Healthy Aging: Antioxidants, Adaptogens & Cognition

Karen Butler
Senior Editor
Informa Markets

Michael Altman, CN, RH (AHG)
Herbalist Nutritionist
Anthocyanins International LLC
(SeattleCancerCareAlternatives.com)

Kieron Edwards, Ph.D.
Chief Scientific Officer
Sibelius Natural Products

David Heber, M.D., Ph.D., FACP, FASN
Professor Emeritus and Founding Director
UCLA Center for Human Nutrition

Katie Stage, N.D., RH (AHG)
Director, Therapeutics Division
Associate Professor, Southwest College of Naturopathic Medicine (SCNM)
Towards healthy aging

Kieron Edwards PhD MBA

www.sibeliusnaturalproducts.com

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Talk outline

- The trends and challenges of aging
- What occurs during aging?
  - Theories, effects, and pathways of aging
- Supporting healthy aging
Aging: The monster at the end of the book
The trends and challenges of aging
What is aging?

- Ageing results from the impact of the accumulation of a wide variety of molecular and cellular damage over time. This leads to a gradual decrease in physical and mental capacity, a growing risk of disease, and ultimately, death. But these changes are neither linear nor consistent, and they are only loosely associated with a person’s age in years (WHO)
Age-related changes to health

- Physical aging
  - Sensory loss, body composition changes, osteoarthritis
- Cognitive aging
- Immune aging
  - Immunosenecence, inflammation
- Cardiovascular health
  - CVD is still the leading cause of death in older adults
- Metabolic health
- Cancer
  - Second leading cause of death in older adults
Living longer and better?

- Human lifespan is increasing
  - Almost 2 years increase per decade
- Age is a major risk-factor in many human diseases and conditions
  - 62% of Americans over 65 have more than one chronic condition (Ward et al., 2013)
- Healthspan has not increased at the same rate

(Bellantuono et al., 2018)
An aging global population

- Global population over 60 years
  - 1980 – 382 million
  - 2017 – 962 million (over 80 137 million)
  - 2050 – 2.1 billion (over 80 425 million)

- Growth much faster in less developed countries

- But still occurring in developed countries

(Statistics from “World population ageing; 2017 highlights” report, United Nations)
An aging global population

- Larger number of older adults but also increasing percentage
  - By 2050 35% of European and 28% of N. American populations will be over 60 (United Nations, 2017)
- Projections in US have older adults (>65) outnumbering children (<18) by 2035
- Great burdens on individuals and society
  - Provision of social- and health-care
Aging: A challenge and an opportunity

- Higher percentage of older adults take supplements
- Healthy aging supplements sales are growing
  - Is the opportunity bigger?
- Not just Baby Boomers
- Millenials taking greater interest
  - Awareness from caring for older relatives
  - Concern for cognitive and physical decline
  - Realisation of importance of lifestyle choices
What occurs during aging?

Programmed, error, or both?

- Pre-programmed process
  - Regulated by the neuronal, endocrine system, and changes in gene expression over time
  - Natural selection will act on longevity if it is beneficial to fitness
- Accumulation of damage or errors over time
  - Cumulative damage form intrinsic and extrinsic factors cause the reduction in function of biological system
Mitochondrial dysfunction and ROS

- Mitochondrial function declines with age
  - Reduced ATP production
  - Increased leakage from electron transport chain – increased ROS and damage to biomolecules (DNA, proteins, lipids...)

- Free-radical theory of aging
  - Gradual accumulation of damage by ROS leads to cellular aging
    - Superoxide dismutase (SOD) proteins present in all aerobic organisms
    - However, hormetic effects of ROS as well and ROS important to cell signalling

(Image credit: Stroo et al., Frontiers in Neuroscience, 2017)
Build up of un-degradable molecules

- Multiple mechanisms lead to build up of molecules
  - Toxic by-products of normal metabolism e.g. Lipofuscin “age-pigment”
  - Mis-processed or mis-folded proteins e.g. Amyloid proteins
  - Advanced glycation end products (AGEs)
- Contributes to breakdown of intracellular processing and transport mechanisms
  - e.g. autophagy and proteolysis
- Intracellular and extracellular aggregates
  - Tau aggregates or Amyloidβ plaques
  - Atherosclerotic plaques

(Image credit: Strooo et al., Frontiers in Neuroscience, 2017)
Senescence

- Stable arrest of the cell cycle
  - Linked to telomere shortening, DNA damage, mitogenic signals...
- Senescent cells accumulate in aged tissues
- SASP: pro-inflammatory conditions may contribute to aging
  - Inflammation a major risk factor in many age-related diseases
- Contributes to decline in stem cell populations with age
  - Reduced regenerative capacity
  - Atrophy and immunosenescence
    - e.g. thymus

(Image credit: Stroo et al., Frontiers in Neuroscience, 2017)
Core pathways of aging

- Studies in model organisms have identified several key pathways of aging conserved across species
  - Insulin IGF-1 Signalling (IIS) pathway strongly conserved
    - Together with its core targets FOXO and mTOR
    - Principally related to glucose sensing
    - Mediates DR/CR benefits
  - Decreased IIS results in lower rates of cell growth and metabolism and therefore lower rates of cellular damage
Core pathways of aging

- Inter-connected aging network
- Nutrient sensing plays a core role
  - IIS – Glucose
  - mTOR – amino acid concentrations
  - AMPK – low energy status [AMP]
  - Sirtuins – low energy status [NAD$^+$]
- Regulates balance of anabolism and catabolism
- Pro-longevity treatments mimic low nutrient availability
  - e.g. Rapamycin

(Barzila et al., Perspectives in Diabetes, 2012)
Supporting healthy aging
Healthy aging

- There is undeniably a strong role of accumulation of error and damage over time in aging
- Some of these factors are intrinsic, but other drivers are external
  - e.g. Environmental damage and stresses
- Can we slow down or even reverse this damage?
  - Slow down the sand-timer
Clues from other species

- What positive interventions to take?
- Calorie restriction has demonstrated increased longevity across multiple species
  - First demonstrated in rodents in the 1930s
- Various treatments also show consistent effects across multiple species
  - Rapamycin, Resveratrol, Curcumin...
  - Act on these core pathways of aging
Clues from long-lived humans

- Role for genetics in longevity, but it is still a plastic trait
- Long-lived people in “Blue-zones” show some consistent behaviours
  - Diet
    - Moderate calorie intake/intermittent fasting
    - Rich in plant-based foods
    - Moderate alcohol
  - Physical activity
  - Sleep
  - Mood
    - Social interaction, sense of purpose, avoidance of chronic stress...
Supporting healthy aging

- Positive lifestyle interventions have the potential to increase longevity and delay the onset of age-related pathologies
  - Supplements can make a key contribution to this
    - Mimic calorie-restriction without the down-sides
- Demonstrating benefits in humans poses a challenge
  - Aging is not recognised as a disease
  - How do you measure aging?
- To date limited evidence of efficacy in humans beyond epidemiological studies
Summary

- Aging poses a significant challenge to individuals and society
- Basic research has identified many of the hallmarks associated with aging
- Slowing down the accumulation of age-related damage has promise to delay the on-set of age-related pathologies
  - Improve peoples healthspan
- Lifestyle interventions, including supplements, have the potential to contribute to this
Going beyond slowing down?

- Lifestyle interventions may slow down – or even reverse – some forms of age-related damage
- Other elements will likely require medical interventions
  - e.g. Senence, tissue atrophy, accumulation of AGEs lipofuscin etc.
- Relevant technologies are being developed so it is conceivable that these could be tackled as well
  - Gene and enzyme therapies, stem-cell therapies, immunotherapies
Well, look at that! This is the end of the book, and the only one here is...

ME.

I, lovable, furry old GROVER, am the Monster at the end of this book.

And you were so SCARED!

I told you and told you there was nothing to be afraid of.
A Nutraceutical Platform Technology for Health

THANK YOU

Sibelius

kieron.edwards@sibeliuslimited.com

Kieron Edwards PhD MBA

www.sibeliusnaturalproducts.com
NEW RESEARCH WITH ANTIOXIDANT INGREDIENTS

David Heber, MD, PhD, FACP, FASN
Professor Emeritus of Medicine and Public Health
Founding Director, UCLA Center for Human Nutrition
DISCLOSURES

► McCormick Science Institute – Honoraria and Travel
► Herbalife Nutrition Institute – Honoraria and Travel
► POM Wonderful – Research Awards
Inflammaging
How Do You Measure Age?

• Chronological age does not correlate perfectly with functional age, i.e. two people may be of the same age, but differ in their mental and physical capacities.

• Each nation, government and non-government organization has different ways of classifying age.

• Divisions are sometimes made between the young old (65–74), the middle old (75–84) and the oldest old (85+).
Dunedin Study

A longitudinal investigation of health and behavior in a complete birth cohort.

Study members (N=1,037) were all born between April 1972 and March 1973 in Dunedin, New Zealand (NZ).

Assessments were carried out at birth and ages 3, 5, 7, 9, 11, 13, 15, 18, 21, 26, 32, and, most recently, 38 years, when 95% of the 1,007 study members still alive took part.

Belsky et al., 2015 (PNAS)
Information Classification: General

Distribution of Pace of Aging in the Dunedin Cohort.
Pace of Aging is denominated in years of physiological change per chronological year.

“0” indicates a cohort member whose physiology remained unchanged between ages 26 and 38.

“1” indicates a cohort member who experienced one year of physiological change per chronological year (the cohort average).

“2” indicates a cohort member aging at a rate of two years of physiological change per chronological year, twice as fast as the population norm.

Successful Aging Begins While We’re Young

Belsky et al., 2015 (PNAS)
Inflammation Markers Increase with Age
Oxidant Stress & Aging

- Environmental Sources (pollution, cigarette smoke)
- Mitochondria
- Cellular Sources (Inflammation, XO, NADPH Oxidase)

Oxidative Stress → ROS → Tissue Damage

Aging and Age-Related Disease

- Immune (Autoimmune Disease)
- Eye (Cataracts, AMD)
- Kidney (Renal disease)
- Skin (Melanoma, etc)
- Lung (Cancer, COPD)
- Brain (AD, PD, stroke)
- Heart (CV disease)
- Joint (Arthritis)
### Aging Disease

<table>
<thead>
<tr>
<th>Age</th>
<th>Grey Zone</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular Stiffness</td>
<td>High Blood Pressure</td>
<td>Atherosclerosis</td>
</tr>
<tr>
<td>Bone Loss</td>
<td>Osteopenia</td>
<td>Osteoporosis</td>
</tr>
<tr>
<td>Decline in Glucose Tolerance</td>
<td>Pre-Diabetes</td>
<td>Diabetes</td>
</tr>
<tr>
<td>Loss of Neurons</td>
<td>MCI</td>
<td>Alzheimer’s and other Neurodegenerative Diseases</td>
</tr>
<tr>
<td>Loss of Visual Accommodation</td>
<td>Presbyopia</td>
<td>Cataract</td>
</tr>
<tr>
<td>(Lens stiffening)</td>
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</tbody>
</table>
A Colorful Diet
Polyphenols

• Polyphenols are a large and heterogeneous group of antioxidant phytochemicals containing phenol rings.

• Several hundred different polyphenols are found in plant-based foods including broccoli, onion and cabbage, fruits, legumes, cereals, plant-derived beverages and chocolate.

• Fruits such as grapes, pears, apples, cherries and various berries contain up to 200–300 mg polyphenols per 100 g fresh weight.

• Approximately 100 mg of polyphenols are found in a cup of coffee or tea or a glass of red wine.
Polyphenols

Hydrobenzoic acids
- Protocatechuic acid
- Gallic acid
- Hydrobenzoic Acids are components of Gallotannins and Ellagitannins

Hydroxycinnamic acids
- Coumaric acid
- Caffeic acid
- Ferulic acid
- Curcumin

Flavonoids

Stilbenes
- Resveratrol

Lignans
- Secoisolariciresinol

Flavonols
- Kaempferol
- Quercetin
- Myricetin

Flavones
- Apigenin
- Luteolin

Isoflavones
- Daidzein
- Genistein

Flavanones
- Naringenin
- Eriodictyol
- Hesperetin

Anthocyanidins
- Pelargonidin
- Cyanidin
- Delphinidin
- Petunidin
- Malvidin

Flavanols
- Catechins
- Gallocechin
Food Sources of Polyphenols

• **Rich colors** like reds, purples or black indicate that plant foods are excellent sources of polyphenols.

  Choose foods such as blueberries, pomegranates, red grapes, cranberries, and red or purple sweet potatoes.

• Blueberries as well as foods such as black rice, purple barley, black sorghum, and purple potatoes are sources of **anthocyanins**, as well as other polyphenols.

• The compound responsible for the color of turmeric, called **curcumin**, also happens to be a polyphenol.
Tea Polyphenols

(-)-epicatechin (EC)  (+)-catechin (CT)  (-)-epigallocatechin (EGC)

(-)-epicatechin gallate (EGC)  (-)-epigallocatechin gallate (EGCG)
Pomegranate Polyphenols

Punicalagins

Ellagic acid (EA)

Dimethyl ellagic acid glucuronide (DMEAG)

Urolithin A

Urolithin B
A Cascade of Events

Polyphenols → Metabolism Prebiotic, & Postbiotic Effects → Cellular Effects → Successful Aging (Life cycle)

Ellagitannins & Micronutrients
- Urolithins A & B
- Ellagic Acid
- Indol-3-Proprionic Acid
- Other Bioactives

Oxidative Stress → Subclinical Inflammation

Mitochondria Health

Blood Flow

Neuroprotection

Muscle Health

Skin Health
How do Muscles Work?

We’ll come back to mitochondria in a bit...
Mitochondria in Aging
Mitochondria Autophagy

Urolithin A induces mitophagy and prolongs lifespan in *C. elegans* and increases muscle function in rodents.

Identified urolithin A (UA) as a natural compound that induces mitophagy both *in vitro* and *in vivo* following oral consumption.

**In *C. elegans***:
1. Prevented the accumulation of dysfunctional mitochondria with age
2. Prolonged normal activity during aging in *C. elegans*, including mobility and pharyngeal pumping, while maintaining mitochondrial respiratory capacity
3. Extended lifespan

**In rodents**:
Improved exercise capacity in two different mouse models of age-related decline of muscle function
Likewise for young rats.

**Author’s Conclusion**: Findings highlight the health benefits of urolithin A and its potential application in strategies to improve mitochondrial and muscle function.
Information Classification: General

Urolithins Map

Pomegranate’s Ellagitannins (e.g., Punicalagin)

- ↓ DOMS, human (1-3)
- ↓ TNFα-induced muscle wasting, mouse (8)
- ↑ Recovery from athletic muscle damage (7)
- ↑ Lifespan, C. Elegans (Li et al., TBD)

• Antioxidant (3)
• Anti-inflammatory (3)
• Anti-Cancer (3)
• ↑ Mitophagy, mouse (6)
• ↑ Lifespan, C. Elegans (6)
• ↑ Muscle function, grip & running, mouse (6)
• ↓ TNFα-induced muscle wasting, mouse (8)

Promotes Muscle Function

- Antioxidant (3)
- Anti-inflammatory (3)
- Anti-Cancer (3)
- ↑ Muscle growth, mouse (11)

Promotes Muscle Growth

- Antioxidant (3)
- Anti-inflammatory (3)
- Anti-Cancer (3)
- ↑ Muscle growth, mouse (11)

3. Espin et al., eCAM. Volume 2013, Article ID 270418
Age-related changes in the brain

In order to recall a memory, you must activate a vast network of interconnecting brain cells called neurons (nerve cells). These brain cells deliver and permanently store messages along neural pathways, primarily in the cerebral cortex, the large, domed outer layer of the brain.

One brain cell communicates with another across a space called a synapse, by way of chemicals known as neurotransmitters. These neurotransmitters activate the receptors on the neighboring cell. Revisiting a memory strengthens the connections between brain cells that are responsible for maintaining that memory.
Aging Brain and Memory

A steady decline in brain functions are seen starting about age 30 especially in many types of memory with aging.

There are changes to the brain though loss of brain cells is minor until age 20. The brain is made of nerves which send out branches called axons. These axons are like wires that conduct electricity and they are coated with a fat called myelin. The length of these wires in the brain shorten 10% per decade after age 20.

However, inflammation is the likely culprit in serious loss of memory function.
Age is the Greatest Single Risk Factor for Memory Loss

Perspectives on Polyphenols.

Research suggests that the consumption of polyphenol-rich foods and drinks (e.g., grape juice, blueberries, & cocoa) and spices including curcumin are associated with cognitive benefits.

Polyphenols are thought to positively affect cognitive function by a variety of mechanisms, including:

1. Inhibiting neuro-inflammation
2. Inducing neurogenesis and synaptic plasticity.

Perspectives on Polyphenols.

1. Improved verbal learning and reduced semantic interference on memory tasks in older adults with mild cognitive impairment were reported after consuming concord grape juice daily for 12 & 16 wks.

Krikorian et al., British Journal of Nutrition (2010), 103, 730–734

2. Supplementation with blueberry concentrate improved brain perfusion and activation in brain areas associated with cognitive function in healthy older adults.

Bowtell et al., Appl Physiol Nutr Metab, 2017 Jul;42(7):773-779

3. Improved cerebral blood flow has been observed in humans after the consumption of cocoa flavonols.

Lamport et al., Psychopharmacology (Berl). 2015 Sep;232(17):3227-34
Research Article

Pomegranate Juice Augments Memory and fMRI Activity in Middle-Aged and Older Adults with Mild Memory Complaints

Susan Y. Bookheimer,¹ ² Brian A. Renner,¹ ² Arne Ekstrom,¹ ² Zhaoping Li,¹ ² Susanne M. Henning,¹ ² Jesse A. Brown,¹ ² Mike Jones,¹ ² Teena Moody,¹ ² and Gary W. Small¹ ²

¹ Center for Cognitive Neurosciences, Department of Psychiatry and Behavioral Sciences and Semel Institute for Neuroscience and Human Behavior, University of California, Los Angeles, 760 Westwood Plaza, Los Angeles, CA 90024, USA
² Center for Human Nutrition, David Geffen School of Medicine, and the UCLA Longevity Center, University of California, Los Angeles, Los Angeles, CA, USA

Correspondence should be addressed to Susan Y. Bookheimer; sbook@ucla.edu

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Despite increasing emphasis on the potential of dietary antioxidants in preventing memory loss and on diet as a precursor of neurological health, rigorous studies investigating the cognitive effects of foods and their components are rare. Recent animal studies have reported memory and other cognitive benefits of polyphenols, found abundantly in pomegranate juice. We performed a preliminary, placebo-controlled randomized trial of pomegranate juice in older subjects with age-associated memory complaints using memory testing and functional brain activation (fMRI) as outcome measures. Thirty-two subjects (28 completers) were randomly assigned to drink 8 ounces of either pomegranate juice or a flavor-matched placebo drink for 4 weeks. Subjects received memory testing, fMRI scans during cognitive tasks, and blood draws for peripheral biomarkers before and after the intervention. Investigators and subjects were all blind to group membership. After 4 weeks, only the pomegranate group showed a significant improvement in the Buschke selective reminding test of verbal memory and a significant increase in plasma trolox-equivalent antioxidant capacity (TEAC) and urceinol A-glucuronide. Furthermore, compared to the placebo group, the pomegranate group had increased fMRI activity during verbal and visual memory tasks. While preliminary, these results suggest a role for pomegranate juice in augmenting memory function through task-related increases in functional brain activity.
Methods: fMRI Visual Memory Task

Taxi-cab memory test

• Taxi drives the subjects through a virtual environment, stopping at stores along the way in several different imaginary towns

• Later, subjects are tested on which stores they saw, where they were located

Bookheimer et al., eCAM. 2013;2013:946298.
Methods: fMRI Visual Memory Task

Example of Visual Memory Task...
Which store did you see?

Original store façade (from encode phase)

Altered store façade

Bookheimer et al., eCAM. 2013;2013:946298.
Results:

Taxicab Visual Memory:
Pomegranate Juice > placebo, \( \text{time}_2 > \text{time}_1 \)

Bookheimer et al., eCAM. 2013;2013:946298.
Results:

3-D View

Bookheimer et al., eCAM. 2013;2013:946298.
Results: Pomegranate Juice Augments Memory and fMRI Activity in Middle-Aged & Older Adults with Mild Memory Complaints

1. PJ group performed significantly better in memory testing compared to baseline (alternating test forms; p=0.017)
2. PJ group recalled more items on consistent long-term retrieval compared to controls (p=0.022).
3. Memory scores were significantly greater in the PJ group on the total recall measure (p=0.029).

Clinical Randomized Controlled Trial: n=28, 4 wks, 8oz PJ daily
Results: Pomegranate Juice Augments Memory and fMRI Activity in Middle-Aged & Older Adults with Mild Memory Complaints

Significant activation in visual pathways (within-group means for both groups and at both time points) including bilateral occipital cortex extending into temporal fusiform and parahippocampal gyrus, as well as activation in subcortical region across the 3 task conditions, consistent with visual memory processing and spatial navigation.

Clinical Randomized Controlled Trial:
n=28, 4 wks, 8oz PJ daily

The POM group (n=28) showed greater fMRI activation than the placebo group in the $t_2$ versus $t_1$ contrast (p=0.05), located bilaterally in regions of the basal ganglia and thalamus.
Double-Blind Placebo-Controlled Study of the Memory Effects of Pomegranate Juice in Middle-aged and Older Adults*

Prabha Siddarth, Ph.D., Zhaoping Li, M.D., Ph.D., Karen J. Miller, Ph.D., Linda M. Ercoli, Ph.D., David A. Merrill, M.D., Ph.D., Susanne M. Henning, Ph.D., David Heber, M.D., Ph.D., Gary W. Small, M.D.

*Oral Presentation at American Association of Geriatric Psychiatry (March, 2019). Manuscript accepted for publication by the American Journal of Clinical Nutrition
Memory and Brain Amyloid and Tau Effects of a Bioavailable Form of Curcumin in Non-Demented Adults: A Double-Blind, Placebo-Controlled 18-Month Trial

Gary W. Small, M.D., Prabha Siddarth, Ph.D., Zhaoping Li, M.D., Ph.D., Karen J. Miller, Ph.D., Linda Ercoli, Ph.D., Natacha D. Emerson, M.A., Jacqueline Martinez, M.B.A., M.S., Koon-Pong Wong, Ph.D., Jie Liu, Ph.D., David A. Merrill, M.D., Ph.D., Stephen T. Chen, M.D., Susanne M. Henning, Ph.D., R.D., Nagichettiar Satyamurthy, Ph.D., Sung-Cheng Huang, D.Sc., David Heber, M.D., Ph.D., Jorge R. Barrio, Ph.D.

Objective:

Highlights

• This is the first long-term (18 months) double-blind, placebo controlled trial of a bioavailable form of curcumin (Theracurmin® containing 90 mg of curcumin twice daily) in non-demented adults.
• We found that daily oral Theracurmin led to significant memory and attention benefits.
• FDDNP-PET scans performed pre- and post-treatment suggested that behavioral and cognitive benefits are associated with decreases in plaque and tangle accumulation in brain regions modulating mood and memory.
• Curcumin’s cognitive benefits may stem from its anti-inflammatory and/or antiamyloid brain effects.
Take Home Messages

1. Polyphenol antioxidants appear to be key to unlocking the mystery of “inflammaging”. Polyphenols’ ability to combat oxidative stress, facilitate proper blood flow, and modulate inflammatory pathways is the basis for their health benefits.

2. Research suggests that polyphenols may support healthy muscle function, which is important to aging adults who are losing strength.

3. Research suggests that polyphenols may support increased brain activity and improvements in verbal memory and learning tasks in adults with age-associated mild memory complaints.
Healthy Aging: Antioxidants, Adaptogens & Cognition

Herbal Extracts, Formulation and Clinical SOPs (Systemic Organ Protection)

By: Michael C. Altman, RH (AHG), CN, MIIS
Adjunct Professor Nutrition & Environmental Health
Southern Oregon University
SeattleCancerCareAlternatives.com
Phyto-Formulation & Wellness Protocol Consultant
Antioxidants – Clinical Clout

- Flavonoids: Anthocyanins include pigmented compounds with abundant research backing and long term use. As formulators we can include sustainably cultivated sources such as Haskap/Honeyberry (Lonicera caerulea), Acai and Black Currants, rather than exclusively wild harvested berries. Synthesizing these compounds? Key Anthos: C3G and D3G

- The Bee’s Knees: Propolis and Bee Specialties
  https://civileats.com/2019/09/12/in-rural-appalachia-beekeeping-offers-a-new-path-for-coal-miners/?fbclid=IwAR0w9oq21RFtQqwZBN-TN_Qx-RBn4Tyy-FcM3Vzt3e7JU_rk4kAVvmQWt9AFcM3Vzt3e7U_rk4kAVvmQs://civileFcM3Vzt3e7JU_rk4kAVvmQWt

- Tannins: Oligomeric Proanthocyanidins from French Maritime Pine, Oak Bark, Hawthorn, Ginkgo, Grape Seed – blood pressure, edema, cancer, allergies
Specialty Cardiovascular Ingredients

- Hippophae rhamnoides, Sea Buckthorn (Hippo phaos) Shining horse
- Angelica keiskei (Ashitaba chalcone)
- Allium sativum (Aged black garlic extract)
- Nattokinase (from Glycine max) Soy based enzyme
- Anthocyanins extracts
- Novel TCM Herbs (Salvia miltiorrhiza aka Dan Shen, Red Sage Root)
  Tanshinones for neurogeneration and cardiovascular support

How do we improve lipids, reduce inflammation, improve vessel elasticity, and reduce resistance to healthy blood flow?
Adaptogens – Upregulating Survival Potential and Healthy Active Aging

Find your Roots, Berries, Shoots, and Fungi

- Panax ginseng
- Withania somnifera (Ashwagandha)
- Oplopanax horridus (Devil’s Club)
- Lepidium meyenii (Maca)
- Aralia racemose (Spikenard)
- Schisandra chinensis
- Ganoderma (Reishi)
- Cordyceps
- Eleutherooccus (Siberian ginseng)

Adaptogens are non-toxic, normalize function and can be used over the long term. They support various systems.

With ginseng, know your species and treatment. Some adaptogens like Aralia and Oplopanax have a respiratory affinity. Others like ginseng and Ganoderma are heart-centric.

With mushrooms, know your substrate, where and on what your raw material is grown, and how it’s extracted

Swim tests, altitude, stress, endocrine and sexual enhancement
Nootropics and Nervous System Support
Nervines, Calm Stimulants, & Anxiolytics

- Bacopa
- Melissa (Lemon balm)
- Avena (Milky oat)
- Piper methysticum (Kava)
- Centella (Gotu Kola)
- Paeonia lactiflora (White Peony)
- Cross reference adaptogens such as Schisandra and Ashwagandha
- Rosmarinus (Terpenes)
- Crocus sativus (Saffron)
- Scutellaria lateriflora (don’t confuse) with Baical Skullcap root
- Cannabis

- Herbs that nourish the nervous and cardiovascular systems, support them with their phytochemical and mineral contributions and help with symptom control: anxiety, tics, tremors, senescence
KATIE STAGE, ND RH (AHG)

HEALTHY AGING: ANTIOXIDANTS, ADAPTOGENS & COGNITION

OCTOBER 16, 2019
OPTIMIZING AN AGING BRAIN

COGNITIVE ENHANCEMENT
OBJECTIVES

• Discover the leading theories on optimizing cognitive function

• Explore herbal therapies that support each mechanism of cognitive enhancement

• Understand concepts in formulating for maximum effect
AGING AND COGNITIVE DECLINE

• Cognitive deficits are the most common consequences of the aging process (Budni, 2015)
• Much of the scientific research on cognition is centered around understanding Alzheimer’s disease and the resulting cognitive dysfunction
  • Accumulation of β-amyloid (Aβ) plaques and neurofibrillary tangles (NFTs)
    • No strict correlation between the number of plaques and cognitive decline
    • NFTs result from hyperphosphorylation of tau, a microtubule-associated protein.
      • NFTs decrease neuronal function and do correlate with cognitive decline (Kinney, 2018)
• Chronic inflammatory changes trigger neurotoxins, further exacerbating Aβ and tau/NFTs (Kinney, 2018)
AGING BRAIN

- Antioxidants
- Perfusion
- Acetylcholine (ACh)
- Inflammation
- Brain-derived neurotrophic factor (BDNF)
Neurons are at high risk of oxidative damage due to high oxygen consumption and energy production.

Oxidative stress is implicated in cognitive decline and neurodegenerative disease.

Unclear whether this is a cause or consequence.

Those with ApoE genotype show higher oxidative damage than others, even before disease has manifested (Wojsiat, 2018).

Oxidative stress damages amyloid plaques formed from beta-amyloids (Aβ) (Lokanathan, 2016), which stimulates more oxidative stress (Wojsiat, 2018).

Clinical data limited; antioxidant intervention must to be able to cross the BBB (Teixeira, 2013).

Antioxidant (beta carotene, vitamin C, and vitamin E) rich diet associated with lower risk of AD dementia (Wojsiat, 2018).
Acetylcholine (ACh) is used widely in the nervous system:
- Attention, cognition, stress response, wakefulness, sleep, and in processing sensory information (Ferreira, 2016)
- Decline in cholinergic neurons / cholinergic transmission is a leading hypothesis for development of Alzheimer’s disease (Lokanathan, 2016)
- Pharmaceutical treatments for dementia are mostly aimed at optimizing ACh
  - Increasing synthesis and up regulation of ACh
  - Using AChE or butyrylcholinesterase (BuChE) inhibitors to slow breakdown of ACh
    - Donepezil, rivastigmine, galantamine (Ferreira-Vieira, 2016)
PERFUSION

- Neurons are particularly sensitive to decreased blood perfusion
  - Clinically, those with Alzheimer’s do show impaired perfusion to the brain (Toda, 2012)
- Decreased perfusion inhibits removal of Aβ; Aβ decreases NO availability and in turn decreases perfusion to the brain
- Decreased NO and endothelial dysfunction seen in conditions with higher risk of Alzheimer’s: age and cardiometabolic diseases
- AChE inhibitors (Donepezil) improve brain perfusion along with effect on ACh (Toda, 2012)
DECREASING INFLAMMATION

- Neuroinflammation is implicated in many neurological disorders including Alzheimer’s, PD, TBI, ALS, MS (Kinney, 2018)
- Chronically activated brain macrophages (microglia) and other immune cells release pro-inflammatory and toxic products
  - Exacerbates both amyloid and tau pathology (Kinney, 2018)
- Chronic inflammation also seen in conditions which increase risk for Alzheimer’s including age, CVD, TBI, and diabetes (Kinney, 2018)
- Neuroinflammation is also seen in memory deficit due to chronic stress (Ar Rochmah, 2019)
ENHANCING BRAIN DERIVED NEUROTROPHIC FACTOR (BDNF)

- BDNF expression is modified by stressors; decreased expression contributes to depression, Alzheimer’s, Parkinson’s, epilepsy (Budni, 2015) and cognitive impairment (Qin, 2016)
- BDNF is a mediator of neuroplasticity
  - Protects against the effects of chronic stress (Ar Rochmah, 2019)
  - Protective against future occurrence of dementia (Weinstein, 2014)
- Because it is induced by exercise and reduced caloric intake, it is thought to mediate the association between healthy lifestyle and successful aging (Weinstein, 2014).
GINKGO
BILOBA

- Gingko, Maidenhair tree
- Leaf
- EGb 761® standardized extract
  - 24% Flavonol glycosides, 6% terpene lactones (ginkgolides, bilobalide), < 5 ppm ginkgolic acids
  - Available by Rx in Europe (Nash, 2015)
- Also used for tinnitus, headaches/migraines, as a cardiovascular tonic
GINGKO BILOBA

- Increases microcirculation to the brain
  - Supports glucose levels and ATP utilization (Silberstein, 2011)
  - Inhibiting the aggregation and toxicity of Aβ protein (Gauthier, 2014)
  - Enhancing neuroplasticity and neuroprotection (Zhang, 2016)
  - Improves outcomes in cerebrovascular disease (Gauthier, 2014)
  - Increases dopamine levels in prefrontal cortex (Gauthier, 2014)
- Dose dependent* use increases working memory (Silberstein, 2011), cognition, neuropsychiatric symptoms, and daily activities (Zhang, 2016)
- Ginkgo flavonols for 4 months increased BDNF (Sangiovanni, 2017)
- Dose: 120-600mg (240mg) a day - safe; ensure standardized extract & authenticity
**Bacopa Monnieri**

- Brahmi, water hyssop
- Whole plant (areal)
- Triterpenoid saponins (bacosides), alkaloids (brahmine, nicotine), saponins (bacopasides)
  - Standardized extract 25% bacoside A or 55% combined bacosides
- Medhya-rasayana (memory enhancer), hepatoprotective, anxiolytic*, mast cell stabilizer, anti-nociceptive (Sangiovanni, 2017)
BACOPA MONNIERI

- Potent anti-oxidant that crosses BBB
  - Protective against environmental neurotoxins (Sangiovanni, 2017)
- Increases cerebral blood flow
  - Inhibition of AChE and production of ACh
  - β-amyloid reduction and monoamine potentiation (Aguiar, 2013)
- Clinical enhancement of memory acquisition, retention, attention, and memory processing - even in those without cognitive decline (Aguiar, 2013)
- Chronic and moderate use (200-400 mg a day) nourishes neurons; results best after 3 months administration (Aguiar, 2013)
- Generally very safe; mild GI upset in some; caution in hyperthyroidism
CENTELLA ASIATICA

- Gotu kola, Indian pennywort, Brahmi, Hydrocotyle asiatica
- Whole plant (leaves*)
- Triterpene saponins (asiatic acid, AA), madecassic acid and heterosides asiaticoside and madecassoside), minerals, flavonoids, EO (Orthan 2012, Lokanathan, 2016).
  - ECa 233: 80% triterpenoid glycosides including asiaticoside (32.3%).
  - TECA: 30% AA, 30% madecassic acid, 40% asiaticoside
- Medhya-rasayana, brain tonic and “miracle elixir of life”, wound healing/anti-fibrotic (Nagoor, 2018, Gohil, 2010), anxiolytic (Gohil, 2010)
CENTELLA ASIATICA

- Asiatic acid (AA) is a potent anti-oxidant (Grey, 2016) able to cross BBB
  - Neuroprotective; attenuates neurotoxin-mediated cognitive decline (Nagoor, 2018)
- Asiaticosides, AA have anti-inflammatory activity in hippocampus (Nagoor, 2018)
- Does not seem to inhibit amyloid plaques directly (Krishnamurthy, 2009), but protects against against Aβ neurotoxicity (Nagoor, 2018) and may inhibit AChE (Lokanathan, 2016, Orthan 2012)
- Asiaticocides prevent stress-related decline in BDNF (Ar Rochmah, 2019)
- Dose dependent (500mg -1,000mg/day) reduction in age-related cognitive decline after 2-6 months (Lokanathan, 2016)
- Generally safe, mild GI upset in some; possible anti-fertility effect (animals)
Huperzia serrata

- Chinese/toothed club moss, qian ceng ta, Lycopodium serratum
- Alkaloid (huperzine A)
  - Licensed anti-AD drug in China (Qian, 2014)
  - Endophytic fungal strain ES026 (Colletotrichum gloeosporioides) is also able to produce Huperzine A (Shu, 2014)
- Traditional uses: fever, swelling, pain, schizophrenia
HUPERZINE A

- Reversibly and selectively inhibits AChE, preventing ACh breakdown (Ohba, 2015)
- More potent AChE inhibitor than Alzheimer’s medications donepezil, tacrine, and rivastigmine (Zhang, 2012)
- No effect on butyrylcholinesterase (BuChE) (Ohba, 2015)
- Reduced Aβ, deposition of amyloid plaques, and hyperphosphorylated tau (Ohba, 2015)
- Four weeks of treatment upregulated BDNF, ameliorated behavioral changes and impaired neurological and cognitive function in post stroke depression rats (Du, 2017); decreased neuroinflammation after TBI (Mei, 2017)
- Dose 150-250 up to 400 mcg 2x/day (Zhang, 2012)
- Interactions with anticholinergic drugs; best avoided in pregnancy and lactation, SE: GI, tachycardia, fatigue, HTN, bradycardia, headache, muscle cramps (Zhang, 2013)
SALVIA OFFICINALIS, S. LAVANDULAEFOLIA

- Garden sage, Spanish sage
- Leaf
- Caffeic acid, rosmarinic acid, flavonoids, terpenes (α/β-thujone, camphor, 1,8-cineole, α-humulene, β-caryophyllene), carnosic acid, ursolic acid, carnosol.
  - Salvia lavandulaefolia does not contain α/β-thujone
- Carminitive, antimicrobial, antringent, anti-inflammatory (Lopresti, 2017)
Salvia officinalis reduced AChE and butyrylcholinesterase (BuChE); Salvia lavandulaefolia reduces AChE only (Lopresti, 2017)

- Potent anti-oxidant and anti-inflammatory properties that cross the BBB
- Rosemarinic acid restored hippocampal BDNF in chronically stressed rats (Lopresti, 2017)
- Caffeic acid attenuates the down-regulation of BDNF during stressful conditions (Lopresti, 2017)
- Improvements in word recall in healthy adults (Spanish sage volatile oil 50 µL 1-3x/day)
- Improved memory performance (333mg/day sage extract), also improved “alertness”, “contentedness”, “calmness” (sage leaf 150mg/day) (Tildesley, 2003)
- α/β-thujone inhibit sGABA-A receptor and may cause excitation and convulsions; EO of Salvia sp containing thujone should not be used internally
BERBERINE

- Isoquinoline alkaloid found in the roots of *Mahonia aquifolium*, *Berberis vulgaris*, *Coptis chinensis*
  - Also available as an isolated extract
  - Poor bioavailability, chloride or sulphate salts are relatively more soluble and are used clinically (Fan, 2019)
Berberine

- Potent anti-inflammatory; reduces cytokines TNF-α, COX-2, and IL-1β (Shal, 2018)
- Restores levels of CREB and BDNF (Shal, 2018)
- Protective against ischemic injury; antioxidant effect (Aski, 2017)
- Acts as AChE inhibitor; protective of cholinergic neurons in the hippocampus (Aski, 2017)
- Berberine (6 months) significantly improved cognitive deficits and insulin resistance in naturally aging rats (Yu, 2018)
- Protective effect on depression, anxiety, and stress response (Fan, 2019)
- Generally safe but CI in pregnancy and lactation; GI upset common, avoid combining with macrolide antibiotics. Dose 500mg- 2,000 mg/day
**HERECIUM ERINACEUS**

- Lion’s mane, Houtou mushroom, Yamabushitake
- Fruiting body, mycelium
- Hericenones (in fruiting body) and erinacines (in mycelium) (Li, 2018)
  - Erinacine A-enriched mycelia
- Immune modulator, anti-depressant, hypoglycemic (I-Chen, 2019)
HERECIUM ERINACEUS

• Hericenones (in fruiting body) and erinacines (in mycelium) increase nerve growth factor (NGF) in neurons, influencing neurogenesis and prolonging availability of ACh (Zhang, 2017)

• Oral administration of lion’s mane fruiting body improved mild cognitive impairment in 50- to 80-year-old Japanese patients (Li, 2018)

• Erinacines are neuroprotective
  • Decreased cerebral Aβ plaque burden, prevention of plaque-associated microglia and astrocytes, enhanced nerve growth factor (NGF), and enhanced neurogenesis (Li, 2018)
  • Erinacine A has protective against ischemic injury, Parkinson’s and Alzheimer’s (Chiu, 2018)
  • Two weeks administration with mycelium activated the BDNF pathways and blocked NF-κB signals in mice (Li, 2018)

• Mycelium and fruiting body given for 2 months reversed the age-decline of recognition memory in frail mice (Ratto, 2018)

• Very safe, typical dose is 1g/day, effects seen in 30-60 days
THE HAPPINESS FACTOR

• Exposure to chronic and acute stress adversely affects cognition
  • Depressive symptoms can be a prodrome to Alzheimer’s (Lopresti, 2017)
• Herbs that support mood and overall resilience support healthy cognition
  • Also support people making healthy lifestyle choices such as eating well, regular exercise and meditation
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Optimizing an Aging Brain

- Herbal treatment shows considerable promise in vitro and in vivo, with a wider range of mechanisms than pharmaceuticals.
- Safe and generally well tolerated for long periods of time.
- Treatment 2-8 months+
- Treatments that optimize a healthy lifestyle also support cognition and healthy aging of the whole person.
Thank you!

Katie Stage, ND RH (AHG) • DrKStage@gmail.com


