Plenary 1- Savoring the Effect of Spices on Brain Health & Mood

Amanda McQuade- Crawford, MNIH, MFCC; Arti Prasad, MD, FACP

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8:15 a.m. – 9:15 a.m.
Savoring Effects of Spices on Brain Health

Amanda McQuade Crawford, MA

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Brain Health & Mood

- Depression
- Anxiety
- Cognition
  - Elders
  - Healthy Volunteers

Depression

- “Recurring state of persistent sadness and the symptoms that go along with this mood”
  - May have identifiable trigger event, or
  - response to systemic disease
  - could be drug reaction
- 2% and 8% of children and adolescents w/ peak during puberty
Depression

Children:
- May be self-limiting
- Estimated 4/10 depressed children have a recurrence
- 1/3 of this population attempting suicide
- Suicide 2nd leading cause of death ages 10–24 (17.4% of deaths) (Heron M, 2014, corrected 6-17, Natl Vital Statistics Report 65(5)

How many of your patients achieved goals on St. Johnswort 3 gm/day X 2-12 months?

Depression & Nutrition

- Depression more closely linked to nutritional habits than previously acknowledged by a conventional medical view
- Omega-3 is one well-studied nutrient w/ relevance to spices
- Evening Primrose Oil (EPO) improves myelin sheath integrity, increases prostaglandins (series I - anti-inflammatory), provides the antidepressant amino acid tryptophan, and has other reputed benefits
  
  Shannon S and Rondeau M, 2012

Omega-3 & Depression

- DBPCT
- N = 51 perinatal women Dx Major Depressive Disorder (MDD)
- Randomized pregnant (2nd trimester) and post-partum mothers in 2 groups: Tx 1.9g daily of Omega-3 (EPA + DHA) or placebo.
- Results: Scores on depression scales reduced in 8 wks w/ Tx group

  Freeman MP et al, 2008
Turmeric (Curcuma longa; curcumin)

- Multiple mechanisms for antidepressant, anxiolytic effects of curcuminoids:
  - Reduced inflammation
  - Oxidative stress in central CNS
  - Increased brain-derived neurotrophic factor (BDNF)
  - Inhibiting astrocyte activation
  - Inhibiting monoamine oxidase
  - Modulation of neurotransmitters

Depression & Turmeric

- RDBPC Cross-over Trial
- N = 30 obese individuals Dx Major Depressive Disorder (MDD)
- Assessed by BAI & BDI
- Tx dose: curcumin (1 g/day) X 30 days
- NB: C3 Complex® (curcumin, demethoxycurcumin, bisdemethoxycurcumin) with bioperine®

Esmaily et al 2015
Turmeric
Depressed Obese on Turmeric DBPCT, con’t:
• Wash-out interval 2 weeks between regimens
• Results: Mean BAI score significantly reduced following curcumin therapy (P=0.03)
• No significant impact on BDI scores (P=0.7)
• Mechanism unknown


Depression & Turmeric
• RDBPCT
• N= 50 Dx MDD
• Assessed: Inventory of Depressive Symptomatology self-rated version (IDSSR30)
• Tx dose: curcumin extract 500 mg bid X 8 weeks
• Results: Curcumin effective in reducing depressive symptoms in people with major depressive disorder

Lopresti et al. (2015) Curcumin and major depression: a randomised, doubleblind, placebo-controlled trial investigating the potential of peripheral biomarkers to predict treatment response and antidepressant mechanisms of change. Eur Neuropsychopharmacol. 25(5):385-0

Depression & Turmeric
• RPCT
• N= 111 Dx MDD
• Assessed by Hospital Anxiety & Depression Scale (HADS) & BDI-II
• N = 75 curcuminoid Tx group
• N= 65 antidepressive therapy alone (control group)

Yunes et al, 2015
Turmeric & Depression

MDD on Turmeric RPCT, con’t:
• Curcumin Tx dose (C3 Complex®) 1000 mg plus 10 mg piperine (Bioperine®) daily X 6 weeks.
• Results: curcuminoids–piperine combination >>> reduced total HADS score & subscales of anxiety and depression versus control group (p < 0.001)
• Reduced BDI-II vs control (P< 0.001)


Anxiety

• Most common psychiatric illness – US & UK
• Greater incidence than depression (estimated 1:10 people in North America)
• Like depression, with which it often co-exists, anxiety more common in women (20%) than in men (8%)
• Approx 20M people in US Dx w/ some form of anxiety each year

Anxiety

Risk factors for anxiety are legion; usually grouped in 4 areas:
• Traumatic experience
• Drugs
• Stressful situations: illness, death, divorce, financial stress, family tensions
• Endocrine imbalance: hyperthyroid state, PMS, post-partum symptoms, midlife changes for both genders

1/3 of the population report using alcohol to self-medicate
Anxiety & Botanicals
Researched or presumed mechanisms:
• Effects on the GABA system either by
  • inducing ionic channel transmission by voltage-gated blockage
  • alteration of membrane structures
• Interactions with several monoamines

Anxiety & Botanicals
Acute anxiolytic activity was found for, among others:
• Lavender
• Gotu Kola
• Sage
• Lemon balm and others

Lavender (Lavandula vera, L. spp.)
• Part used: Flowers, EO
• Aromatic, acrid, drying
• Nervine relaxant
• Decongestant – saponin-rich, mild stimulating effect on respiratory & GI systems
### Lavender (Lavandula vera, L. spp.)

- **Indications:**Esp when grief or prolonged melancholy accompanies:
  - chronic bronchitis
  - Pneumonia
  - bronchial asthma
  - nonspecific nervous indigestion

### Lavender

- **Dose:** Tea of whole or broken dried flower: 1 ounce to one pint, standard infusion
  - Note – effective water extracts may taste soapy
- **EO (essential oil) formulations, gel caps or other dose-equivalent preparations may improve patient compliance**
- **Glycerite or Tincture:** glycerine or water/alcohol extracts of recently dried flowers (1:3 in menstruum 60:40)
- **Sig.** 2.5-5ml (1/2-1 tsp) bid-tid

### Lavender Product & Anxiety

- **Silexan**
- **Essential oil capsule for internal use**
- From steam-distilled fresh flowering tops of lavender and standardized to contain approximately 70% of the compounds linalool and linalyl acetate
  
  *(Keller, A, 2014, HerbClips TM, American Botanical Council)*

- **Preliminary studies compare favorably to paroxetine for anxiety**
  
  *(Kaspar S et al, 2014)*
Lavender Product & Anxiety

Lavender EO & Anxiety RDPCT, con’t:

- Measured two doses compared to placebo and to paroxetine
- N = 600 men and women (ages 18-65)
  - From general and psychiatric practices in Germany, determined to have quantifiable Sx w/o psychosis
- Assessed by Hamilton Anxiety Scale (HAMA) total score
  14 Sx of anxiety on a severity scale of 1 (no symptoms) to 4 (severe symptoms)

Kasper S et al, 2014

Lavender Product & Anxiety

Lavender EO & Anxiety RDPCT, con’t:

- 2 Outcomes: Any change after 10 wks, and a change of 50% or more (HAMA score down by 10 or more points)
- 2 Tx doses Silexan: 80 mg & 160 mg; paroxetine dose 20mg
- 10 wk washout prior

Kasper S et al, 2014

Lavender Product & Anxiety

At beginning of study, 2/3-3/4 of each randomized group
- Tx
- Placebo
- Paroxetine
  - ...had other health problems (vascular, musculoskeletal, metabolic, or nutritional)
- Safety and efficacy measured every 2 wks

Kasper S et al, 2014
Lavender Product & Anxiety
Lavender EO & Anxiety RDPCT, con’t:

• AEs including g.i. disorders, infections, and nervous system problems
  25.0% of 160 mg/d Silexan group
  34.8% in 80 mg/d of Silexan
  40.9% of those taking paroxetine
  30.9% in the placebo group

Kasper S et al, 2014

Lavender Product & Anxiety
Lavender EO & Anxiety RDPCT, con’t:

• Results: At 4 wks & later, greatest change in HAMA score compared to placebo was in higher dose group taking 160 mg/d Silexan.
• Regarding the change of symptoms equal or greater than 50%:
  • Approx 60% of 160 mg/d patients & approx 52% of 80 mg/d Px
  • Compared to approx 38% of placebo group

Kasper S et al, 2014

Lavender Product & Anxiety
Lavender EO & Anxiety RDPCT, con’t:

• Both Silexan groups and paroxetine group:
  • Hi’er % of people with “much/very much” or “moderate/marked” improvement
  • Compared to placebo

Lavender EO

- Observational Study
- N = 20 HV
- Method: inhaled essential oil (EO) of Lavender vs. sweet almond oil.
- Assessed before and after w/ paired t test statistical procedure:
  - ANS blood pressure, heart rate, respiratory rate, and skin temperature
  - Subjective behavioral arousal
  - EEG recorded from 31 electrodes on the scalp

Sayorwan et al. 2012

Lavender EO

Lavender Observation con’t:

- Results: Inhaling lavender EO caused significant decreases of blood pressure, heart rate, and skin temperature
- Mood responses: lavender EO subjects categorized themselves as more active, fresher, and relaxed than other subjects.
- Compared with base oil, lavender oil increased the power of theta (48 Hz) and alpha (813 Hz) brain activities


Spices, Herbs & Cognition

- CNS changes in AD:
  - senile plaque
  - neurofibrillary tangle formation
  - oxidative/inflammatory processes
  - neurotransmitter disturbances
- Older studies (2004, 2007) establish oxidative damage as early event in pathogenesis of AD
- Presymptomatic prevention may target oxidative stress

(Markesbury, W. Damage to Lipids, Proteins, DNA, and RNA in Mild Cognitive Impairment. Arch Neurol. 64(7):954-956; 2007)
Antioxidants & Cognition

- N=4750 ≥65yo
- Use of both Vitamins C & A reduced AD by 78%


Bacopa monniera

- Contains: various; “main” constituent bacoside A
- Brahmi mechanism: preclinical shows various CNS actions including antioxidant, nootropic, antidepressant, anxiolytic effects
  - Modulates acetylcholine, dopamine, serotonin, and noradrenaline (norepinephrine) pathways
  - Increases protein kinase activity within the hippocampus
- Anxiolytic effects in people with cognitive decline
### Brahmi (Bacopa monniera)
- RDBPCT
- N = 46 HV
- Tx dose: 300 mg daily of brahmi (Keenmind) X 12 wks
- Assessed: STAI-State anxiety score
- Results: significant reduction in anx while primarily examining cognitive function


### Alzheimer Disease
- Cholinergic deficit correlated with severity of AD
- Tx may target availability of acetylcholine (ACh) released into the neuronal synaptic cleft
- Inhibit ACh hydrolysis by acetylcholinesterase (AChE), use of AChE inhibitors
- Rx donepezil (Aricept), rivastigmine (Exelon), galantamine (Reminyl)

### Snowdrops (Galanthus nivalis)
### AD & Galantamine

- Galantamine, an alkaloid from Snowdrop (*Galanthus nivalis* L., Amaryllidaceae)
- Traditional use Bulgaria, Turkey for neurological conditions (Shu, 1998)
- Alkaloid also in *Narcissus* spp. and *Lycorus radiata* (Bores et al., 1996)
- Licensed in US & Europe for AD treatment
- Well tolerated, significantly improved cognitive function of AD patients (multi-center RCTs)

(Wilcock et al., 2000; Wilkinson and Murray, 2005, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5137937/)

### Other Botanical Compds Inhibit AChE

- Ferulic acid (4-hydroxy-3-methoxycinnamic acid, FA): antioxidant, anti-inflammatory
- FA widely distributed in plant cell walls, esp whole grains
- Mouse study: FA ameliorated beta-amyloid-induced reduction in ACh levels in cortex and beta-amyloid-induced inflammation in hippocampus in mice; also improved cognitive function
  (Yan et al., 2001)

### Other Botanical Compds Inhibit AChE

- Huperzine A, from moss *Huperzia serrata*, is a lycopodium alkaloid related to quinolizidines
- Huperzine A improved memory retention processes in cognitively impaired aged and adult rats (Lu et al, 1988)
Club Moss (Huperzia serrata)

Huperzine A

- Multi-centre DBT:
- Huperzine A significantly improved memory and behaviour in AD patients
- More selective for AChE than butyrylcholinesterase (BuChE), another enzyme implicated in AD
- Less toxic than the synthetic AChE inhibitors donepezil and tacrine

(Small et al., 1997; Shu, 1998)

Other Botanical Cmpds Inhibit AChE

- Essential oil monoterpenes (Mukherje PK et al (2007)
- Conflicting reports - terpenoid antiChE activity
Lemon Balm (*Melissa officinalis*)

- Major constituent is ‘citral,’ a naturally occurring mixture of the isomers neral (20 – 36%) & geranial (25 – 48%)
- Citral is a strong antibacterial & antifungal with very low toxicity – used as ‘lemon’ flavoring

Citronellal (1 – 8%): sedative, antiseptic
Linalool (0.5 – 8%): sedative, antifungal, antiseptic
Lemon balm oil is antiseptic, antispasmodic, calming

Lemon Balm (*Melissa officinalis*)

- Contains: volatile compounds, terpenoids, phenolic acids and flavonoids
- Pharmacological effects:
  - Anxiolytic
  - Antiviral
  - Antispasmodic
- Effects on mood, cognition and memory shown in clinical trials
Lemon Balm

- Mechanism(s):
  - AChE inhibitory activity
  - Stimulation of acetylcholine and GABAA receptors
  - Inhibition of matrix metallo proteinase2 (Scholey 2014)
  - Inhibit GABA-transaminase activity
  - methanol extract - largest amount of dose-dependent inhibition
  - Rosmarinic acid, ursolic acid and oleanolic acid inhibit GABA-transaminase activity (Sarris 2013)

Lemon Balm

- Open-label pilot study - anxiolytic effects of commercially available preparation of lemon balm
- N = 20 adult outpatients with a DSM Dx: anxiety disorder & sleep disturbance
- All received 300mg bid X 15 dys
  - Lemon balm leaf extract standardized to at least 7% rosmarinic acid and 15% hydroxycinnamic acid

Cases J et al, 2011

Lemon Balm

- Open-label pilot, con't:
- Assessed by Free Rating Scale for Anxiety
- Results: significant reduction in anxiety (18% decline) & associated symptoms (15% decline) from baseline
- Insomnia reduced significantly: 42%
- Cannot rule out better than placebo

Lemon Balm

- RDBPC Cross-over Trial
- N = 20 healthy young adults
- Tx dose: 300, 600 and 900 mg of *M. officinalis* (Pharmaton) or a matching placebo at 7 day intervals
- Assessed by CDR battery

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Lemon Balm RDBPCT con’t:

- Results:
  - 600 mg - Accuracy of Attention sustained improvement
  - 300 mg – “calmness" elevated
  - "Alertness" significantly reduced


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Rosemary (*Rosmarinus officinalis*)

Cineole, a monoterpen, can represent up to 60% of the essential oil
Sage (*Salvia spp.*)

Salvia officinalis  Salvia apiana

Lavender (*Lavandula spp.*)

Lavender & Rosemary EO’s

- N = 144 HV
- Assessed by CDR (Cognitive Drug Research computerized cognitive assessment battery) VAS before and after
- Method: exposed to either one of the two odors or no odor (control)

Moss 2003
Lavender & Rosemary EO’s

Lavender, Rosemary AT con’t:

• Results:
  • Lavender - significantly decreased working memory, impaired reaction times for both memory and attention based tasks compared to controls
  • Rosemary - significant enhancement overall quality of memory and secondary memory factors

Moss, 2003

Lavender & Rosemary EO’s

Lavender, Rosemary AT con’t:

• Results:
  • Control and lavender groups significantly less alert than the rosemary
  • However, the control group was significantly less content than both rosemary and lavender


Lavender & Rosemary EO’s

• N=40 adults
• Assessed by EEG activity, alertness, and mood by POMS, STAI-A, self-report
• Tx: 3 minutes Aromatherapy (AT) = inhaled aromas - lavender (relaxing) or rosemary (stimulating)
• Subjects given simple math computations before and after

Diego 1998
Lavender & Rosemary EO’s

- Aromatherapy Trial, con’t:
  - Lavender group: increased beta power, suggesting increased drowsiness
  - Rosemary group: decreased frontal alpha and beta power (increased alertness)


Sage (Salvia officinalis L, various Salvia spp.)

- Many constituents of the Salvia genus
  - Terpenoids (a-pinene, b-pinene, 1,8-cineole, thujone, camphor and geraniol)
  - Regarded as main active constituents affecting CNS
  - Potent acetylcholinesterase and butrylcholinesterase inhibitors
  - In vitro: affinity to benzodiazepine brain receptors could explain calming effect

Sage & AD

- RDBPCT
- Conducted in 3 centers
- N = 42 (18 women) 65-80 yo Dx mild to moderate AD

Akhonzadeh 2003
### Sage & AD

- **Sage & AD RDBPCT, con’t:**
  - Assessed by:
    - ≥12 on the cognitive subscale of Alzheimer’s Disease Assessment Scale (ADAS-cog)
    - ≥2 on the Clinical Dementia Rating (CDR)
  - Tx dose: 60 drops daily food grade sage extract * X 16 weeks
    - *1 : 1 in alcohol 45% (1 kg dried herb (leaf) to 1 L of alcohol)

  Akhonzadeh 2003

### Sage & AD

- **Sage & AD RDBPCT, con’t:**
  - Outcome measured: change in ADAS-cog and CDR-Sum of Boxes scores compared with baseline
  - Results: At 4 months, S. officinalis extract produced significantly better outcome on cognitive functions than placebo


### Sage & AD

- **DBRPCT**
  - N=42 w/ mild to moderate AD
  - Result: significant improvement on 60 gtt of tincture (product not specified) compared to placebo

**Sage & Healthy Elderly**
- RDBPC cross-over Trial
- N= 20 > healthy 65yo
- Tx doses: 167, 333, 666, 1332 mg, placebo w/ 7 day washout
- Assessed by CDR (Cognitive Drug Research battery) at Baseline and at 1, 2.5, 4, 6 h post Tx
- Results: 333 mg dose significantly enhanced secondary memory, accuracy compared to placebo; other doses effective but less so

(Scholey AB et al. (2008) An extract of Salvia (Sage) with anticholinesterase properties improves memory and attention in healthy older volunteers. Psychopharmacology 198(1):127–39)

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**Sage & Healthy Adults**
- Acute, DBRC cross-over Trial
- N = 30 HV
- Tx doses: 300 vs 600 mg of dried sage leaf
- Assessed by STAI-State
- Result: 300 mg dose of sage significantly reduced anxiety
- Note: after 20 min using a multitasking battery (designed to elicit stress-related physiological responses), reduced anxiety effect abolished


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**Turmeric**
Turmeric (Curcuma longa) & curcumin

Theoretical Mechanism re Cognition:

- Monoamines, dopamine in particular, involved in working memory (Ellis and Nathan, 2001).
- Dopamine release increased during working memory and attention tasks in healthy adults; correlates with task performance (Aalto et al, 2005).

Turmeric

- Animal studies - curcumin inhibits monoamine oxidase (MAO), increases serotonin, dopamine levels 1 h after administration (Kulkarni et al, 2008)
- Similar enhancement also reported 24 h after the cessation of chronic curcumin treatment (Kumar et al, 2010; Pyrzanowska et al, 2010).
- Hypothesis: observed improvements in cognitive task performance following acute and chronic treatment due to curcumin on monoaminergic neurotransmission.

Turmeric & Healthy Elderly

- RDBPCT – Acute, Chronic, Acute-on-chronic
- N= 60 (60-85 yo); Telephone Interview for Cognitive Status (TICS-M; de Jager et al., 2003) prior to R/O dementia.
- Doses: 400 mg of Longvida® (80 mg curcumin) X 4 wks
- Assessed by Computerised Mental Performance Assessment System (Northumbria University) for inclusion, (MMSE and TICS-M scores), pre-morbid intellect (National Adult Reading Test (NART) score), trait anxiety (STAI-T) or depressive symptoms (BDI-II)
Turmeric & Healthy Elderly

RDBPCT, con't:

- Measures at 1, 3 h; at 4 wks, 1.3 h after chronic curcumin administration
- Compliance ($M = 99.07\%$, $SD = 4.89$)
- Results: One hour after administration curcumin significantly improved performance on sustained attention and working memory tasks vs. placebo
- Working memory and mood (general fatigue and change in state calmness, contentedness and fatigue induced by psychological stress) significantly better following chronic treatment

Cox 2015

Turmeric & Healthy Elderly

RDBPCT, con't:

- Significant acute-on-chronic treatment effect on alertness and contentedness also observed.
- 1 H after dose led to significant beneficial effect on number of correct responses during serial three subtraction task ($p = 0.030$).
- Even low dose (approx 80 mg curcumin) may improve important cognitive functions, reduce fatigue and improve resilience to the detrimental effects of psychological stress on mood

Cox 2015

Turmeric & Healthy Elderly

RDBPCT, con't:

- Hematological safety measures incl significantly reduced total and LDL cholesterol
- Authors: “safe and well tolerated in an elderly population”

Gotu Kola (Centella asiatica)

- Traditional in Ayurveda, Traditional Chinese Medicine
- Long used in European and North American phytotherapy
- Part used: Leaf
- Cooling, bitter vegetable & medicine
- Grows in hot, wet bioregions
  - Food of elephants
- Used for memory, concentration, multisystem benefits
  - Nervous system optimization and/or vs. damage
  - Skin damage, from autoimmune to scarring

Gotu Kola

- Contains:
  - Various alkaloids include hydrocotylin (Duke & Ayensu, 1985)
  - Essential oil monoterpenes: bornyl acetate, alpha-pinene, beta-pinene and y-terpinene (Asakawa et al., 1982)
- Mechanism: EO known to inhibit AChE (Miyazawa et al., 1997; Perry et al., 2000; Ryan and Byrne, 1988)
- Since gotu kola leaf is a vegetable, the dose can be very high. Add to smoothies or take 1 Tbl of fresh juice every morning. Many products provide 1 gram per day in capsules.
- Dose: 1-4 g per day, 1 Tbl juice, 1c tea
- Korean study: components in gotu kola show potential for treating AD (Singhal et al 2012)
Gotu Kola

- Acute DBRCT
- N= 40 HV
- Tx: gotu kola single dose = 12 g (vs placebo)
- Result: Gotu kola significantly reduced the amplitude of startle response at both 30 and 60 min


Gotu Kola

- Open Label Study
- N= 33 Dx w GAD
- Tx: leaf extract (500 mg bid X 8 wks
- Results: gotu kola significantly reduced anxiety by 26 % at study endpoint
- In addition, reduction in stress and depression ratings
- Limits of study: unvalidated assessment scale, inadequate reporting


Savoring the Effects of Spices on Brain Health