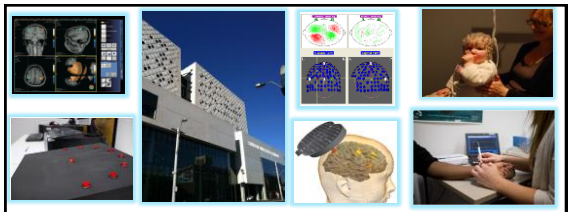

Cognitive enhancers

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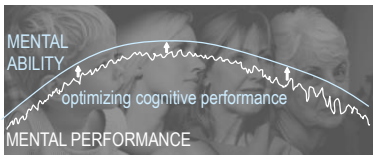
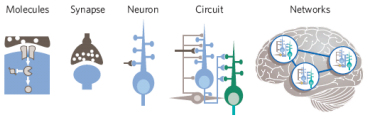
www.humanpsych.com

GP EDUCATION DAY 2015

Optimal mental performance

Swinburne Centre for Human Psychopharmacology



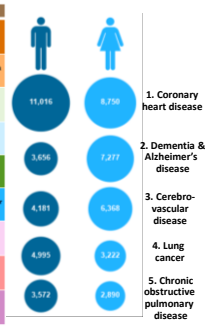


PLANT EXTRACTS
- *Ginkgo biloba*
- *Panax ginseng**
- *Ginseng quinquefolius**
- *Ginkgo-ginseng combination*
- *Melissa officinalis**
- *Salvia officinalis**
- *Salvia lavandulaefolia**
- *Valerian*
- *Guaraná**
- *Ginkgo-phosphatidylserine**
- Cocoa polyphenols*
- *Bacopa monnieri**
- Pycnogenol*
- Enzogenol*
- EGCG
- Soy isoflavones
- Curcumin*

OTHERS
- oxygen*
- glucose
- aromatherapy oils
- caffeine
- theanine
- water
- chewing gum*
- alcohol [low dose]
- DHA
- multivitamins
- MedDi

Australian Institute of Health and Welfare
Leading underlying causes of 147,678 deaths in 2013 (released 20.10.15)

	1st	2nd	3rd	4th	5th
Age < 1	Other: Perinatal & congenital	Other: SIDS	Other: Ill-defined causes	External: Accidental threats to breathing	Other: Selected metabolic disorders
Age 1–14	External: Land transport accidents	Other: Perinatal & congenital	Cancer: Brain cancer	External: Accidental poisoning	Other: Cerebral palsy & related
Age 15–24	External: Suicide	External: Land transport accidents	External: Accidental poisoning	External: Assault	External: Event of undetermined intent
Age 25–44	External: Suicide	External: Accidental poisoning	External: Land transport accidents	Circulatory: Coronary heart disease	Cancer: Breast cancer
Age 45–64	Circulatory: Coronary heart disease	Cancer: Lung cancer	Cancer: Breast cancer	Cancer: Colorectal cancer	External: Suicide
Age 65–74	Circulatory: Coronary heart disease	Cancer: Lung cancer	Respiratory: COPD	Circulatory: Cerebrovascular disease	Cancer: Colorectal cancer
Age 75–84	Circulatory: Coronary heart disease	Circulatory: Cerebrovascular disease	Other: Dementia & Alzheimer disease	Cancer: Lung cancer	Respiratory: COPD
Age 85–94	Circulatory: Coronary heart disease	Other: Dementia & Alzheimer disease	Circulatory: Cerebrovascular disease	Respiratory: COPD	Circulatory: Heart failure
Age 95+	Circulatory: Coronary heart disease	Other: Dementia & Alzheimer disease	Circulatory: Cerebrovascular disease	Circulatory: Heart failure	Respiratory: Influenza & pneumonia



1. Coronary heart disease
2. Dementia & Alzheimer's disease
3. Cerebro-vascular disease
4. Lung cancer
5. Chronic obstructive pulmonary disease

Alzheimer's Disease: Progression

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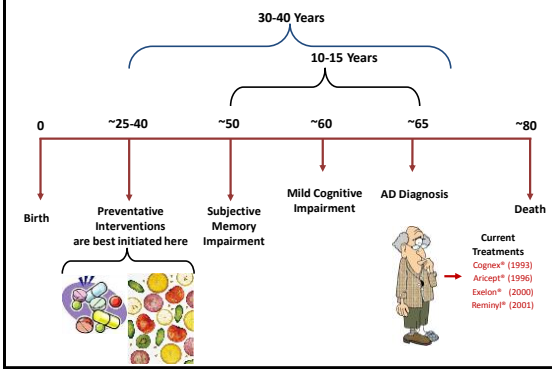

SMI/SCI: 3-yr longitudinal cohort study of 2415 healthy older adults aged 75+

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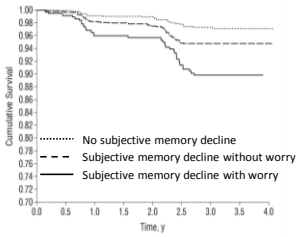
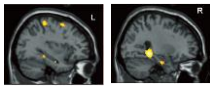
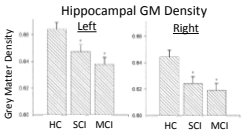


(Jessen et al, 2010, Arch Gen Psych)

Regions showing more grey matter atrophy in the MCI and SCI groups compared to the healthy control group.





(Saykin et al., 2006, Neurology)

SCI may be early, subtle, neurocognitive dysfunction amenable to intervention
focus of Cognitive Ageing, Nutrition and Neurogenesis (CANN) trial

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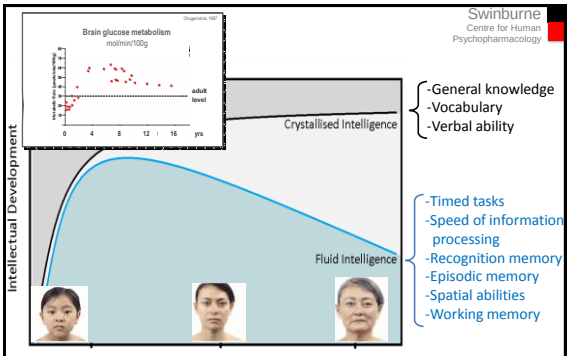
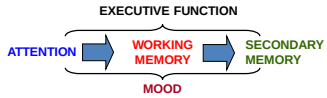


A simple model of cognition

Swinburne Centre for Human Psychopharmacology



ATTENTION
- Simple Reaction Time
- Choice Reaction Time
- Four Choice Reaction Time
- Stroop Task

WORKING MEMORY
- Numeric Working Memory
- Alphabetic Working Memory
- N-back
- Corsi Blocks

SECONDARY MEMORY
- Word Recognition
- Face Recognition
- Picture Recognition

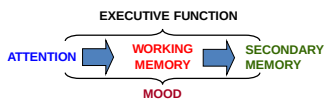
EXECUTIVE FUNCTION
- Serial 3 Subtraction
- Serial 7 Subtraction
- RVIP

MOOD
- Visual Analogue scales
- Emotional stroop
- others

digit span

backward

Translation to everyday cognition



ATTENTION
- concentration
- staying 'on task'
- distractibility

WORKING MEMORY
- remembering a new pin/room number
- walking into a room and forgetting why
- starting to dial a number

SECONDARY MEMORY
- names-to-faces
- birthdays
- information
- where car is parked
- "tip-of-the-tongue" effect

EXECUTIVE FUNCTION
- multi-tasking
- planning
- inhibition of inappropriate responses

Aging and neurocognitive Decline

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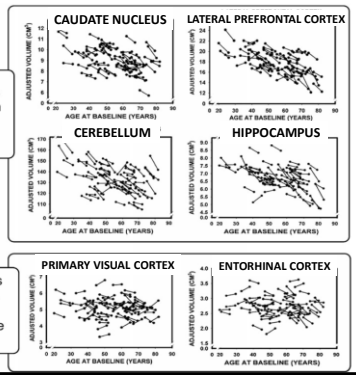
Brain regions that reduce in volume with age.

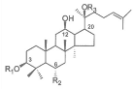
Brain regions with minimal reduction or stable volume with age.



Panax ginseng (Asian ginseng)

Swinburne Centre for Human Psychopharmacology

- Used in Chinese medicine for several millennia as a tonic, restorative and prophylactic agent
- Considered a treatment for the whole body because of it's human torso shaped root
- 325-year-old wild harvested plant was sold in August 2012 for US$1.57 million
- Amongst the most widely taken herbal supplement throughout the world – alleviation of fatigue/'pick me up'
- Active components are ginsenosides
  - promotes Yang energy (TCM)
  - anti-fatigue
  - improves circulation
  - increases blood supply
  - revitalises and aids recovery from weakness
  - stimulates the body
- Extract G115 standardised to 4%



EEG confirms central bioactivity

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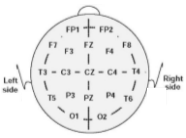

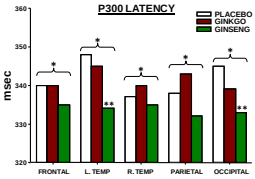

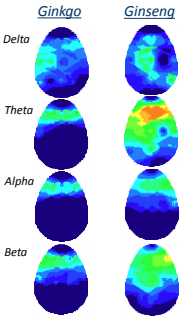

Kennedy, Scholey et al (2003) *Pharmacol, Biochem, Behav* 75, 701-709

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Special Article

NUTRITION REVIEWS

Effects and mechanisms of ginseng and ginsenosides on cognition

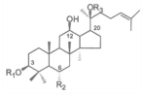
Imogen Smith, Elizabeth M Williamson, Sophie Putnam, Jonathan Farrimond, and Benjamin J Whalley

Table 1 **The major ginsenosides from *P. ginseng* and *P. quinquefolius* extracts, along with their effects on the CNS.**

Compound	Occurrence[a]	CNS effects reported in published studies	No. of hits (no. remaining after filtering for CNS relevance)
Rb_1	*P. ginseng* ++ *P. quinquefolius* ++++	Neuroprotective; improved spatial memory and reduced memory impairment in animal models; neurotrophic[79,80,98,133–138]	529 (94)
Rb_2	*P. ginseng* + *P. quinquefolius* (tr)	Anticholinergic activity	62 (8)
Rb_3			3 (9)
Rc			9 (14)
Rd			7 (32)
Re			(28)
Rf			(12)
Rg_1			(120)
Rg_2			
F11			22 (4)
Ro			45 (2)

Abbreviations: CNS, central nervous system.
[a] Occurence stratified according to relative abundance in *P. quinquefolius* and *P. ginseng*.[7]

Positive effects on:
NO signalling,
Anti-oxidant activity,
ACh activity,
NMDA-glutamate, GABA, 5-HT receptors
Intracellular signalling pathways
(esp. Rb1)



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Ginseng for cognition (Review)

Geng J, Dong J, Ni H, Lee MS, Wu T, Jiang K, Wang G, Zhou AL, Malouf R

THE COCHRANE COLLABORATION®

double-blind and single-blind randomized, placebo-controlled trials assessing the effects of ginseng on cognitive function. Five trials investigating the effects of ginseng on healthy participants had extractable information for efficacy and were included in the review. Ginseng appeared to have some beneficial effects on cognition, behavior and quality of life. More rigorously designed studies are needed on this important issue.

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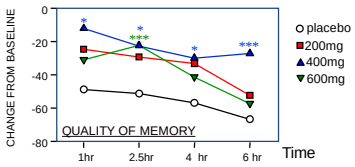
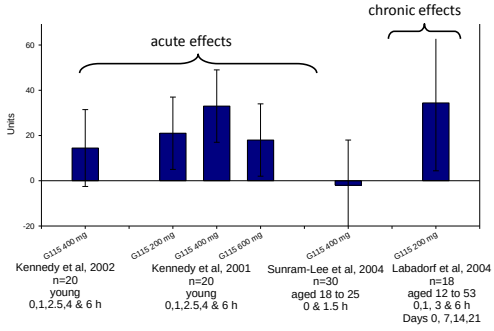
Panax (Asian) *ginseng:* cognitive effects



Kennedy DO, Scholey AB & Wesnes KA (2001) *Nutritional Neuroscience* **4**, 295-310.

EFFECTS OF GINSENG (GINSANA/ G115) ON QUALITY OF MEMORY

Scores expressed as mean improvements over placebo with 95% Confidence Intervals



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Effects of Gincosan (ginkgo/ginseng combination): multicentre trial

Randomised
Double-blind
Placebo-controlled
Parallel group
320 mg Gincosan (120 GK501; 200 G115)
14 week repeated assessment trial
in 256 normal middle aged (40-65) volunteers

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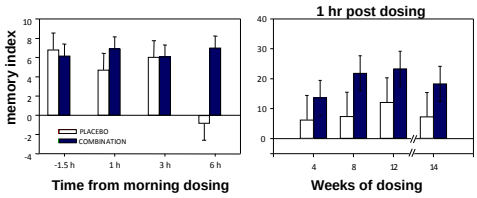
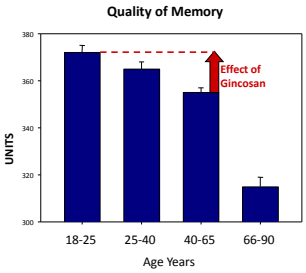
Gincosan (Ginkgo-Ginseng combination): results of multicentre trial

Effects of combination on 'quality of memory' factor



Data from CDR database of over 6000 normal individuals aged 18-87– show ability of Gingko/Ginseng combination to reverse effects of normal ageing



- Data on left indicate the decline due to normal ageing.
- The study population in Wesnes et al (2000) were aged 40-65 years
- Peak improvement averaged over the 14 weeks of the study was 19 units (average was 7.5%)
- This would have counteracted the decline due to normal ageing between 18-25 and 40-65

Ginseng: possible recommendations

Swinburne Centre for Human Psychopharmacology

- *ginseng* could be an appropriate recommendation for a young adult needing mental boost
- *gincosan* (Ginkgo—ginseng combination) could be suitable for a middle-aged person worried about their memory

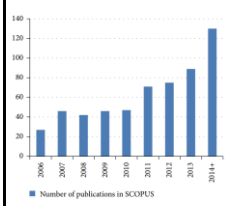
Bacopa

Swinburne Centre for Human Psychopharmacology

- Use has been documented for 3000 years
  - inflammation
  - pain
  - pyrexia
  - epilepsy
  - memory
  - attention behaviour in children
- Chemical investigation of bacopa first published in 1944 by CDRI
- Standardised extract of bacopa launched by Indian Prime Minister in 1996 after 50 years of research
- Bacosides thought to be the most important constituent

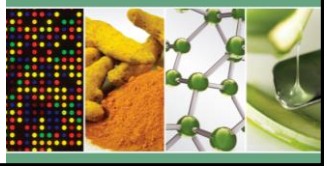
2015 SPECIAL ISSUE

eCAM Evidence-Based Complementary and Alternative Medicine



Mechanisms, Efficacy, and Safety of *Bacopa monnieri* (Brahmi) for Cognitive and Brain Enhancement

Guest Editors: Con Stough, Hemant Singh, and Andrea Zangara



Author/ Year	Dosage	n	Sample	Trial Design	Outcome Measures	Results	Effect Size	Q /10
Stough et al. (2001)	KM 300mg daily BC: min 55%	46 23(B) 23(P)	18-60 yrs	12-week DB, PC	Full cognitive testing battery inc: IT, AVLT, reaction time, digit span	BM significantly improved Speed of visual information processing (IT), learning rate and memory consolidation on AVLT	VP & A[2]: 0.25 L & M[2]: 0.27 L & M[2]: 0.52 L & M[2]: 1.01	8
Nathan et al. (2001)	KM 300mg single dose BC: min 55%	38 18 (B) 20 (P)	18-60 years	0 and 2 hours DB, PC	No effect on any measure	No acute effects of BM on a battery measures		8
Roodenrys et al. (2002)	KM 300mg (ppts < 90kg) 400mg (ppts 90kg+) BC:55%	76 37 (B) 39 (P)	40 – 65 years	0 and 3 months DB, PC	Cognitive testing battery including story recall, w pair	Positiv	23	6
Raghav et al. (2006)	CDRI 250mg daily BC: min 55%	40 20 (B) 20 (P)	55+ years Parti			d associate	WM & EF: 0.83 L & M[2]: 1.56 L & M[2]: 0.12	7
Stough et al. (2008)	KM 300					ant Working Memory[a] and RVIP improvements[a]	WM & EF[2]: 0.47 VP & A[2] 0.30	9
Calabrese et al. (2008)					VLT, Stroop, DAT, WAIS letter digit test	Significant AVLT[a] and Stroop[a] improvements.	L & M[2]: 0.36 WM & EF[2]: 0.32	9
Barbhaiya et al. (2008)	BC: A[1] > 50 g/w	21 (P)	years MMSE 24+	0, 12 and 24 weeks DB, PC Treatment 0 – 12 wks	Cognitive testing battery @12 weeks treatment and 24 week follow up.	Significant improvements in digit cancellation and visual retention @12 week. Comparisons not between treatment groups but change from baseline in each group	N/A	9
Morgan & Stevens (2010)	BM 300mg daily BC: 40 – 50%	81 36 (B) 45 (P)	55+ years	0 and 12 weeks DB, PC	Multiple cognitive measures: AVLT, CFT, TMT, MAC-Q	Significant improvements on verbal learning, memory acquisition and delayed recall AVLT measures No significant differences on CFT, TMT or MAC-Q	L & M[2]: 0.95 L & M[2]: 0.53 L & M[2]: 0.57	10

robust improvement in speed of processing and memory

e.g. Stough et al (2001, 2008)

90 days Keenmind™ Bacopa extract

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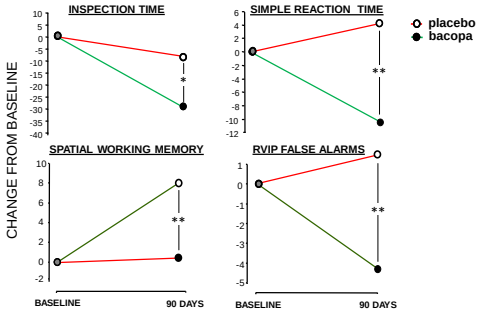

CONFIRMED IN RECENT NEUROIMAGING TRIAL

Bacopa: possible recommendations

Swinburne Centre for Human Psychopharmacology

- Bacopa could be suitable for middle-aged individuals worried about their memory
- There is also some evidence of anxiolytic effects

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CURCUMIN

Curcumin publications 1985-2014

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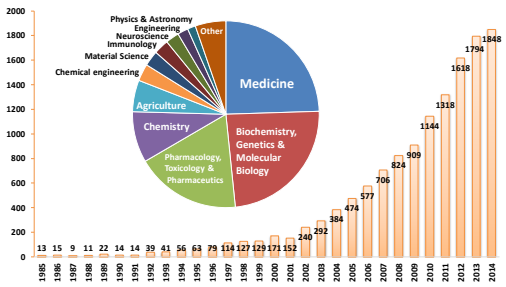

Curry consumption and cognitive function in the elderly
N = 1010 60-93 yr-olds

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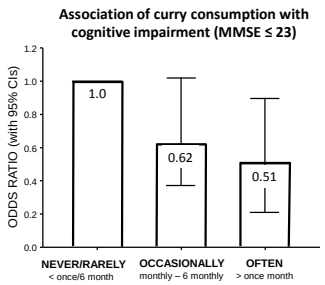

Adjusted for **age, gender, ethnicity, educational levels, instrumental activities of daily living/basic activities of daily living dependence (hierarchical levels), social activities (three levels), productive activities (three levels), fitness activities (three levels), visual impairment, hearing impairment, hypertension, dyslipidemia, coronary artery disease, congestive heart failure, diabetes, stroke, asthma, chronic obstructive pulmonary disease, depression, frequency of nonsteroidal anti-inflammatory drug use, frequency of steroid use, alcohol consumption, smoking**

Plotted using data from Ng et al (2006) *Am J Epidemiol* **164**, 898-906

Original Paper

Investigation of the effects of solid lipid curcumin on cognition and mood in a healthy older population

Katherine HM Cox, Andrew Pipingas and Andrew B Scholey

Psychopharm

- Polyphenol found in turmeric (gives its bright yellow colour)
- Used as ingredient in food (e.g. curry) also as a food preservative and natural colour (E100)
- Used as a traditional medicines to treat wide variety of conditions
- Modern medicine benefits published since the 1930s
- Some evidence that more curry => less cognitive decline
- our study 28 day intervention with Longvida™ in 60-85 yr-olds

Why are we interested in curcumin?

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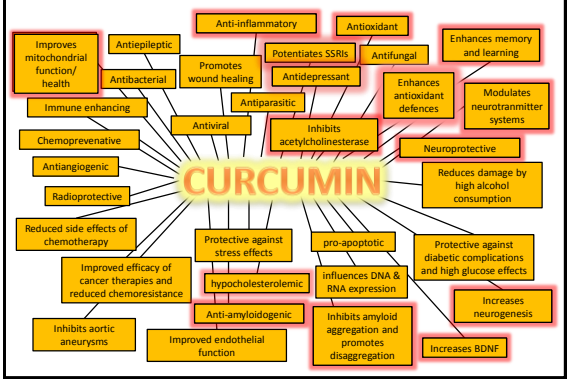
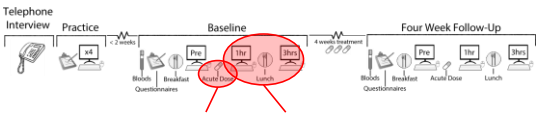
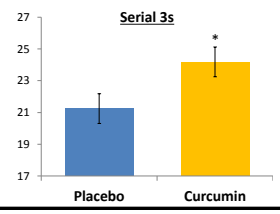
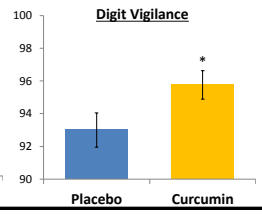


Acute Effects = Single Dose



Single-dose Assessments at 1 h and 3 h after 1st dose





Chronic Effects = 4 Weeks Treatment

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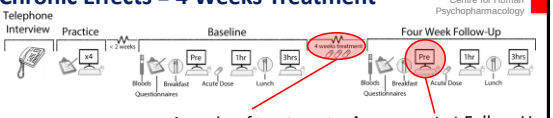
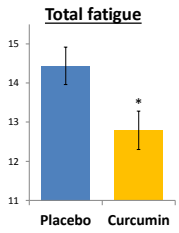
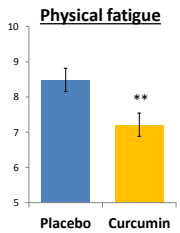
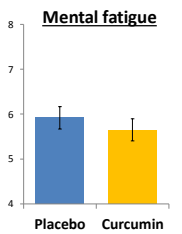
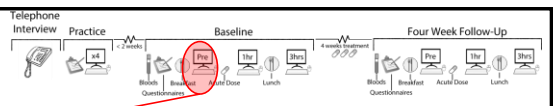


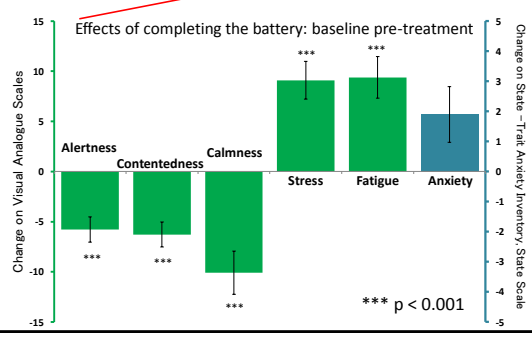
4 weeks of treatment Assessment at Follow-Up



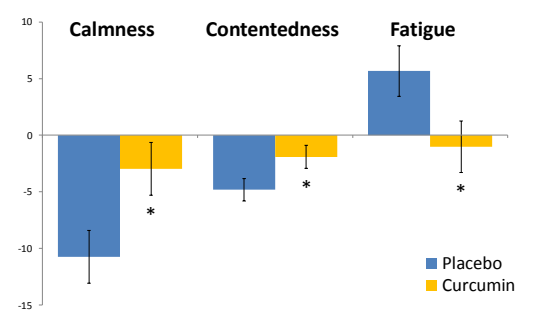








Chronic Effects: State Mood during cognitive battery



* p < 0.05 , Controlling for Baseline, pre-dose change

Chronic Effects: Biomarkers

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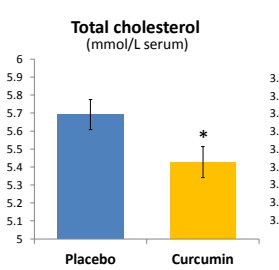

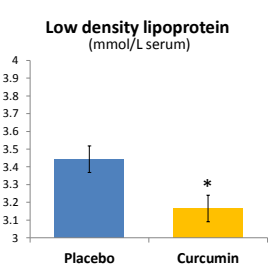

* *p* <0.05 , Controlling for pre-dose performance

Curcumin: possible recommendations

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Acute (one dose):

- Could be suitable for older people needing an acute 'lift'

Chronic (4 weeks):

- Could be suitable for older people
  - suffering from fatigue/ worried about energy levels
  - needing 'buffering' against workload stress
- Note
  - also reduced total cholesterol and LDL
  - reduced inflammatory markers
- Also anecdotal evidence from participants!

How do natural ingredients measure up to pharma?

BJCP British Journal of Clinical Pharmacology

Modafinil: largest effect size (d): (visuospatial working memory) = 0.77

Ginseng: largest effect sizes (d):
cognitive (reaction time) = 0.86
mood (mental fatigue) = 1.40

Bacopa: largest effect size (d):
(delayed word recall) = 0.95

Editorial

Current Drug Abuse Reviews, 2012, Vol. 5, No. 4 255

Editorial

Cognitive Enhancement: Are we Barking Up the Wrong Tree?

Andrew Scholey[1], Con Stough[1] and Joris C. Verster*[1,2,3]

[1]Centre for Human Psychopharmacology, Swinburne University, Melbourne VIC 3122, Australia
[2]Utrecht Institute for Pharmaceutical Sciences, Division of Pharmacology, Utrecht University, Utrecht, The Netherlands

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mechanisms?

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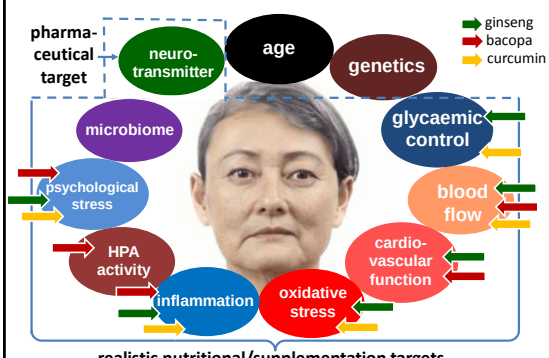
components of cognitive aging



realistic nutritional/supplementation targets

Ginkgo biloba

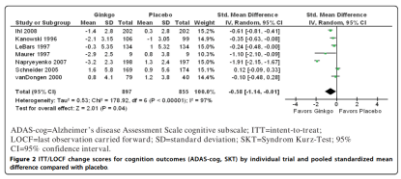
- **Most research on extract Egb761**
- evidence for EGB 761 and Alzheimer's Dementia?
- Recent systematic review identified 9 double blind randomized controlled clinical trials in Alzheimer's patients
- 8 of these found a statistically significant superiority of EGb 761 to placebo

Effects of Ginkgo biloba in dementia: systematic review and meta-analysis

BMC Geriatrics

Swinburne Centre for Human Psychopharmacology

Stefan Weinmann[1*], Stephanie Roll[1], Christoph Schwarzbach[2], Christoph Vauth[2], Stefan N Willich[1]



Study or Subgroup	Ginkgo Mean	Ginkgo SD	Ginkgo Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
Ihl 2008	-1.4	2.8	202	0.3	2.8	202	15.2%	-0.61 [-0.81, -0.41]
Kanowski 1996	-2.1	3.15	166	-1	3.05	89	14.9%	-0.35 [-0.63, -0.08]
LeBars 1997	-0.3	5.35	134	1	5.32	134	15.0%	-0.24 [-0.48, -0.00]
Maurer 1997	-2.9	2.5	9	0.8	3.8	9	10.3%	-1.10 [-2.10, -0.09]
Napryeyenko 2007	-3.2	2.3	198	1.3	2.4	197	15.0%	-1.91 [-2.15, -1.67]
Schneider 2005	1.6	5.8	169	0.9	5.6	174	15.1%	0.12 [-0.09, 0.33]
vanDongen 2000	0.8	4.1	79	1.2	3.8	40	14.4%	-0.10 [-0.48, 0.28]
Total (95% CI)			897			855	100.0%	-0.38 [-0.14, -0.61]

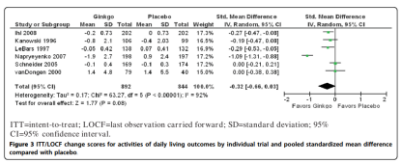
Heterogeneity: Tau² = 0.53; Chi² = 178.92, df = 6 (P < 0.00001); I² = 97%
Test for overall effect: Z = 2.01 (P = 0.04)

Favors Ginkgo — Favors Placebo

ADAS-cog=Alzheimer's disease Assessment Scale cognitive subscale; ITT=intent-to-treat; LOCF=last observation carried forward; SD=standard deviation; SKT=Syndrom Kurz-Test; 95% CI=95% confidence interval.

Figure 2 ITT/LOCF change scores for cognition outcomes (ADAS-cog, SKT) by individual trial and pooled standardized mean difference compared with placebo

cognitive benefit



Study or Subgroup	Ginkgo Mean	Ginkgo SD	Ginkgo Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
Ihl 2008	-0.2	0.73	202	0	0.73	202	17.3%	-0.27 [-0.47, -0.08]
Kanowski 1996	-0.8	2.1	166	-0.4	2.03	89	16.5%	-0.19 [-0.47, 0.08]
LeBars 1997	-0.05	6.42	138	0.07	6.41	132	16.9%	-0.20 [-0.51, 0.05]
Napryeyenko 2007	-1.9	2.7	198	0.9	2.4	197	17.2%	-1.09 [-1.31, -0.88]
Schneider 2005	-0.1	5.4	169	-0.1	6.3	174	17.2%	0.00 [-0.21, 0.21]
vanDongen 2000	1.4	4.8	79	1.4	6.5	40	15.0%	0.00 [-0.38, 0.38]
Total (95% CI)			892			844	100.0%	-0.32 [-0.66, 0.03]

Heterogeneity: Tau² = 0.17; Chi² = 63.27, df = 5 (P < 0.00001); I² = 92%
Test for overall effect: Z = 1.77 (P = 0.08)

Favors Ginkgo — Favors Placebo

ITT=intent-to-treat; LOCF=last observation carried forward; SD=standard deviation; 95% CI=95% confidence interval.

Figure 3 ITT/LOCF change scores for activities of daily living outcomes by individual trial and pooled standardized mean difference compared with placebo

Activities of Daily Living benefit

Amieva et al (2013) *PLoS One*

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- 3612 non-demented patients
- EGB761 (589), Piracetam (149), neither (2874)
- 20 year duration
- MMSE scores for cognitive decline
- Less decline in EGB761 group than other groups

- 240mg a day may be good for patients with AD
- Not protective

Other evidence-based interventions for mood and cognition

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- B-vitamins/broad spectrum micronutrients for mood, energy, (cognition) in adults (all ages) and children aged 8-12.
- Fish oil for inattention/hyperactivity problems in children e.g.
  - 3-4 caps Lyprinol green lipped mussel extract (Kean, Stough)
  - 650 mg each DHA, EPA Omega-3 (Bos et al., 2015)

Take home messages

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- Not all herbal medicines are equivalent
- Not all have been researched
- Use high quality herbals which have been subjected to research
- Sadly, price and quality are usually correlated

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