Exploring the effects of herbal extracts on cognition in older adults

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www.sibeliusnaturalproducts.com
Sibelius Natural Products

- Sibelius Limited is a spin-out from Oxford University
  - Based on ageing and epigenetics research at Oxford and MIT
- Our mission is to increase people’s healthspan and well-being by supporting the development of natural products
- We utilise assays to help identify, characterise, and optimise innovative natural products
Healthy ageing

- Human lifespan is increasing
  - Almost 2 years increase per decade
- Age is a major risk factor in many human diseases and conditions
  - From cancer, through to sarcopenia and dementia
- Healthspan has not increased at the same rate
  - Slow increase in average age of onset for age related conditions
Cellular ageing

- Cellular ageing is a complex process involving multiple mechanisms
- The process is marked by defined changes to the genome, epigenome, and cellular physiology

(Horvath, 2013)
Cellular ageing

- The pathways influencing ageing and age-related conditions are highly-conserved across species
- Treatments that target these pathways increase lifespan across many species
  - e.g. Calorie restriction, Rapamycin...
- Our lifestyle impacts the ageing program
  - The environment, stresses, the food we eat and when we eat it
- Positive interventions therefore provide potential to delay the onset of age-related conditions
Chronoscreen™: The heart of Sibelius

- Chronoscreen™ is Sibelius’ platform to identify and characterise natural products that impact the ageing process.
- We take advantage of conservation of ageing pathways across species to use the model organism *C. elegans* (roundworm).
- Many benefits to using *C. elegans* as a model:
  - Strong conservation with humans (orthologs for 40-80% human genes present in *C. elegans* genome).
  - Small size, short generation time, and defined life-cycle.
  - Whole organism readout integrates on- and off-target effects.
Lifespan: A measuring-stick for biological activity across age-related conditions
Lifespan: A measuring-stick for biological activity across age-related conditions

- Sibelius’ premise: Treatments that extend lifespan on Chronoscreen™ have beneficial effects on age-related diseases
  - Indicates systematic resetting of cellular health controls
- Treatments for age-related diseases should extend lifespan on Chronoscreen™
Cognition

Neurodegeneration

“In terms of health issues consumers care about maintaining mental sharpness with age was the number one health concern globally in 2016”

Health Focus International
March 2017
Cognitive decline with age

- Crystallised intelligence is maintained or even improves with age
  - Skills, abilities, knowledge
  - Well practiced and familiar

- Fluid intelligence declines with age
  - Problem solving, memorising and processing information
  - Stronger decline in complex tasks – divided attention
Physiological differences

- Volume of brain declines with age
- Hippocampus size correlates with memory and cognitive performance
  - Size reduced by AD, diabetes, obesity, depression, sleep apnia...
- Reduction in grey matter not due to reduced number neurons
  - Only ~10% reduction in number, but structure and connectivity change
  - Dendrites and axons shrink, fewer synapses
Dementia

- Research suggests symptoms of dementia appear when 40% lower number of synapses than normal adult (Terry et al. 1991)

- Diseases such as Alzheimer’s can accelerate this process and lifestyle factors can delay it

![Graph showing synaptic density over age for normal adult, Alzheimer's Disease, Positive interventions, and Dementia Threshold.](Adapted from Murman 2015, based on data from Terry & Katzman 2001)
Improved cognitive ageing

- Lifestyle factors associated with improved cognitive ageing
  - Intellectually engaging activities
    - Education, puzzles, reading...
  - Physical activity
    - Cardiovascular exercise, gardening...
  - Social interaction
    - Friends and family, travel...
  - Diet
    - Healthy balanced diet
Improved cognitive ageing

- Herbal extracts have been applied to support cognition by different traditional medicines
  - Ayurvedic, TCM, European...
- Show acute and chronic benefits
- Plants also provide the basis for treatments of AD
  - Galantamine from *Galanthus nivalis* (Snow drop) or *Narcissus pseudonarcissus* (Daffodil)
  - Anti Cholinesterase activity
Herbal treatments for cognition

<table>
<thead>
<tr>
<th><strong>Bacopa monnieri (Brahmi)</strong></th>
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<tbody>
<tr>
<td>• Ayurvedic herb – memory enhancer</td>
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<tr>
<td>• Bacosides (saponins) have pro-Cholinergic &amp; anti-oxidant effects</td>
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<td>• Improves mitochondrial function</td>
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<td>• Evidence for chronic rather than acute effects</td>
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<tr>
<th><strong>Salvia (Sage)</strong></th>
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<tr>
<td>• Ancient Greek and Ayurvedic application in cognition</td>
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<tr>
<td>• Anti-oxidant, anti-inflammatory and anti-AChE activity</td>
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<td>• Improvements to memory</td>
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<tr>
<th><strong>Ginkgo biloba (Ginkgo)</strong></th>
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<tr>
<td>• Used in TCM for multiple conditions</td>
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<tr>
<td>• Marketed as memory enhancer and slowing progression of neurodegeneration</td>
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<tr>
<td>• Activity from Ginkolides and Bilobalides (terpenoids) and flavanoids</td>
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<td>• Free-radical scavenging, inhibition of PAF, pro-Cholinergic effects</td>
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<tr>
<th><strong>Panax species (Ginseng)</strong></th>
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<tr>
<td>• Traditionally used in TCM to provide energy</td>
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<tr>
<td>• Activity from Ginsenosoids (saponins)</td>
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<tr>
<td>• Stimulate choline acetyltransferase and ACh release</td>
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<td>• Memory and attention benefits, particularly for more demanding tasks</td>
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Sibelius: Sage

- Sibelius has a pipeline to support the development and manufacture of a portfolio of innovative natural products
- Our first product, Sibelius Sage, is backed by clinical evidence showing improved cognitive performance in older adults
Sibelius: Sage and cognition

Effects of a standardized extract of **Sibelius: Sage** (*S. Officinalis*) on cognitive factors derived from Cognitive Drug Research computerized assessment battery. Mean change from baseline scores are shown for (a) secondary memory and (b) accuracy of attention. Asterisks signal significant effects compared to placebo score (* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$; **** $P < 0.0005$).

(Adapted from Scholey et al., 2008)
Summary

- Declines with cognitive performance with age associated with physiological changes
- Pathways of ageing are well conserved across species
- Treatments, including herbal extracts, can beneficially effect cellular ageing in biological systems
  - This includes cognitive ageing
- Herbal extracts show acute benefits to cognition
  - Mechanisms such as AChE inhibition
- As well as benefits from chronic treatment
  - Potentially related to anti-inflammatory, anti-oxidant effects
  - Synergistic benefits of complex mixture in herbal extracts
Why Sibelius?

- Sibelius is a science-led company built out of research on ageing and epigenetics from Oxford University and MIT
- Chronoscreen™ is a first-in-class platform that enables us to optimise development of efficacious natural products
  - A single platform for effects across a range of age-related (health span) conditions
- It is fundamental to our internal product development efforts
  - Sibelius: Sage and Sibelius: Sage for seniors
  - Sibelius: Chamomile
- Chronoscreen™ can support our partners product development efforts too
A Nutraceutical Platform Technology for Health

THANK YOU

Sibelius

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