

Approccio nutraceutico alla gestione del declino cognitivo iniziale

Arrigo F.G. Cicero, MD, PhD Medical and Surgical Sciences Dept. Alma Mater Studiorum University of Bologna

ALMA MATER STUDIORUM – UNIVERSITA DI BOLOGNA



Contents lists available at ScienceDirect

Maturitas

journal homepage: www.elsevier.com/locate/maturitas



Review article

Mild cognitive decline. A position statement of the Cognitive Decline Group of the European Innovation Partnership for Active and Healthy Ageing (EIPAHA)

- Prevalence: 5.5-7.7% over 60 years, 22% over 70
- Evolution to dementia 10%/year (strongly variable data)
- Reversibility each year: till 45% of cases !!!

Maturitas. 2016 Jan;83:83-93

ALMA MATER STUDIORUM ~ UNIVERSITÀ DI BOLOGNA



Contents lists available at ScienceDirect

Maturitas

journal homepage: www.elsevier.com/locate/maturitas



Review article

Mild cognitive decline. A position statement of the Cognitive Decline Group of the European Innovation Partnership for Active and Healthy Ageing (EIPAHA)

RISK FACTORS

- Age
- АроЕ
- Behavioural: Smoking, Sedentariety, Alcoholic abuse, Wrong dietary habits
- Cardiovascular: Diabetes, Hypertension, Dyslipidemia, Obesity, Arrhytmia
- Psychosocial: Low educational, Isolation, Depression
 Maturitas. 2016 Jan;83:83-93

ALMA MATER STUDIORUM - UNIVERSITÀ DI BOLOGNA



A time-less war...

Epidemiology RCTs

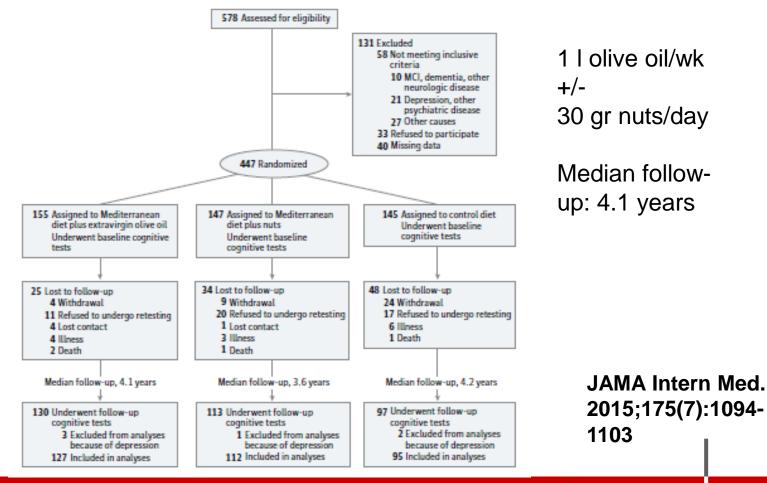
- Dietary approach

- Single nutraceutical approach
- Combined nutraceutical approach

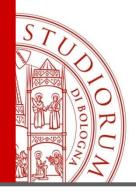
ALMA MATER STUDIORUM - UNIVERSITÀ DI BOLOGNA



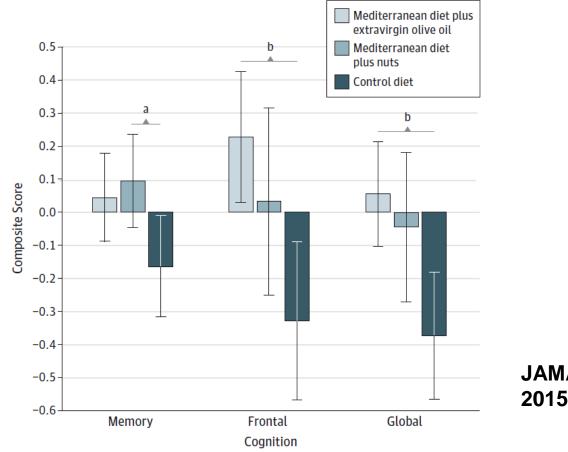
Mediterranean Diet and Age-Related Cognitive Decline A Randomized Clinical Trial



ALMA MATER STUDIORUM - UNIVERSITÀ DI BOLOGNA



Mediterranean Diet and Age-Related Cognitive Decline A Randomized Clinical Trial



JAMA Intern Med. 2015;175(7):1094-103

ALMA MATER STUDIORUM ~ UNIVERSITÀ DI BOLOGNA

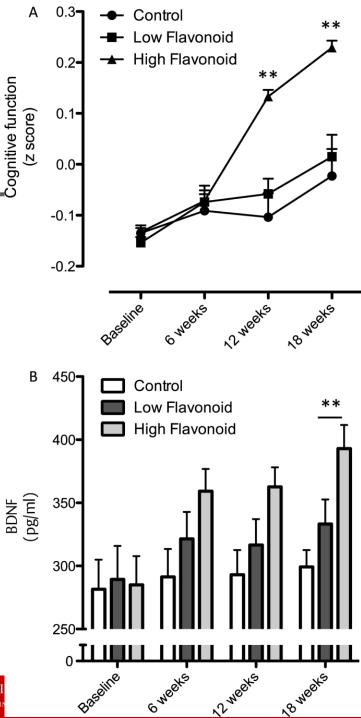


Influence of fruit and vegetable (flavonoid) intake on cognition and serum brain-derived neurotrophic factor

Nutr Healthy Aging. 2016; 4(1): 81–93.

ALMA MATER STUD

IL PRESENTE MATERIALE È RISERVATO AL PERSONALE DELL'UNIVERSITÀ DI BOLOGNA E NON PUÒ ESSERE UTILIZZATO AI TERMIN





Association between tea intake and the cognitive disorders based on ethnicity

PLoS One. 2016; <u>11(11): e0165861.</u>

	Study		%
	ID	OR (95% CI)	Weight
	1 Chinese	i	
	Chen (2012)	0.82 (0.68, 1.00)	4.93
	Cheng (2014)	0.84 (0.73, 0.98)	5.38
	Ding (2012)	➡ 0.52 (0.44, 0.62)	5.78
	Guo (2011)	0.69 (0.38, 1.24)	2.10
	Huang (2009)	• 0.46 (0.33, 0.62)	5.11
	Lian (2013)	0.73 (0.47, 1.13)	2.89
	Luo (2015)	0.53 (0.41, 0.69)	5.19
	Ng (2008)	• 0.37 (0.29, 0.48)	5.73
	Pan (2012)	0.75 (0.59, 0.95)	4.68
	Shen (2015)	◆ 0.68 (0.62, 0.75)	6.02
	Song (2007)	↔ 0.68 (0.57, 0.80)	5.51
	Sun (2012)	++ 0.78 (0.61, 1.00)	4.47
	Wang (2012)	• <u>1</u> 0.37 (0.20, 0.69)	3.82
	Wang (2014)	0.48 (0.26, 0.89)	3.02
	Wu (2011)	• 0.56 (0.46, 0.69)	5.48
	Xu (2012)		4.46
	Yao (2010)	• 0.57 (0.42, 0.77)	4.68
	Yin (2012)		1.75
	Subtotal (I-squared = 76.4%, p = 0.000)	Q 0.61 (0.54, 0.69)	80.99
	ACTIVITY CONTRACTOR AND A		
	2 European	1	
	Forster (1995)	1.40 (0.81, 1.63)	2.24
	Nurk (2009)	• <u>1</u> 0.33 (0.16, 0.69)	3.58
	Eskelinen (2009)	1.27 (0.84, 1.91)	1.54
	Subtotal (I-squared = 91.3%, p = 0.000)	0.98 (0.21, 1.75)	7.36
	3	i	
	3 Japanese	1	
	Dai (2006)	1.22 (0.94, 1.57)	3.05
	Kuriyama (2006)	0.51 (0.34, 0.76)	4.26
	Noguchi-Shinohara (2014)	0.61 (0.44, 0.85)	4.33
	Subtotal (I-squared = 86.0%, p = 0.001)	0.76 (0.39, 1.13)	11.65
	Overall (I-squared = 79.4%, p = 0.000)	0.65 (0.57, 0.72)	100.00
_	NOTE: Weights are from random effects analysis		
	-1.5 0	I 1.5	
		1.0	

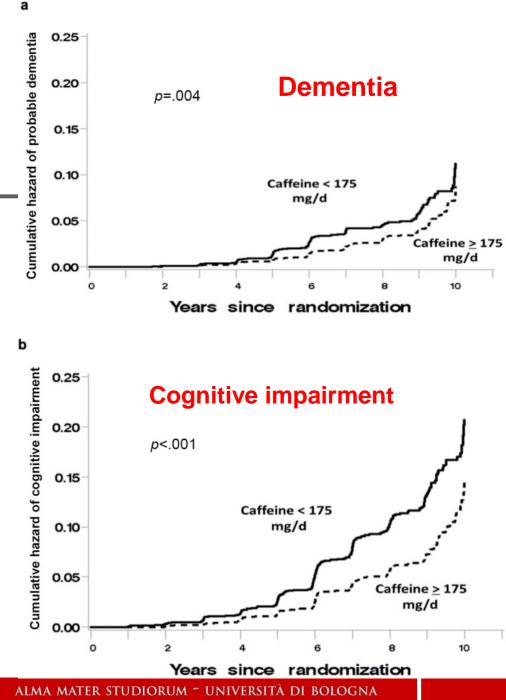
ALMA MATER STUDIORUM ~ UNIVERSITÀ DI BOLOGNA



The Women's Health Initiative Memory Study

Association that baseline selfreported caffeine intake has with the distribution of times until (a) probable dementia and (b) composite cognitive impairment (mild cognitive impairment + dementia).

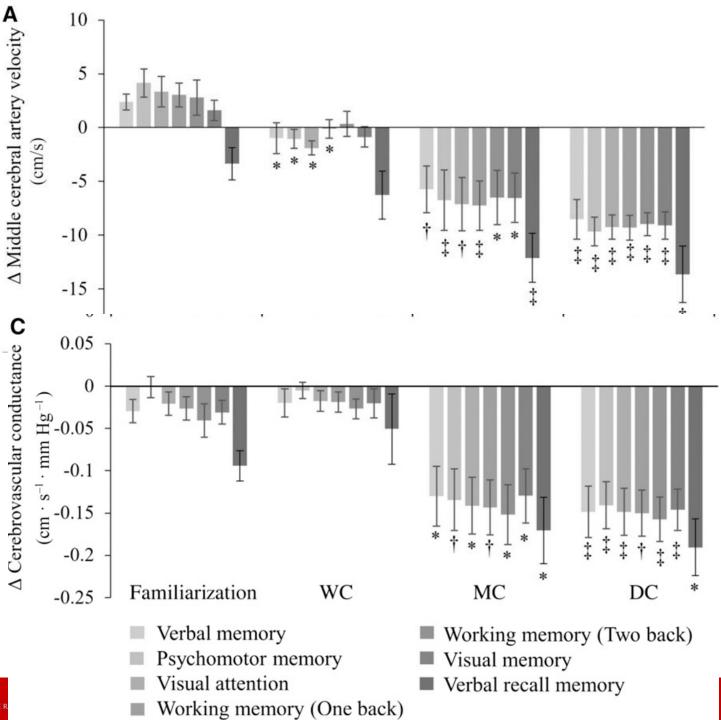
<u>J Gerontol A Biol Sci Med Sci. 2016;</u> 71(12): 1596–1602.

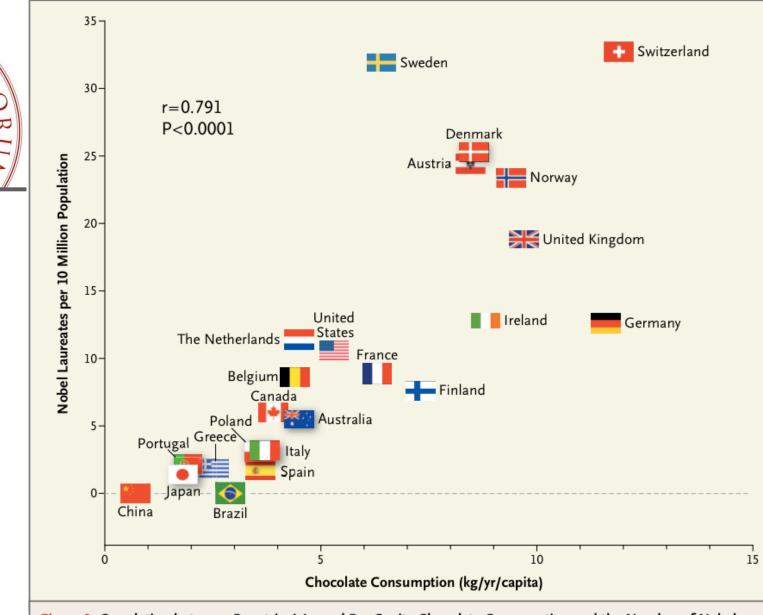




Impacts of chocolate containing different concentrations of cocoa on cerebral blood flow velocity in response to individual cognitive tasks performed by postmenopausal women

J Nutr 2017;147: 1686–92





BOLC

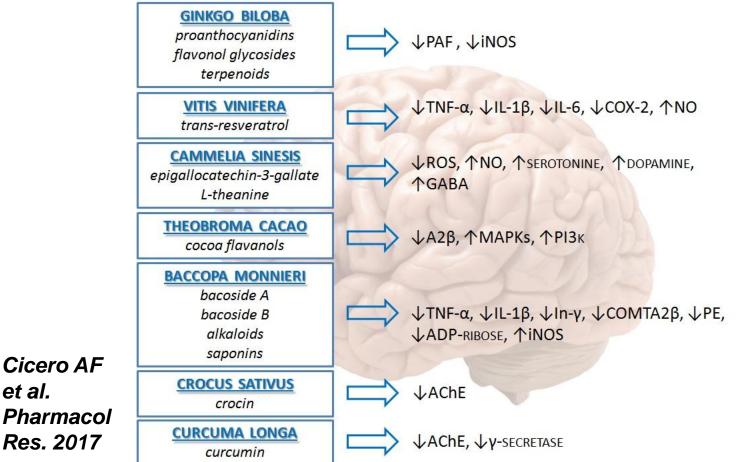
Figure 1. Correlation between Countries' Annual Per Capita Chocolate Consumption and the Number of Nobel Laureates per 10 Million Population.

ALMA MATER STUDIORUM - UNIVERSITÀ DI BOLOGNA

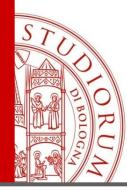


et al.

Botanicals active on cognitive decline



ALMA MATER STUDIORUM ~ UNIVERSITA DI BOLOGNA



Gingko biloba: metanalysis of RCT

- 9 RCTs, 22–26 weeks duration, 2,561 patients.
- EGb761 at 240 mg/day is able to stabilize or slow decline in cognition, function, behavior, and global change at 22–26 weeks in cognitive impairment and dementia, especially for patients with neuropsychiatric symptoms.
- No important safety concerns with EGb761.

J Alzheimers Dis. 2015;43(2):589-603.

ALMA MATER STUDIORUM - UNIVERSITÀ DI BOLOGNA

1.2 Patients with NPS subgroup

	EC	3b761	1	Pla	cebo)		Mean Difference	Mean Difference
Study or Subaroup	Mean	SD	Total	Mean	SD	Total	Weight	IV. Fixed, 95% CI	IV. Fixed, 95% Cl
1.2.1 EGb761 240mg vs. P	lacebo								
Herrschaft et al., 2012	-2.9	4.2	200	-0.4	5.2	202	19.4%	-2.50 [-3.42, -1.58]	-
lhi et al., 2011	-1.8	3.7	202	0.4	3.7	202	31.9%	-2.20 [-2.92, -1.48]	
Napryeyenko et al., 2007	-4.2	3	198	1.7	3.1	197	45.8%	-5.90 [-6.50, -5.30]	
Schneider et al., 2005	0.6	5.8	42	2.8	5.7	47	2.9%	-2.20 [-4.59, 0.19]	
Subtotal (95% CI)			642			648	100.0%	-3.95 [-4.36, -3.55]	•
Heterogeneity: Chi ² = 74.46	6, df = 3	(P < (0.00001	1); 2 = §	6%	74			
Test for overall effect: Z = 1	9.03 (P	< 0.0	0001)						
			4						.
Total (95% CI)			642	2		648	100.0%	-3.95 [-4.36, -3.55]	•
Heterogeneity: Chi ² = 74.46	6, df = 3	(P < (0.00001	1); 17 = 9	6%	×			
Test for overall effect: Z = 1	9.03 (P	< 0.0	0001)	- I					-10 -5 0 5 10 Favours [EGB761] Favours [Placebo]
Test for subgroup difference	es: Not a	applic	able						Pavous [EGB/01] Pavous [Placebo]
			_						

1.3 AD subgroup

	0				
1.3 AD subgroup					
	EGb761	Placebo	Mean Difference	Mean Difference	Score
Study or Subaroup		I Mean SD Tot	al Weight IV. Fixed, 95% CI	IV. Fixed, 95% Cl	
1.3.1 EGb761 240mg vs. P					
lhi et al., 2012	-1.8 3.8 163		0 26.7% -2.20 [-2.99, -1.41]	-	
Kanowski et al., 2003	-3 4.1 79		'9 10.1% -1.70 [-2.98, -0.42]		
Napryeyenko et al., 2009	-3.9 3 104				
Schneider et al., 2005	1.3 5.5 170			A 75	
Subtotal (95% CI)	516		3 71.8% -2.76 [-3.24, -2.28]	•	
Heterogeneity: Chi ² = 72.94					
Test for overall effect: Z = 1	1.29 (P < 0.00001))			
1.3.2 EGb761 160mg vs. P	facebo				
Mazza et al., 2006	-4.3 2.7 25		9.0% -5.60 [-6.95, -4.25]	X	
Subtotal (95% CI)	2	5 2	6 9.0% -5.60 [-6.95, -4.25]	•	
Heterogeneity: Not applicab	e e				
Test for overall effect: Z = 8	.10 (P < 0.00001)				
1.3.3 EGb761 120mg vs. P	facebo				
Le Bars et al., 2000	-0.6 5.2 104	4 1.1 5.3 9	9 7.9% -1.70 [-3.15, -0.25]		
Schneider et al., 2005	1.6 5.8 169	9 0.9 5.6 17	4 11.3% 0.70 [-0.51, 1.91]	1-	J Alzheimers Dis.
Subtotal (95% CI)	273	3 27	3 19.2% -0.29 [-1.21, 0.64]	•	J AIZHEIMEI J DIS.
Heterogeneity: Chi ² = 6.24,	df = 1 (P = 0.01); I	² = 84%			0045.40/01.500 000
Test for overall effect: Z = 0	.61 (P = 0.54)				2015;43(2):589-603.
Total (95% CI)	814	83	2 100.0% -2.54 [-2.94, -2.13]	•	
Heterogeneity: Chi ² = 122.3	1, df = 6 (P < 0.00	001); I² = 95%		-10 -5 0 5 10	
Test for overall effect: Z = 1	2.26 (P < 0.00001))		Favours [EGb761] Favours [Placebo]	I
Test for subgroup difference	es: Chi² = 43.13, dt	f = 2 (P < 0.00001)	, l ² = 95.4%	ravera (content ravera (nacebo)	

ALMA MATER STUDIORUM ~ UNIVERSITÀ DI BOLOGNA

Efficacy

on the

ADAC

Efficacy on the ADL Score

2.2 Patients with NPS subgroup

	E	Gb761		PI	acebo			td. Mean Difference	Std. Mean Difference	
Study or Subaroup	Mean	SD	Total	Mean	SD	Total	Weight	IV. Fixed, 95% Cl	IV. Fixed, 95% Cl	
2.2.1 EGb761 240mg vs.Pl	acebo									
Herrschaft et al., 2012	-0.11	0.36	200	0.04	0.29	202	34.8%	-0.46 [-0.66, -0.26]		
lhi et al., 2011	-0.2	0.4	202	0	0.4	202	34.8%	-0.50 [-0.70, -0.30]		
Napryeyenko et al., 2007	-1.9	2.7	198	0.9	2.4	197	30.5%	-1.09 [-1.31, -0.88]		
Subtotal (95% CI)			600			601	100.0%	-0.67 [-0.78, -0.55]	•	
Heterogeneity: Chi ² = 22.66	6, df = 2	(P < 0.	0001);	l² = 919	ю	S.				
Test for overall effect: Z = 1	1.18 (P	< 0.00	001)			-				
									•	
Total (95% CI)			600			601	100.0%	-0.67 [-0.78, -0.55]	. 🗣. 🛛	
Heterogeneity: Chi ² = 22.66		-		l ² = 919	%				-1 -0.5 0 0.5 1	
Test for overall effect: Z = 1						7 A			Favours [EGB761] Favours [Placebo]	
Test for subgroup difference	es: Not a	applica	ble							
2.3 AD subgroup										
0,										
	E	Gb761		PI	acebo		5	Std. Mean Difference	Std. Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% Cl	IV, Fixed, 95% Cl	
2.3.1 EGb761 240mg vs. P	lacebo									
lhl et al., 2012	-0.16	0.29	163	0	0.33	170	20.7%	-0.51 [-0.73, -0.29]		
Kanowski et al., 2003	-1	2	79	-0.4	2.3	79	10.1%	-0.28 [-0.59, 0.04]		
Napryeyenko et al., 2009	-1.6	2.7	104	0.8	2.1	110	12.2%	-0.99 [-1.28, -0.71]		
Schneider et al., 2005	0.1	0.4	170	0.1	0.3	174	22.1%	0.00 [-0.21, 0.21]	• T	
Subtotal (95% CI)			516			533	65.1%	-0.39 [-0.52, -0.27]	•	
Heterogeneity: Chi ² = 32.03); I ² = 91	1%					
Test for overall effect: Z = 6	5.24 (P <	0.000	01)							
										J Alzheimers
2.3.2 EGb761 120mg vs. P	lacebo									
						404	10.00/	0.441.0.60 0.441		
Le Bars et al., 2000	-0.09		104	0.06		101	12.9%	-0.41 [-0.69, -0.14]		Die 2015
Le Bars et al., 2000 Schneider et al., 2005		0.34 0.4	169		0.38 0.3	174	22.0%	0.00 [-0.21, 0.21]	-	Dis. 2015;
Le Bars et al., 2000 Schneider et al., 2005 Subtotal (95% CI)	-0.09 0.1	0.4	169 273	0.1					•	•
Le Bars et al., 2000 Schneider et al., 2005 Subtotal (95% CI) Heterogeneity: Chi ² = 5.44,	-0.09 0.1 df = 1 (F	0.4 P = 0.0	169 273	0.1		174	22.0%	0.00 [-0.21, 0.21]	•	Dis. 2015; 43(2):589-603.
Le Bars et al., 2000 Schneider et al., 2005 Subtotal (95% CI)	-0.09 0.1 df = 1 (F	0.4 P = 0.0	169 273	0.1		174	22.0%	0.00 [-0.21, 0.21]	•	•
Le Bars et al., 2000 Schneider et al., 2005 Subtotal (95% CI) Heterogeneity: Chi ² = 5.44, Test for overall effect: Z = 1	-0.09 0.1 df = 1 (F	0.4 P = 0.0	169 273 2); I ² =	0.1		174 275	22.0% 34.9%	0.00 [-0.21, 0.21] -0.15 [-0.32, 0.02]		•
Le Bars et al., 2000 Schneider et al., 2005 Subtotal (95% CI) Heterogeneity: Chi ² = 5.44, Test for overall effect: Z = 1 Total (95% CI)	-0.09 0.1 df = 1 (F	0.4 P = 0.0 = 0.07)	169 273 2); I ² = 789	0.1 82%	0.3	174 275	22.0%	0.00 [-0.21, 0.21]	•	•
Le Bars et al., 2000 Schneider et al., 2005 Subtotal (95% CI) Heterogeneity: Chi ² = 5.44, Test for overall effect: Z = 1 Total (95% CI) Heterogeneity: Chi ² = 42.53	-0.09 0.1 df = 1 (F 1.78 (P =	0.4 P = 0.0 0.07) (P < 0.4	169 273 2); l ² = 789 00001)	0.1 82%	0.3	174 275	22.0% 34.9%	0.00 [-0.21, 0.21] -0.15 [-0.32, 0.02]	-1 -0.5 0 0.5 1	•
Le Bars et al., 2000 Schneider et al., 2005 Subtotal (95% CI) Heterogeneity: Chi ² = 5.44, Test for overall effect: Z = 1 Total (95% CI)	-0.09 0.1 df = 1 (F 1.78 (P = 3, df = 5 (5.09 (P <	0.4 P = 0.0 0.07) (P < 0.0 0.000	169 273 2); I ² = 789 00001) 01)	0.1 82%); I² = 88	0.3	174 275 808	22.0% 34.9% 100.0%	0.00 [-0.21, 0.21] -0.15 [-0.32, 0.02]	-1 -0.5 0 0.5 1 Favours [EGb761] Favours [Placebo]	•

ALMA MATER STUDIORUM - UNIVERSITÀ DI BOLOGNA



Efficacy on the NeuroPsychiatric Index (NPI) Score

4.1 Patients with NPS subgroup

	EGb 761		Placebo				Mean Difference	Mean Difference		
Study or Subaroup	Mean	SD	Total	Mean	SD	Total	Weight	IV. Fixed, 95% CI	IV. Fixed, 95% Cl 🦢	
4.1.1 EGb761 240mg vs. P	lacebo									
Gavrilova et al., 2014	-7	4.5	80	-5.5	5.2	79	17.0%	-1.50 [-3.01, 0.01]		
Herrschaft et al., 2012	-4.6	7.2	200	-2.1	6.5	202	21.6%	-2.50 [-3.84, -1.16]	-	
lhl et al., 2011	-3.2	6.2	202	0	6.5	202	25.3%	-3.20 [-4.44, -1.96]		
Napryeyenko et al., 2007	-6.5	5	198	2.4	5.5	197	36.1%	-8.90 [-9.94, -7.86]	•	
Subtotal (95% CI)			680			680	100.0%	-4.82 [-5.44, -4.20]	•	
Heterogeneity: Chi ² = 96.07	² , df = 3	(P <)	0.0000	1); $ ^2 = 5$	97%					
Test for overall effect: Z = 1	15.16 (P	< 0.0	0001)							
Total (95% CI)			680			680	100.0%	-4.82 [-5.44, -4.20]		
Heterogeneity: Chi ² = 96.07, df = 3 (P < 0.00001); l ² = 97%									-10 -5 0 5 10	
Test for overall effect: Z = 1	5.16 (P	< 0.0	0001)							
Test for subgroup difference	es: Not	applic	able						Favours [EGb761] Favours [Placebo]	

J Alzheimers Dis. 2015;43(2):589-603.

ALMA MATER STUDIORUM ~ UNIVERSITÀ DI BOLOGNA



Adverse events

J Alzheimers Dis. 2015;43(2):589-603.

5.2 Patients with NPS subgroup

		EGb761	Placebo		Odds Ratio	Odds Ratio
	Study or Subaroup	Events Total	Events Total	Weight	M-H. Fixed, 95% Cl	M-H. Fixed. 95% Cl
	5.2.1 EGb761 240mg vs. Pl	acebo				
	Herrschaft et al., 2012	91 205	82 205	37.4%	1.20 [0.81, 1.77]	
	lhi et al., 2011	139 206	141 204	37.8%	0.93 [0.61, 1.41]	
	Napryeyenko et al., 2007	166 200	178 200		0.60 [0.34, 1.07]	
	Subtotal (95% CI)	611	609	100.0%	0.95 [0.73, 1.22]	•
	Total events	396	401			
	Heterogeneity: Chi ² = 3.73, (df = 2 (P = 0.15);	² = 46%			
	Test for overall effect: Z = 0.	.41 (P = 0.68)				
	Total (95% CI)	611	609	100.0%	0.95 [0.73, 1.22]	—
	Total events	396	401			
	Heterogeneity: Chi ² = 3.73, (12 = 46%			01 02 05 1 2 5 10
	Test for overall effect: Z = 0.					Favours [EGb761] Favours [Placebo]
	Test for subgroup difference	es: Not applicable				
5	i.3 AD subgroup	0				
		EGb761	Placebo		Odds Ratio	Odds Ratio
	Study or Subaroup		Events Total	Weight	M-H. Fixed. 95% Cl	M-H, Fixed, 95% Cl
-	5.3.1 EGb761 240mg vs. Pt		Events Total	TTOTUL	BETE FIX 90.85% 61	18-11-11-12-02-02-02-1

	EGb7	51	Placet	00		Odds Ratio	Odds Ratio				
Study or Subaroup	Events	Total	Events	Total	Weight	M-H. Fixed. 95% Cl	M-H. Fixed. 95% Cl				
5.3.1 EGb761 240mg vs. Placebo											
lhi et al., 2012	105	167	120	171	29.6%	0.72 [0.46, 1.13]					
Napryeyenko et al., 2009	80	106	96	112	15.4%	0.51 [0.26, 1.02]					
Schneider et al., 2005	112	170	124	174	28.2%	0.78 [0.49, 1.23]					
Subtotal (95% CI)		443		457	73.2%	0.70 [0.52, 0.93]	-				
Total events	297		340								
Heterogeneity: Chi2 = 1.01, c	ff = 2 (P =	= 0.60);	l ² = 0%								
Test for overall effect: Z = 2.41 (P = 0.02)											
5.3.2 EGb761 160mg vs. Pla	acabo										
Mazza et al., 2006	0	25	0	26		Not estimable					
Subtotal (95% CI)	v	25	0	26		Not estimable					
Total events	0	23	0	20		Notestimable					
Heterogeneity: Not applicable	*		0								
Test for overall effect: Not applicable	-										
resctor overall effect. Not ap	picable										
5.3.3 EGb761 120mg vs. Pla	acebo										
Schneider et al., 2005	114	169	124	174	26.8%	0.84 [0.53, 1.32]					
Subtotal (95% CI)		169		174	26.8%	0.84 [0.53, 1.32]					
Total events	114		124								
Heterogeneity: Not applicable	е										
Test for overall effect: Z = 0.	76 (P = 0	.44)									
Total (95% CI)		637		657	100.0%	0.74 [0.58, 0.94]	-				
Total events	411		464								
Heterogeneity: Chi ² = 1.42, c	ff = 3 (P :	= 0.70);	P = 0%				0.1 0.2 0.5 1 2 5 10				
Test for overall effect: Z = 2.	45 (P = 0	.01)					Favours [EGb761] Favours [Placebo]				
Test for subgroup differences: Chi ² = 0.42, df = 1 (P = 0.52), I ² = 0% Favours [EGD/b1] Favours [Placebo]											

ALMA MATER STUDIORUM ~ UNIVERSITÀ DI BOLOGNA



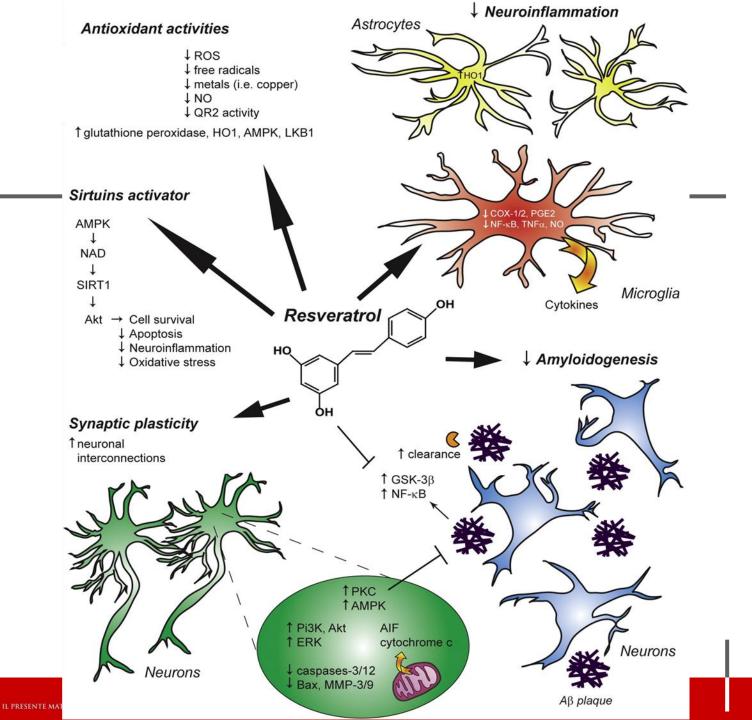
RCTs on resveratrol

Molecules 2016, 21, 1243

Reference or ID (Location)	Study Design	Resveratrol Preparation and Dose [Other Medication]	Duration	Subjects <i>n</i> Age Disorder/Status	Purpose Outcome Measures	Main Results
Kennedy et al. <mark>[111]</mark> (Newcastle upon Tyne, UK)	r, db, pc, co	Trans-resveratrol from Biotivia Bioceuticals (Vienna, Austria) 250 mg or 500 mg	21 days	24 18–25 years Healthy 9 further subjects underwent bioavailability assessment	To investigate the ability to modulate mental function and increase cerebral blood flow	Cognitive function not affected. Increase in œrebral flow
Wong et al. [112] (Adelaide, Australia) ACTRN12611000060943	r, db, pc, co	Resvida (resveratrol 75 mg/day)	12 weeks	28 45–70 years Obese but otherwise healthy	Effects of resveratrol on circulatory function and cognitive performance in obese adults	Increase of circulatory function. No effects on blood pressure, arterial compliance, and cognitive function
Witte et al. [113] (Berlin, Germany)	R, DB, PC,	Resveratrol 200 mg/day in a formula with quercetin	26 weeks	46 50–80 years Healthy overweight	To investigate the ability to enhance cognitive performance	Significant retention of memory, significant increase of hyppocampal FC, improvement of glucose metabolism
Wightman et al. [114] (Newcastle upon Tyne, UK)	r, db, pc, co	Trans-resveratrol 250 mg/day or trans-resveratrol 250 mg/day with 20 mg piperine	21 days	23 19–34 years Healthy 6 healthy men underwent bioavailability assessment	To assess if piperine affects the efficacy and bioavailability of resveratrol	Piperine henances the effect of resveratrol on cerebral blood flow but not the cognitive performance and bioavailability
Turner et al. [115] (Georgetown, USA) NCT01504854	R, DB, PC, MC Phase 2	Resveratrol 500 mg/day with dose excalation by 500 mg increments ending with 2 g/day	52 weeks	119 >49 years Mild-to-moderate AD	To assess safety and efficacy	Decrease of CSF and plasma Aβ ₄₀ levels. No significant effects on cognitive score
Wong et al. [116] ACTRN12614000891628 (New castle, Australia)	R, DB, PC, CO Phase 2	Resvida 75 mg/day, 150 mg/day, 300 mg/day	4 weeks	36 40–80 years Type 2 diabetes mollitur	Improvement of cerebrov ascular responsiveness	Increase of cerebrovascular responsiveness

ALMA MATER STUDIORUM ~ UNIVERSITÀ DI BOLOGNA

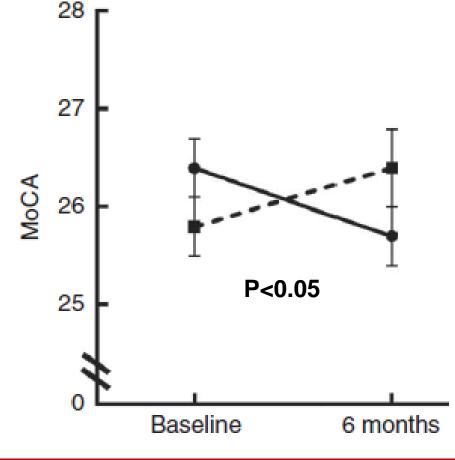




Cicero et al. Arch Med Sci 2018; in press.



Curcumin and cognition: a RCT of community-dwelling older adults

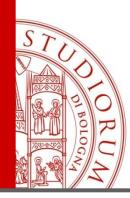


Montreal Cognitive Assessment (MoCA) scores (adjusted for age, sex, years of education and APOE **ɛ**4 allele carriage)

- - -, Curcumin group; ----, placebo group.

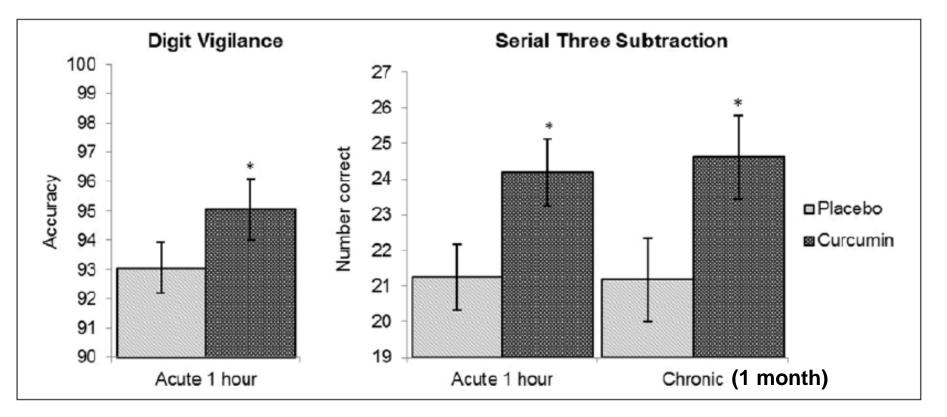
British Journal of Nutrition (2016), 115, 2106-2113

ALMA MATER STUDIORUM - UNIVERSITÀ DI BOLOGNA



Effects of solid lipid curcumin 400 mg on cognition and mood in 60 healthy elderly (60-85 yo)

J Psychopharmacol. 2015 May;29(5):642-51

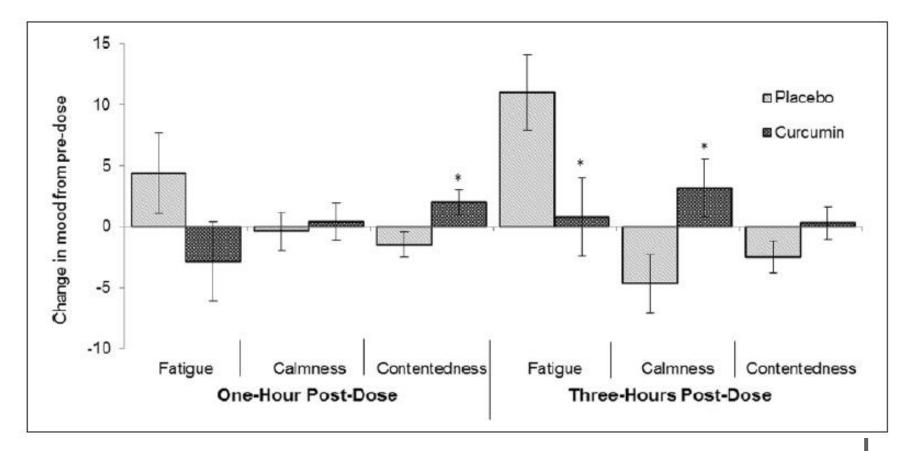


ALMA MATER STUDIORUM - UNIVERSITÀ DI BOLOGNA



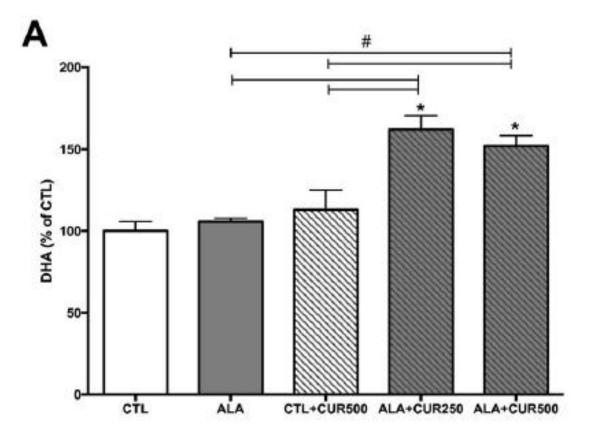
Effects of solid lipid curcumin 400 mg on cognition and mood in 60 healthy elderly (60-85 yo)

J Psychopharmacol. 2015 May;29(5):642-51



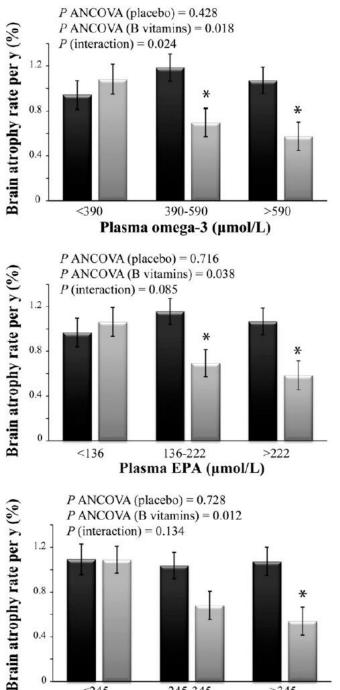
ALMA MATER STUDIORUM - UNIVERSITÀ DI BOLOGNA

Curcumin boosts DHA in the brain: implications for the prevention of anxiety disorders



Biochim Biophys Acta. 2015; 1852(5): 951–961.

ALMA MATER STUDIORUM - UNIVERSITÀ DI BOLOGNA



0.8

0.4

<245

245-345

Plasma DHA (µmol/L)

>345

Omega 3 and B vitamins

Brain atrophy rates (mean 6 SEM) among subjects receiving placebo (black) and high-dose B vitamins (gray) according to tertiles of plasma baseline combined v-3 (top)

Am J Clin Nutr 2015;102:215-21.

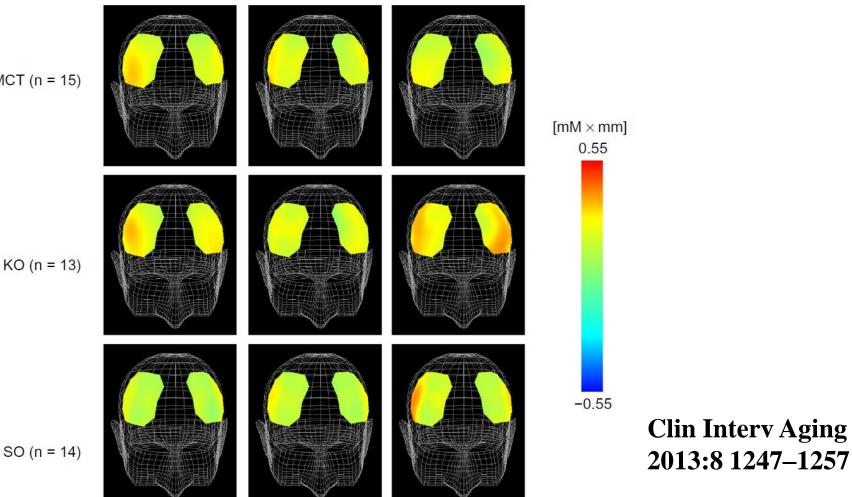
UNIVERSITA DI BOLOGNA JDIORUM

UNIVERSITÀ DI BOLOGNA E NON PUÒ ESSERE UTILIZZATO AI TERMINI DI LEGGE DA ALTRE PERSONE O PER FINI NON ISTITUZIONALI



Topographic maps of changes in oxy-hb concentration at 225.0 seconds during working memory task

MCT (n = 15)



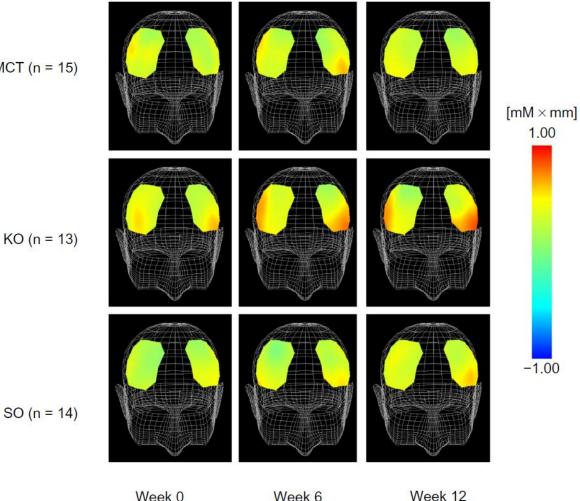


Topographic maps of changes in oxy-hb concentration at 150.0 seconds during the calculation task

Clin Interv Aging

2013:8 1247-1257

MCT (n = 15)





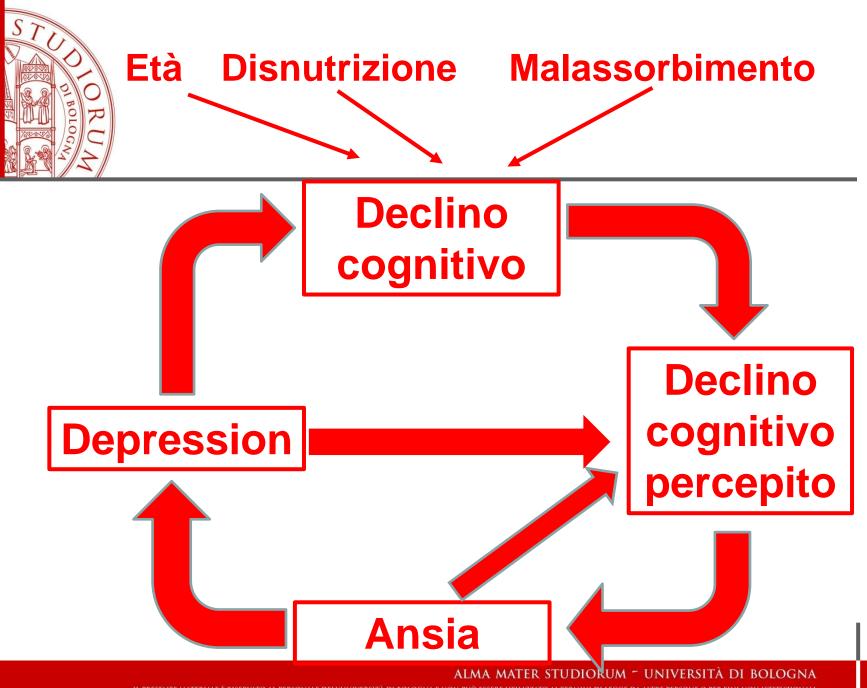
<u>A multicomponent approach:</u> <u>the possible solution?</u>

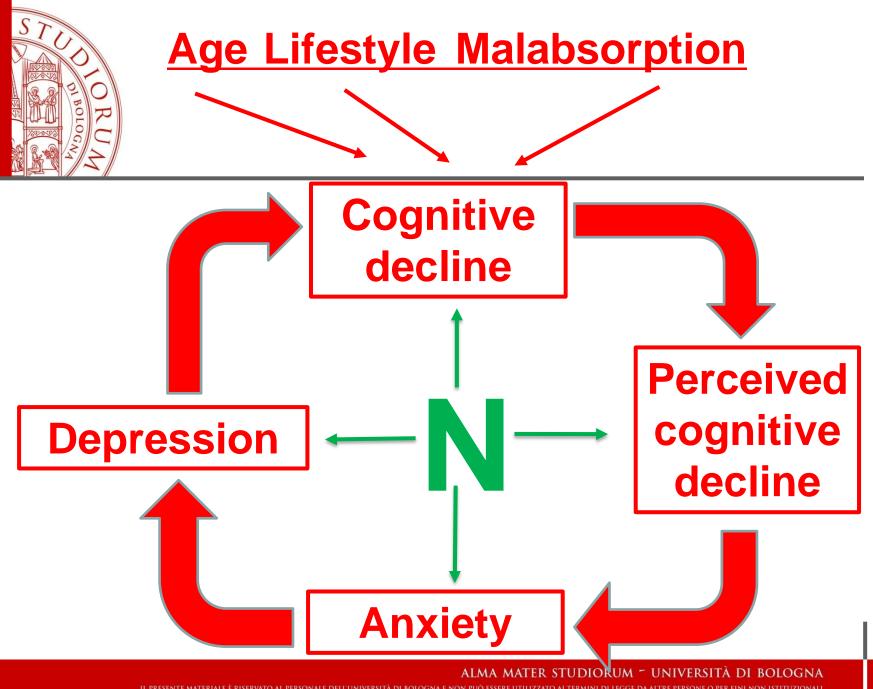
Gingko + DHA + Vitamin B

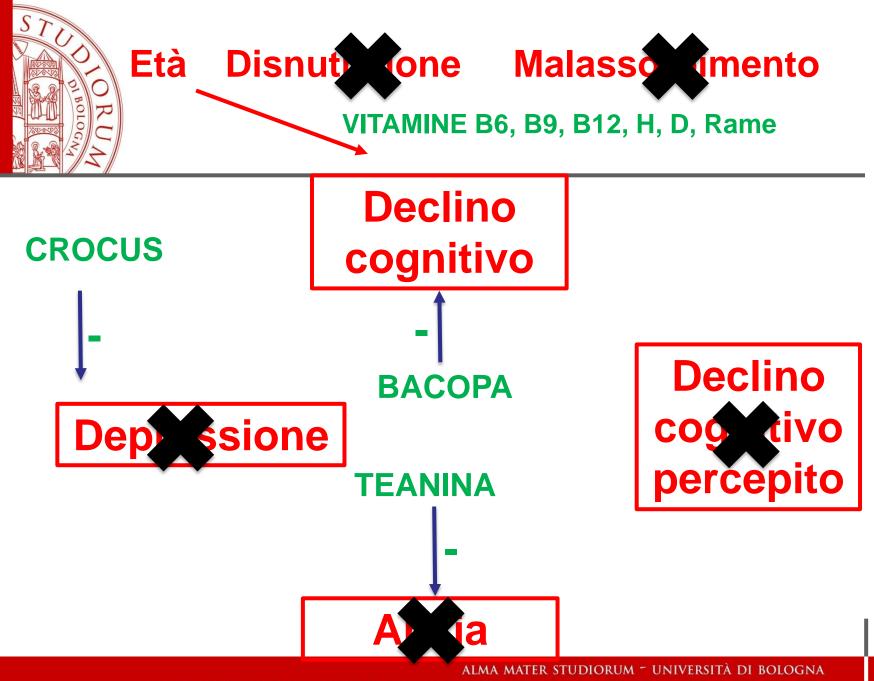
Variable	Baseline Mean (SD)	Six Months Mean (SD)	Adjusted Mean (SD)	p Value
Cognition				
MOT latency (ms)				
Placebo	1171 (276)	1162 (180)	1170 (162)	.038
Intervention	1171 (275)	1058 (190)	1052 (162)	
VRM immediate free ree	call (words)			
Placebo	9.2 (1.7)	8.0 (2.2)	7.7 (1.7)	.029
Intervention	8.7 (2.3)	8.8 (2.1)	9.0 (1.7)	
Mobility				
HW Speed (m/s)				
Placebo	1.35 (0.20)	1.32 (0.15)	1.29 (0.08)	.031
Intervention	1.30 (0.24)	1.33 (0.25)	1.36 (0.10)	

J Gerontol A Biol Sci Med Sci, 2016;71(2):236-242

ALMA MATER STUDIORUM ~ UNIVERSITÀ DI BOLOGNA









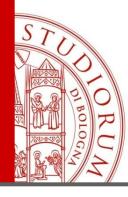
PHYTOTHERAPY RESEARCH Phytother. Res. (2012) Published online in Wiley Online Library (wileyonlinelibrary.com) DOI: 10.1002/ptr.4864

An Acute, Double-Blind, Placebo-Controlled Crossover Study of 320 mg and 640 mg Doses of a Special Extract of *Bacopa monnieri* (CDRI 08) on Sustained Cognitive Performance

Luke A. Downey,¹ James Kean,¹ Fiona Nemeh,¹ Angela Lau,¹ Alex Poll,¹ Rebecca Gregory,¹ Margaret Murray,¹ Johanna Rourke,¹ Brigit Patak,¹ Matthew P. Pase,¹ Andrea Zangara,^{1,2} Justine Lomas,¹ Andrew Scholey¹ and Con Stough¹*

¹Centre for Human Psychopharmacology, Swinburne University of Technology, Melbourne, Australia
²Soho Flordis International, Sydney, Australia

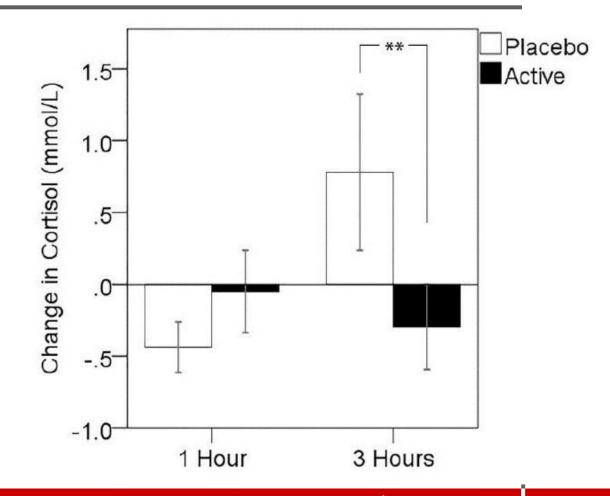
Standardized extracts of the traditional Ayurvedic medicine *Bacopa monnieri* (BM) (Brahmi) have been recently shown to have cognitive enhancing effects in chronic administration studies. Pre-clinical work has also identified a number of acute anxiolytic, nootropic, and cardiovascular effects of BM. There has, however, been little research on the acute effects of BM on cognitive function. The current study aimed to assess the acute effects of a specific extract of BM (KeenMind[®] - CDRI 08) in a double-blind, placebo-controlled study in normal healthy participants who completed a cognitively demanding series of tests. Twenty-four healthy volunteers completed six repetitions of the Cognitive Demand Battery (CDB) after consuming a placebo, 320 mg BM or 640 mg of BM in a cross-over design and provided cardiovascular and mood assessments before and after treatment. Change from baseline scores indicated that the 320 mg dose of BM improved performance at the first, second, and fourth repetition post-dosing on the CDB, and the treatments had no effect upon cardiovascular activity or in attenuating task-induced ratings of stress and fatigue. It was concluded that assessment of an earlier pharmacological window and use of less memory-specific cognitive tests together with more temporally sensitive measures of brain activity may improve our understanding of the acute neurocognitive properties of BM. Copyright © 2012 John Wiley & Sons, Ltd.



Anti-Stress Effects of L-Theanine: A Randomised, Double-Blind, Placebo-Controlled, Crossover Trial

Change in cortisol from pre- to poststressor for both post-dose assessments and treatment visits

Nutrients **2016**, 8, 53; doi:10.3390/nu8010053



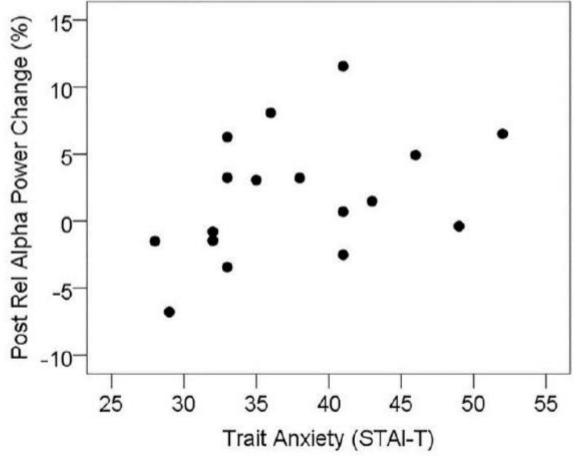
ALMA MATER STUDIORUM - UNIVERSITÀ DI BOLOGNA



Anti-Stress effects of L-Theanine: the impact on magnetoencephalography

Association between trait anxiety and treatment-related change in resting relative alpha power in posterior sensor sites (positive change = increased alpha during active treatment visit).

Nutrients **2016**, 8, 53; doi:10.3390/nu8010053



ALMA MATER STUDIORUM - UNIVERSITÀ DI BOLOGNA



Contents lists available at ScienceDirect

Journal of Affective Disorders

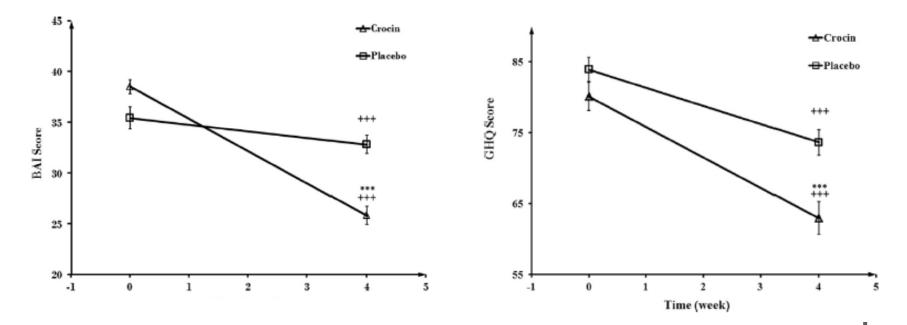
journal homepage: www.elsevier.com/locate/jad

Affective Disorders

CrossMark

Research report

Crocin, the main active saffron constituent, as an adjunctive treatment in major depressive disorder: A randomized, double-blind, placebo-controlled, pilot clinical trial



ALMA MATER STUDIORUM ~ UNIVERSITÀ DI BOLOGNA

Short-Term Impact of a Combined Nutraceuticals on Cognitive Function, Perceived Stress and Depression in Young Elderly with Cognitive Impairment: A Pilot, Double-Blind, Randomized Clinical Trial

A.F. Cicero¹, M. Bove¹, A. Colletti¹, M. Rizzo², F. Fogacci¹, M. Giovannini¹, C. Borghi¹

Table 2. Modification of the biometric test carried out on the volunteers in both groups of treatment												
	Active		Placebo									
	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment								
MMSE	23.1±0.9	24.5±1.0*°	23.2±1.1	23.1±0.9								
PSQ Index	2.7±0.4	2.2±0.7*° -	2.6±0.8	2.4±0.9								
SRDS	42.8±8.4	37.1±7.6* 🖊	43.6±9.3	40.9±8.8*								

*P<0.05 Vs. baseline ; ° P<0.05 Vs. placebo

*Mini-Mental State Examination *Perceived Stress Questionnaire Index *Self-rating Depression Scale

ALMA MATER STUDIORUM - UNIVERSITA DI BOLOGNA



Interesting results but ...

- Short term studies (compared with disease pathogenesis)
- Small studies (compared with large patient heterogenity)
- Different botanical extracts (doses and bioavailability not always adequate)
- Risk factors not always optimized at the baseline !
- ... beyond that they function !!!



- >60 years (but also before)
- With perceived cognitive decline
- Asking help to manage the problem
- With psychological co-morbidity
- With cardiovascular disease risk factors





ALMA MATER STUDIORUM ~ UNIVERSITÀ DI BOLOGNA