiterpenes, monoterpenes
- Mechanism: thought to be via gastric effects by-passing CNS (unlike other anti-emetics), increasing gastric tone, peristalsis via anticholinergic, antiserotonergic activity

Morning Sickness

Ginger

- Inhibits platelet aggregation
- Inhibits thromboxin formation
- Decreases serum thromboxane levels by 37% in humans


Morning Sickness

Ginger – Safety:

- Past concerns regarding theoretical mutagenic activity of 6-gingerol largely dismissed
- Whole rhizome does not appear to have a mutagenic effect; zingerone suppresses mutagenic activity of 6-gingerol

Ginger & Morning Sickness

Doses:
• 1000 mg SE equivalent to:
  • 1 tsp fresh grated rhizome
  • 2 droppers (2 mL) liquid extract
  • 2 tsp (10 mL) syrup
  • 4 c ginger tea bags
  • 4 c tea of ½ tsp fresh grated rhizome infused 5-10 min
  • 8 oz. ginger ale (real rhizome)
  • 2 pcs crystallized rhizome 1”X ¼” thick

Ginger & Morning Sickness

• Herbalists caution against using large doses of ginger for some women
• May increase blood flow to uterus
• Dried ginger preparations are more heating than fresh ginger

Ginger & Morning Sickness

• RDBPCT
• N= 70 women at or before 17 weeks’ gestation
• Tx: 1g ginger po per dy X 4dys
  • (250-mg capsule TID after meals + 1 capsule h.s. X 4 dys

Vutyavanich T et al, 2001
Ginger & Morning Sickness

RDBPCT, con’t:
• Assessed by VAS for severity
• # of vomiting episodes 24 h before and during 4 dys
• At a follow-up visit in 7 dys, 5-item Likert scales for severity of Sx
• Results: All participants except 3 in placebo group completed study

Vutyavanich T et al, 2001

Ginger & Morning Sickness

RDBPCT, Results con’t:
• VAS measured in centimeters post-therapy minus baseline
• Nausea decreased significantly in ginger group
• # vomiting episodes decreased significantly

Vutyavanich T et al, 2001

Ginger & Morning Sickness

• Safety: No adverse effect of ginger on pregnancy outcome detected
• No infants had any congenital anomalies recognized and all were discharged in good condition

Menopause

• Average onset perimenopause in US 47.5 y
• Duration Sx 4 y
• Median age for 12 mo amenorrhea 51.4 y
• N= 3302
• CVS Sx (vasomotor) in 50%+ 7 y


Menopause

• Connected Sets of Sx
• CVS
  • Increased sensitivity of blood vessels to fluctuating levels of estrogen
  • Hot Flashes/Flashes, Night Sweats
  • Increased risk of heart disease with age

Sage (Salvia officinalis L, various Salvia spp.)
**Sage (Salvia officinalis L, various Salvia spp.)**

- Constituents of the Salvia genus:
  - Tannins, bitter principles (diterpenes), steriods, flavonoids, volatile oil rich in terpenes
  - Terpenoids (a-pinene, b-pinene, 1,8-cineole, thujone, camphor and geraniol)
    - Regarded as main active constituents affecting CNS
    - Potent acetylcholinesterase and butrylcholinesterase inhibitors

**Sage & Menopause**

- Antispasmodic, astringent, other effects may explain use in excessive perspiration and hot flashes
- In vitro study showed affinity to benzodiazepine brain receptors - could explain calming effect
- Dose: range of 2-3 grams BID-TID

**Sage & Menopause**

Controlled Clinical Trial
- N= 30 women
- Tx: combination of sage leaf and alfalfa, dose not given in Eng abstract, X 3 mo’s
- Results: hot flashes and night sweats disappeared completely for 20
  - Another 4 - response good
  - In 6 others Sx reduced

Sage & Menopause

Open Multicenter Trial

- N= women mean age of 56.4±4.7 years
- Menopausal for at least 12 months
- 5+ hot flashes dy
- Tx: once-daily tablet of fresh sage leaves for 8 wks

Bommer S et al (2011)

Sage & Menopause

Open Multicenter Trial, con’t:

- Assessed by: Total score of the mean number of intensity-rated hot flushes (TSIRHF)
- MRS – at baseline and 2 mo’s
- Results: significant decrease in TSIRHF by 50% within 4 weeks; by 64% within 8 weeks
- Mean # of mild, moderate, severe, and very severe flashes decreased over 8 weeks


Nutraceuticals & Menopause

RDBPC Crossover Trial

- N = 43 postmenopausal women MRS =>20
- Examined role of probiotics on phytoestrogens & Sx relief
- All took probiotics
- Tx: NUT (soy isoflavones 80 mg, Angelica sinensis 50 mg, Morus alba leaf 200 mg, and magnesium 56.25 mg)
- Results: in NUT group MRS sores reduced compared to baseline and placebo period

Menopause

- Connected Sets of Sx
- Reproductive system changes
- Vaginal thinning/dryness
- Libido

Menopause & Libido

- Tribulus (Tribulus terrestris)
- Marketed as Horny Goat Weed
- Contains: steroidal saponins (furostanols)
- Dose: 2-4 grams taken BID-TID
- C/I in pregnancy

Tribulus terrestris
Menopause & Libido

• Tribulus (*Tribulus terrestris*)
• Indicated for maintaining normal male and female physiology and function
  • Believed to relieve menopausal symptoms
  • Promote endurance and general well-being
  • Especially in the mature

Tribulus & Menopause

• RDBPCT
• N= 60 fertile women with hypoactive sexual desire
• Tx: 7.5 mg Tribulus extract/dy X 4 wks (N=30)
• Assessed by: Female Sexual Function Index (FSFI)
• Groups compared by repeated measurement ANOVA test

Akhtari et al, 2014

Tribulus & Menopause

• RDBPCT, con't:
• Results:
  • Tribulus terrestris group: significant improvement
    • Total FSFI
    • Desire
    • Arousal
    • Lubrication
    • Satisfaction
    • Pain domains of FSFI
• Frequency of side effects similar between the two groups

Tribulus Combo Product & Menopause

- Aphrodit – A Combination of Herbs
- Tribulus (Tribulus terrestris) fruit effective in sexual performance in women (Mazora et al, 2010)
- Saffron (Crocus sativus) - experimental studies, clinical trials indicate saffron effective in mild to moderate depression (Akhoundzadeh BA et al, 2007)

Tribulus Combo Product & Menopause

- RDBPCT
- N = 80 postmenopausal women 50-60 yo
- Tx: Aphrodit BID X 4 wks
- Each capsule: Tribulus terrestris 40 mg, Zingiber officinale 12.27 mg, Crocus sativus extract 3 mg, Cinnamomum zeylanicum 11 mg

Taavoni S, 2017

Tribulus Combo Product & Menopause

- Aphrodit RDBPCT, con’t:
- Assessed by: MRS, Demographic questionnaire
- Results:
  - Total mean scores of MRS –
  - Aphrodit group: 21.93 ±3.83 before & 13.11 ±2.91 after intervention
  - Placebo group: 22.13 ±3.36 before & 22.13 ±3.38 after intervention

Taavoni S, 2017
**Tribulus Combo Product & Menopause**

- Aphrodit RDBPCT, con't:
- Significant difference between 2 groups after intervention ($p = 0.006$)
- Limits: small sample, short term


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**Menopause**

- Connected Sets of Sx
- Nervous System
  - Memory
  - Mood
  - Depression linked to cognitive decline


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**Menopause & the NS**

- Herbalists traditionally Tx:
  - NOT w/ “herbal antidepressants”
  - Example: Bitter Hops (*Humulus lupulus*) or Digestive aromatic Lemon Balm (*Melissa officinalis*) over
  - St. Johnswort (*Hypericum perforatum*)
Menopause

- Connected Sets of Sx
- MusculoSkeletal
  - Osteopenia vs. Osteoporosis (OP)

OP Secondary Causes & Risk Factors Other than Lo Estrogens

- Endocrinopathies
- Steroid Rx, other med's
- Early menarche, early menopause
- No exercise
- Smoking
- Lifelong low calcium or Vit D intake
- High protein intake
- High sat. fat intake
- High salt > 1/10th oz./week
- Caffeine > 5c/day
- Weight
- FH
- Caucasian ethnicity

OP & Phytoestrogens

Plant substances w/ weak estrogenic receptor activity

Found in:
- Legumes (green beans, peas)
- Soy
- Apples
- Carrots
- Garbanzo beans
- Garlic
- Red Clover
- Barley, oats and rye
- Citrus
- Cherries
- Cranberries
- Blueberries, bilberries
- Grape skins
OP & Menopause

- Hops (Humulus lupulus)
- Contains: prenylflavanones
- Mechanism:
  - Promoting osteoblastic bone formation
  - Inhibiting osteoclastic bone resorption
- Efficacy more potent than two classic phytoestrogens, genistein and daidzein


Hops (Humulus lupulus)

Flavonoid chalcone “xanthohomols” w/ central open ring

Hops

Closure of the central ring changes the chalcone into flavanone with potent phytoestrogenic activity
Hops

Add a dimethylallyl group, & it becomes 6-DMA-N, a strongly anti-androgenic molecule

OP & Menopause

• Hops & OP
• DBPC Crossover Pilot Study
• N= 36 menopausal women
• Tx: Hops extract X 8 wks each group of 18
• Assessed by: Kupperman Index (KI), Menopause Rating Scale (MRS), multifactorial Visual Analogue Scale (VAS) at baseline, 8 & 16 wks

Erkola et al, 2010

Menopause & OP

• Hops & OP, DBPC Crossover Pilot, con't:
  • Results:
  • At 16 wks, only Tx after placebo reduced Sx
  • Placebo after Tx >>> increased Sx

Women

- Spices & Herbs for:
- PMS
- N/V of Pregnancy
- Menopause

Savoring the Effects of Spices on Women’s Health