VII CONGRESSO NAZIONALE B&M 2018

III SESSIONE

Prof. Giovanni Scapagnini
Professore Associato di Biochimica Clinica
Facoltà di Medicina e Chirurgia,
Università degli Studi del Molise

BRAIN AND MALNUTRITION
Chronic Diseases Association ONLUS

Università degli Studi del Molise
Via De Sanctis - 86100 Campobasso - Tel. +39 0874 4041

Blanchette Rockefeller Neurosciences Institute
West Virginia University

Consiglio Nazionale delle Ricerche
Istituto di Scienze Neurologiche

L'effetto della curcuma sul SNC

Giovanni Scapagnini, MD, PhD

SINut
Società Italiana di Nutraceutica

Brain is poised for oxidative damage

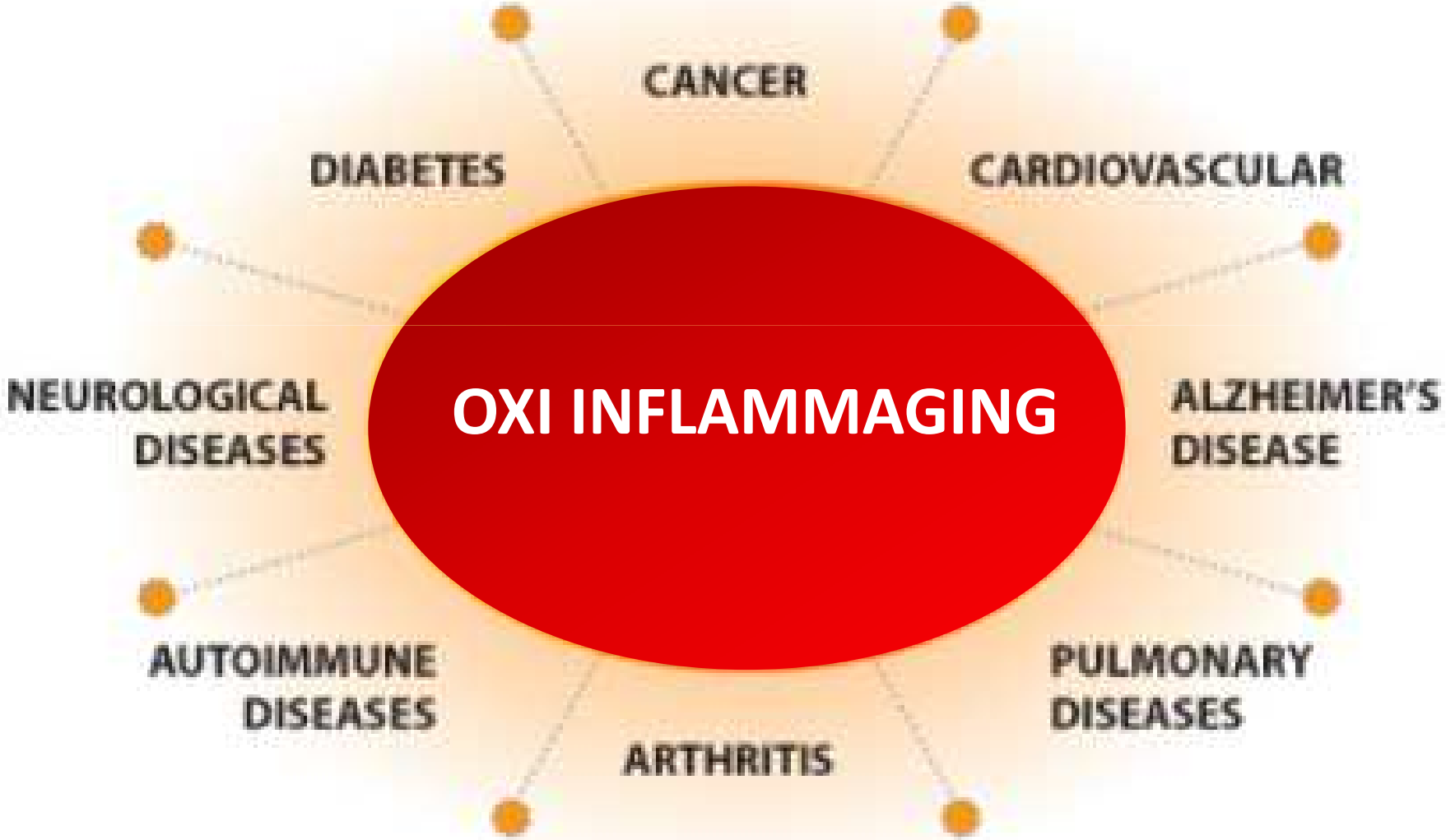
Rich in PUFA
(polyunsaturated fatty acids)

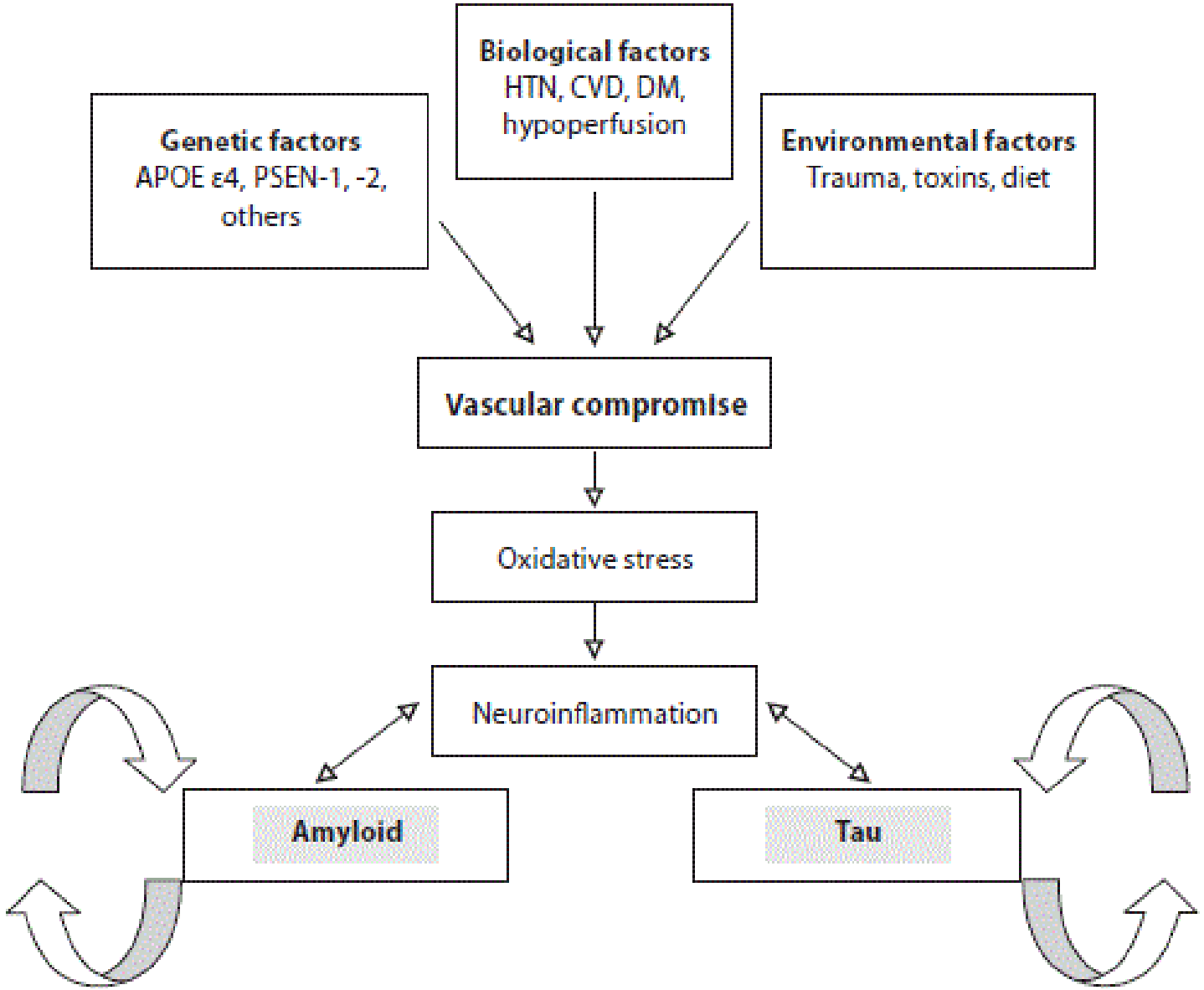
High use of
oxygen

Areas rich in
iron

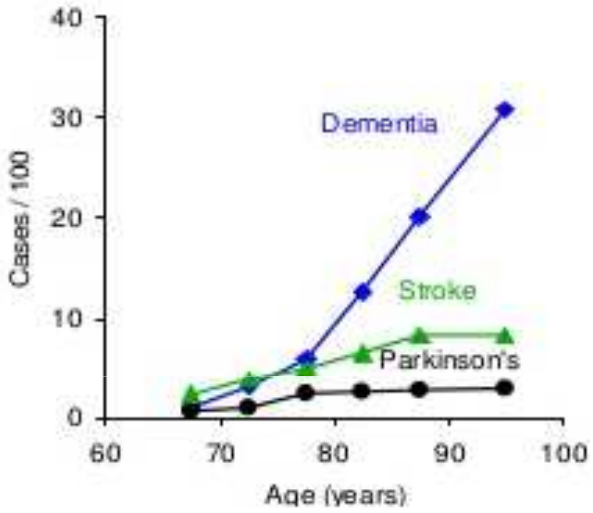
Low antioxidant
Capacity (Catalase,
GSH and SOD less
than 1/5 compared
to liver)

Oxidation and Inflammation
The link with age related chronic diseases

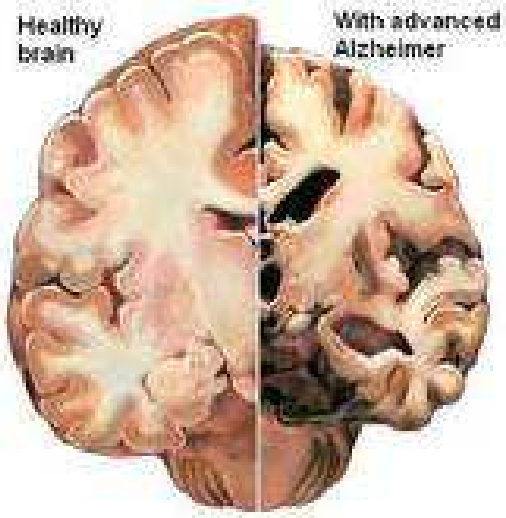



Biological factors
HTN, CVD, DM, hypoperfusion
Genetic factors
APOE ε4, PSEN-1, -2, others
Environmental factors
Trauma, toxins, diet
Vascular compromise
Oxidative stress
Neuroinflammation
Amyloid
Tau

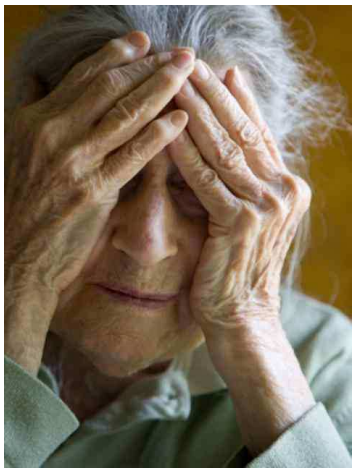
How many dementia cases in the future?



	Number of cases	Societal costs (€)
2010	6,000,000	72,000,000,000
2040	12,000,000	144,000,000,000

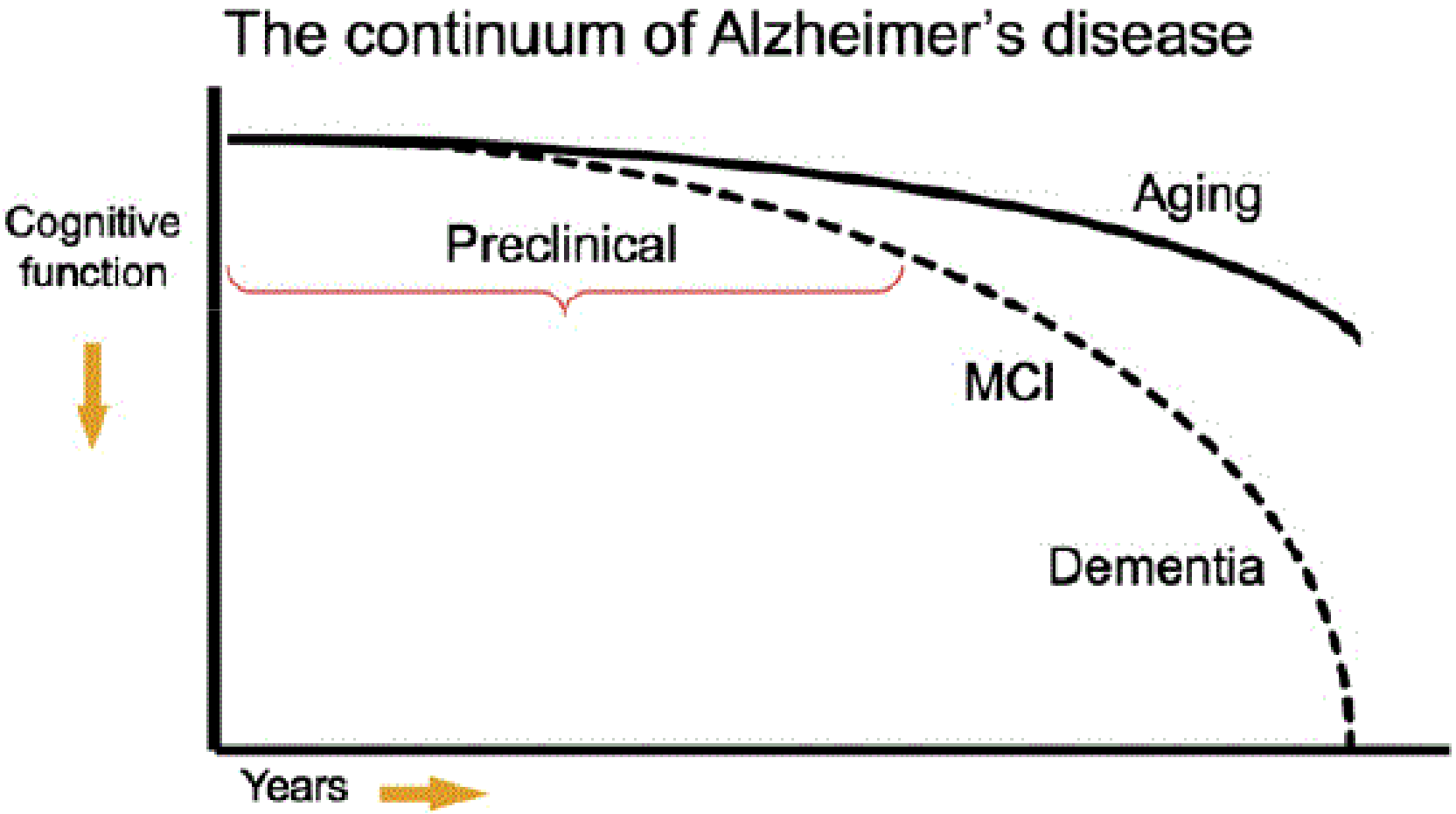


A major societal challenge for the coming years



Toward defining the preclinical stages of Alzheimer's disease:

Recommendations from the National Institute on Aging and the Alzheimer's Association workgroup



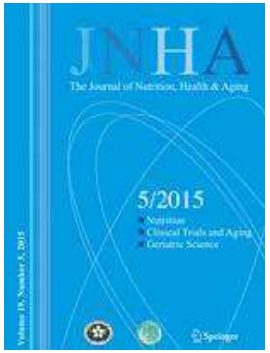
THE JOURNAL OF NUTRITION, HEALTH & AGING©

EPIGENETIC NUTRACEUTICAL DIETS IN ALZHEIMER'S DISEASE

S. DAVINELLI[1,2], V. CALABRESE[2,3], D. ZELLA[4], G. SCAPAGNINI[1,2]

1. Department of Medicine and Health Sciences, University of Molise, Campobasso 86100, Italy; 2. Inter-University Consortium "Sannio Tech", Benevento, 82030, Italy; 3. Department of Biomedical Sciences, University of Catania, Catania, 95124 Italy; 4. Department of Biochemistry and Molecular Biology, University of Maryland-School of Medicine, Baltimore, MD 21201, USA. Corresponding author: Giovanni Scapagnini, Department of Medicine and Health Sciences, University of Molise, Campobasso 86100, Italy, g.scapagnini@gmail.com

Abstract: There is growing support that environmental influences and individual genetic susceptibility may increase the incidence and accelerate the onset of Alzheimer's disease (AD). Epigenetic mechanisms encompass a complex regulatory network of modifications with considerable impact on health and disease risk. Abnormal epigenetic regulation is a hallmark in many pathological conditions including AD. It is well recognized that numerous bioactive dietary components mediate epigenetic modifications associated with the pathophysiology of several diseases. Although the influences of dietary factors on epigenetic regulation have been extensively investigated, only few studies have explored the effects of specific food components in regulating epigenetic patterns during neurodegeneration and AD. Epigenetic nutritional research has substantial potential for AD and may represent a window of opportunity to complement other interventions. Here, we provide a brief overview of the main mechanisms involved in AD, some of which may be epigenetically modulated by bioactive food.



Potentially Relevant Effects of Epigenetic Dietary Compounds in AD

Dietary components	Sources	Epigenetic effects	References
B vitamins	meat and vegetables but B12 vitamin is not available from plant products	DNA methylation	(23, 24)
Resveratrol	grapes, red wine, peanuts	DNA methylation, Histone-modifications, miRNA	(26, 53, 72)
Catechins	green tea, cocoa, blackberries	DNA methylation, Histone-modifications, miRNA	(31, 57, 70, 76)
Caffeic acid	coffee, barley grain	DNA methylation	(32)
Chlorogenic acid	apples, pears, berries	DNA methylation	(32)
Isoflavones	soy products	DNA methylation, Histone-modifications, miRNA	(33, 34, 58, 74)
Isothiocyanates	cruciferous vegetables	DNA methylation	(35)
Sodium butyrate	cheese, butter	Histone-modifications	(45, 46)
Flavonols	grape, blueberry, citrus fruits	Histone-modifications, miRNA	(48, 49, 55, 56, 73)
Curcumin	tumeric	miRNA	(70, 75)

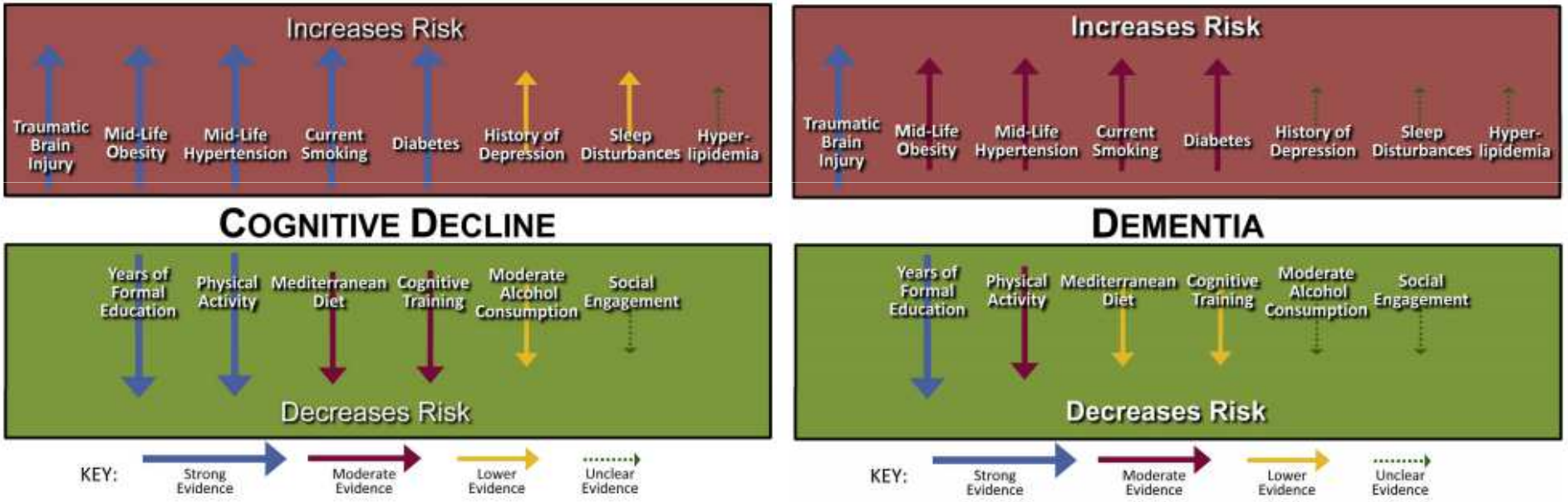
Alzheimer's & Dementia 11 (2015) 718-726

Summary of the evidence on modifiable risk factors for cognitive decline and dementia: A population-based perspective

Matthew Baumgarta , Heather M. Snyderb, *, Maria C. Carrillob , Sam Fazioc , Hye Kima , Harry Johnsd

Alzheimer's & Dementia

In 2014, the World Dementia Council (WDC) requested the Alzheimer's Association evaluate and report on the state of the evidence on modifiable risk factors for cognitive decline and dementia.

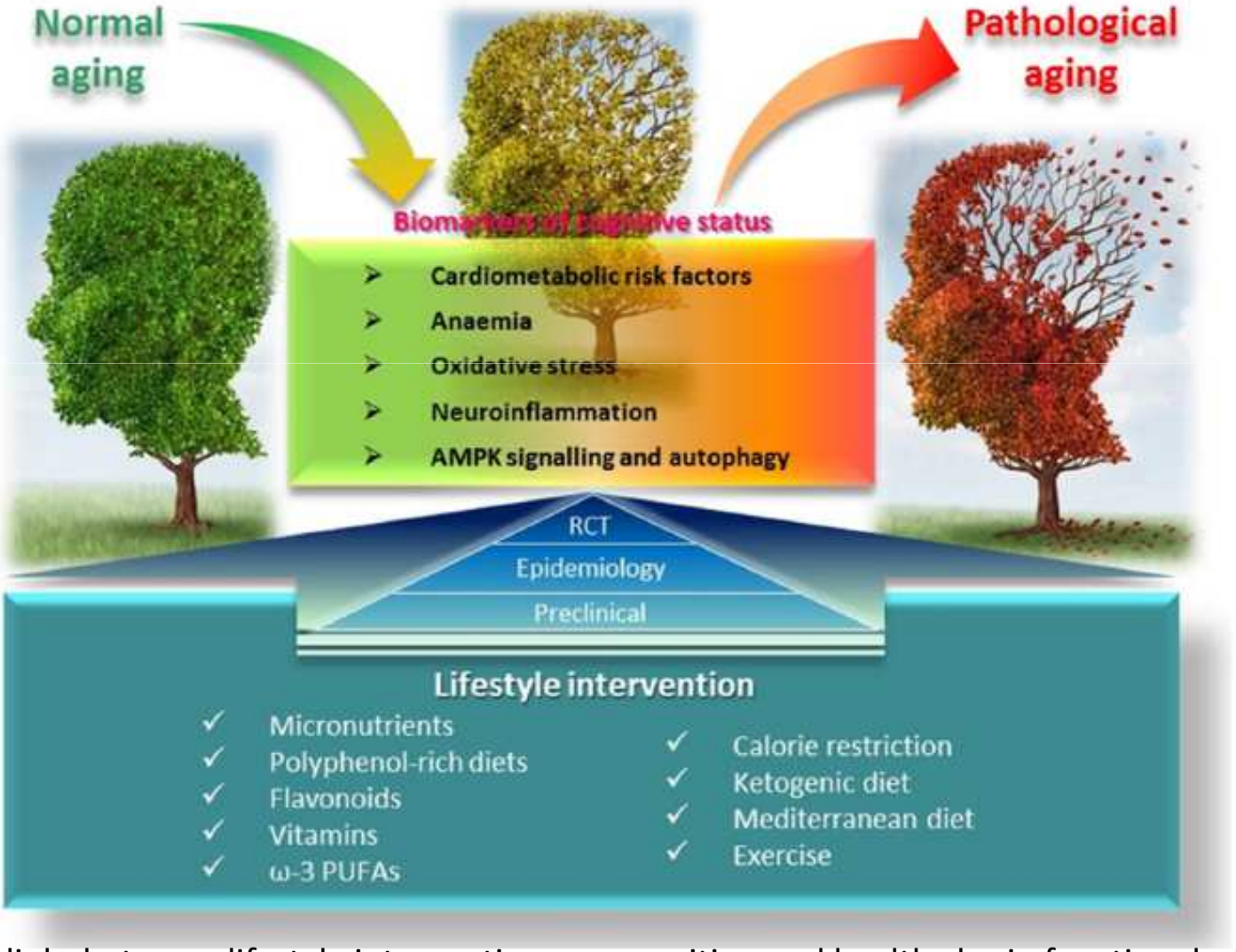


The Association believes there is sufficiently strong evidence, from a population-based perspective, to conclude that regular physical activity and management of cardiovascular risk factors (diabetes, obesity, smoking, and hypertension) reduce the risk of cognitive decline and may reduce the risk of dementia. The Association also believes there is sufficiently strong evidence to conclude that a healthy diet and lifelong learning/cognitive training may also reduce the risk of cognitive decline.

Ageing Research Reviews

Nutrition for the ageing brain: Towards evidence for an optimal diet

Vauzour D, et al. 2016



Overview of links between lifestyle interventions on cognition and healthy brain function during ageing.

Mediterranean Diet, Alzheimer Disease, and Vascular Mediation

Nikolaos Scarmeas, Yaakov Stern, Richard Mayeux, Jose A. Luchsinger.
Arch Neurol. 2006;63:1709-1717

Higher adherence to the MeDi is associated with a reduced risk for AD. The association does not seem to be mediated by vascular comorbidity. This could be the result of other biological mechanisms (oxidative or inflammatory) being implicated.

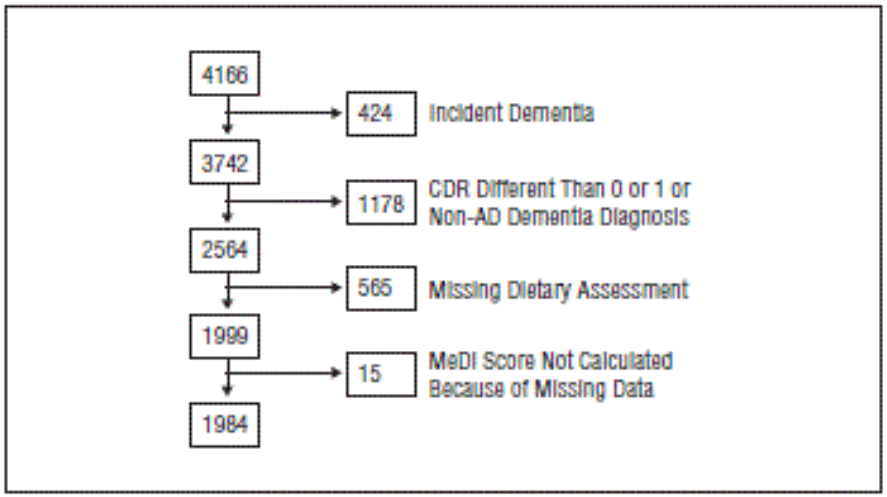


Figure 1. Flowchart describing sample size. AD indicates Alzheimer disease; CDR, Clinical Dementia Rating; MeDi, Mediterranean diet.

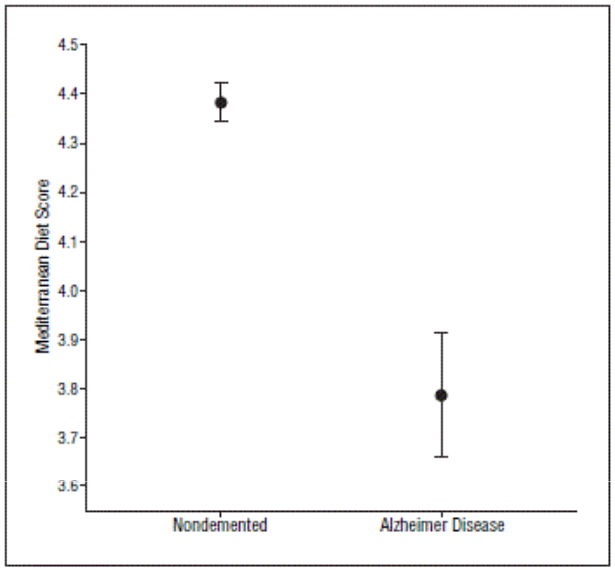


Figure 2. Means and standard errors of Mediterranean diet score for subjects with Alzheimer disease and nondemented subjects.

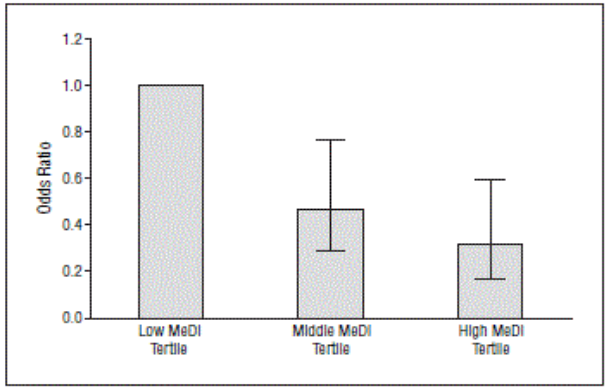
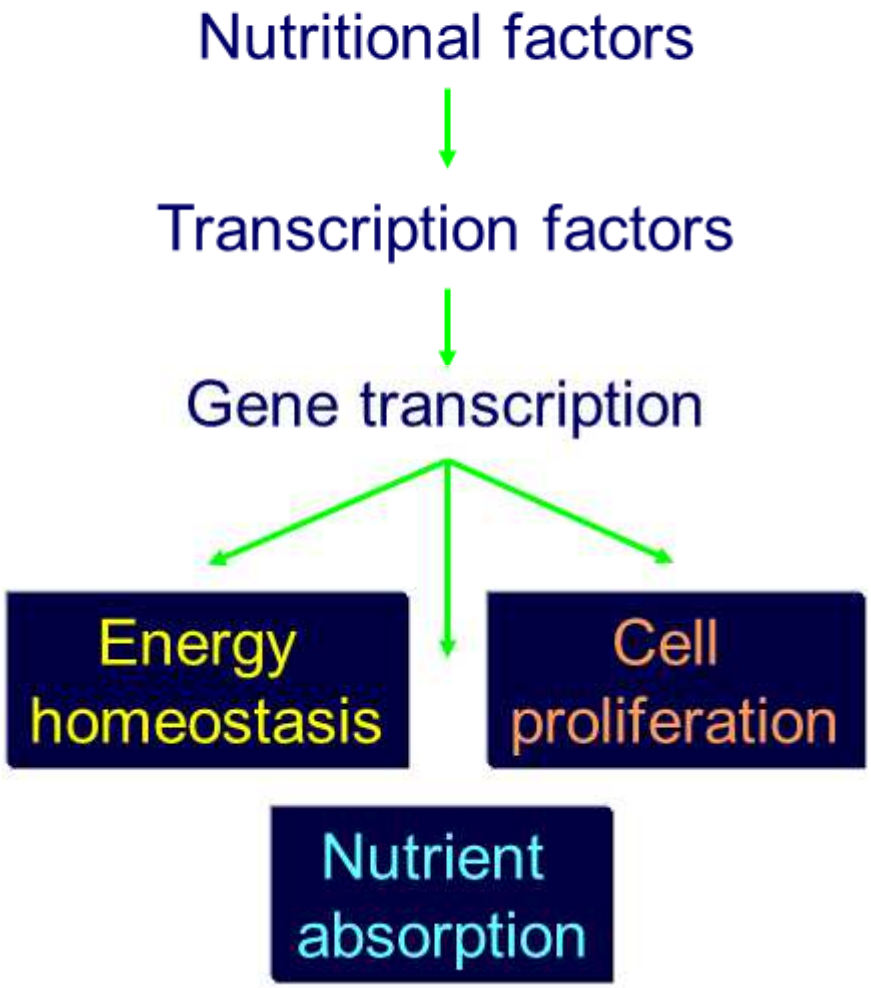
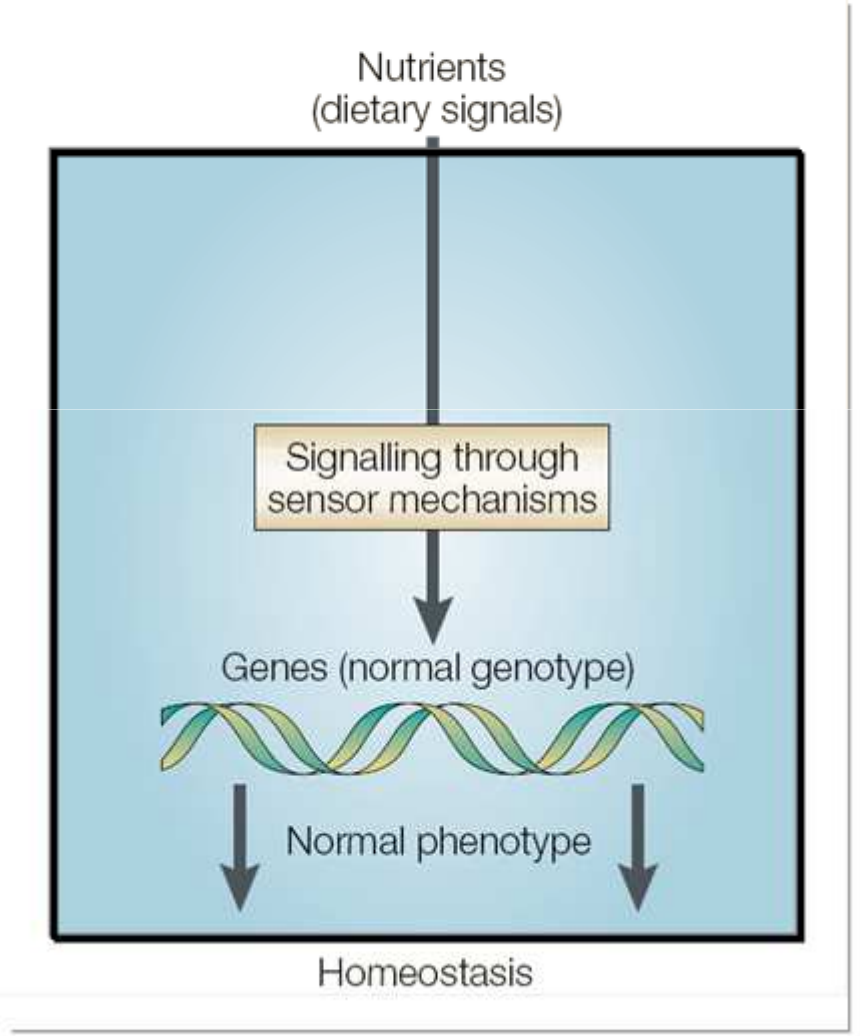


Figure 3. Odds ratios and 95% confidence intervals (bars) for subjects with Alzheimer disease vs nondemented subjects, for each Mediterranean diet (MeDi) adherence tertile based on logistic regression models that adjusted for cohort, age, sex, ethnicity, education, apolipoprotein E genotype, caloric intake, smoking, comorbidity index, and body mass index (calculated as weight in kilograms divided by height in meters squared).

Nutrients acts as dietary signals





EMBO reports

EMBO reports VOL 13 | NO 3 | 2012

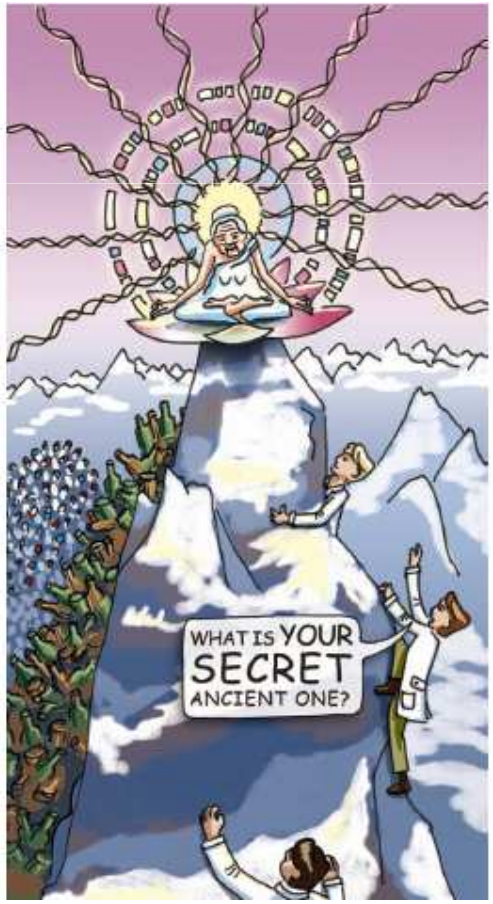
science & society

‘Positive biology’ as a new paradigm for the medical sciences

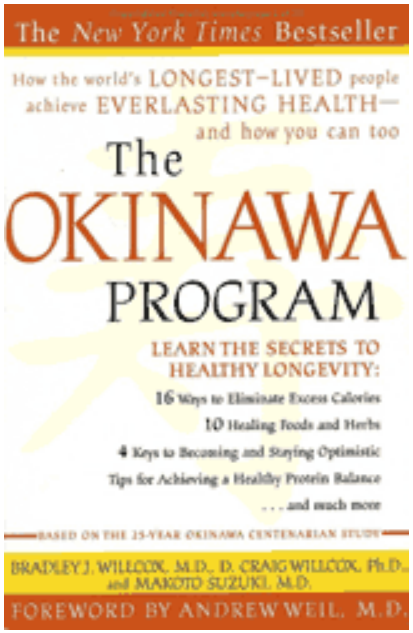
Focusing on people who live long, happy, healthy lives might hold the key to improving human well-being

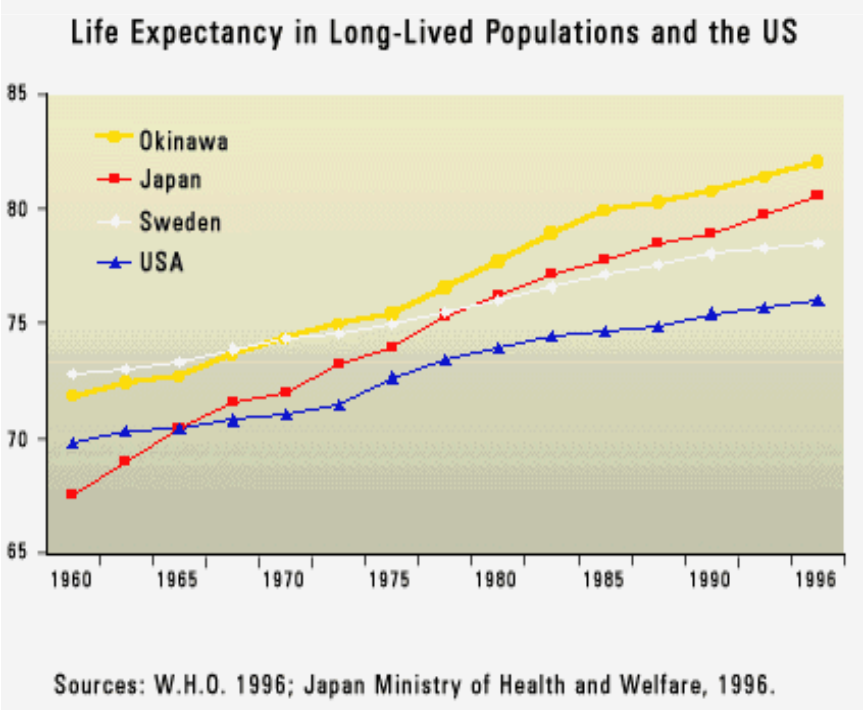
Colin Farrelly

> Eliminating all types of cancer would increase life expectancy in the USA by approximately only three years

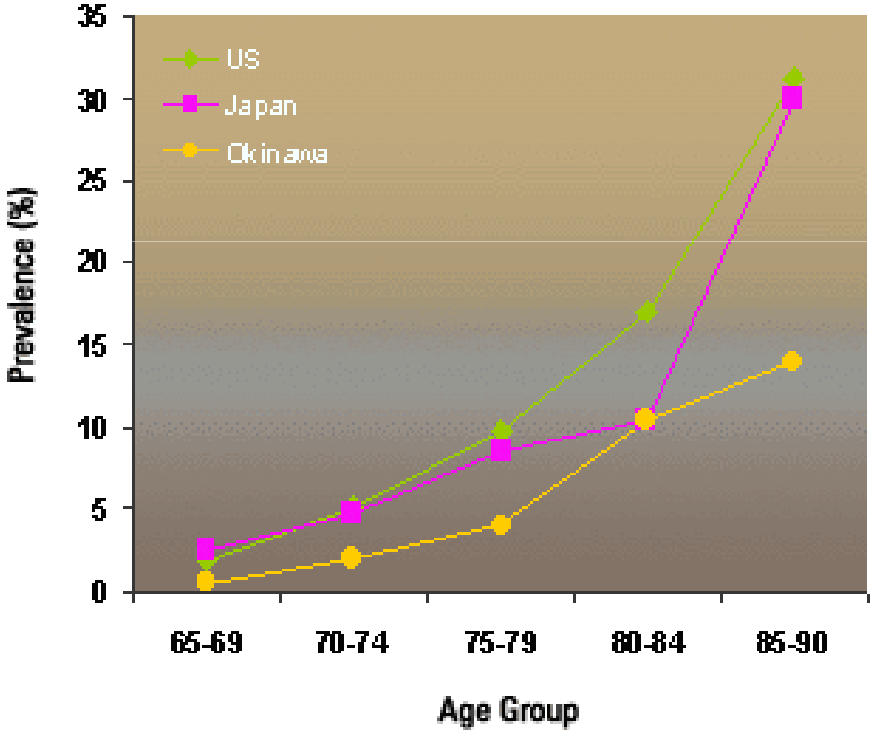



Sea of Japan
JAPAN
Tokyo
Pacific Ocean
Okinawa


The New York Times Bestseller
How the world's LONGEST-LIVED people achieve EVERLASTING HEALTH— and how you can too
The
OKINAWA
PROGRAM
LEARN THE SECRETS TO HEALTHY LONGEVITY:
16 Ways to Eliminate Excess Calories
10 Healing Foods and Herbs
4 Keys to Becoming and Staying Optimistic
Tips for Achieving a Healthy Protein Balance
. . . and much more
BASED ON THE 25-YEAR OKINAWA CENTENARIAN STUDY
BRADLEY J. WILLCOX, M.D., D. CRAIG WILLCOX, Ph.D., and MAKOTO SUZUKI, M.D.
FOREWORD BY ANDREW WEIL, M.D.


Life Expectancy in Long-Lived Populations and the US
85
80
75
70
65
Okinawa
Japan
Sweden
USA
1960
1965
1970
1975
1980
1985
1990
1996
Sources: W.H.O. 1996; Japan Ministry of Health and Welfare, 1996.

Prevalence of Dementia

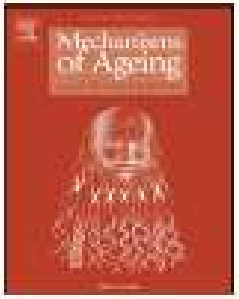


Sources: Yamada, M., et al. J Am Geriatr Soc 1999;47:189-95. Kokmen, E., et al. Mayo Clin Proc 1996;71:275-82. Ogura, C., et al. Internatl J Epidemiol 1995;24:373-80.

Mechanisms of Ageing and Development 136–137 (2014) 148–162

Healthy aging diets other than the Mediterranean: A focus on the Okinawan diet

Donald Craig Willcox[a,b,c,*], Giovanni Scapagnini[d], Bradley J. Willcox[b,c]



Key Features of Traditional Okinawa Diet

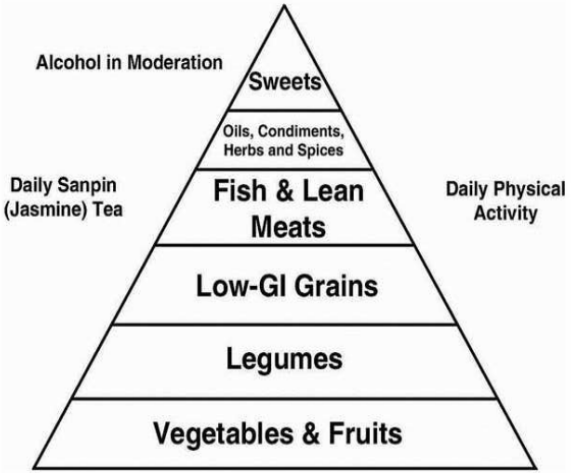
1) Low Caloric Density (plant-based, low fat, moderate protein from soy, fish, lean meats)

2) High Nutrient Density (Vitamins A,C, E, potassium, magnesium, folate, and healthy oils)

3) Phyto-nutrient Rich (polyphenols, carotenoids mostly from green leafy, yellow root vegetables and seaweed)

4) Low in Glycemic Load (high quality carbohydrates from staple sweet potato)

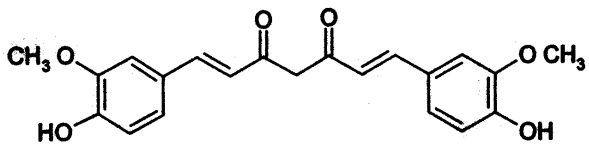
5) Anti-inflammatory (CR, polyphenols, omega 3 fatty acids)



Traditional Okinawan diet food pyramid

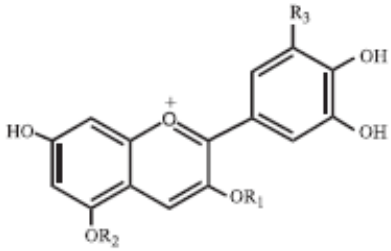
Healthy aging diets other than the Mediterranean: A focus on the Okinawan diet.
Willcox DC, Scapagnini G, Willcox BJ. Mech Ageing Dev. 2014 Jan 21.

Curcuma longa



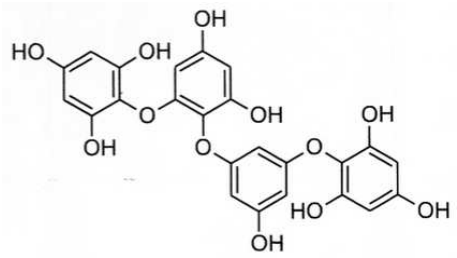
Curcumin

Ipomoera batatas cultivar Ayamurasaki



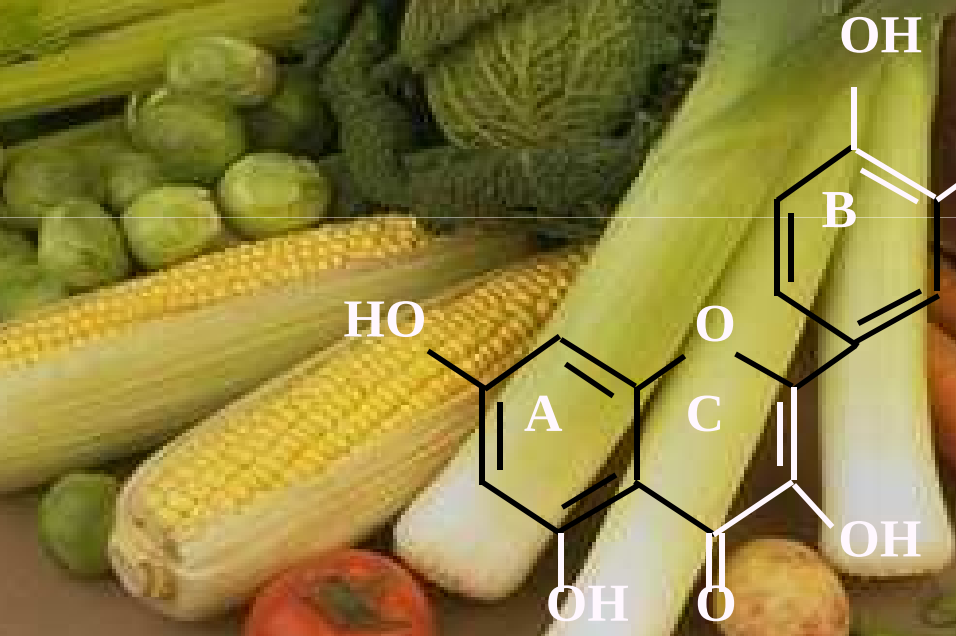
Anthocyanin

Wakame Undaria pinnatifida



Phlorotannin

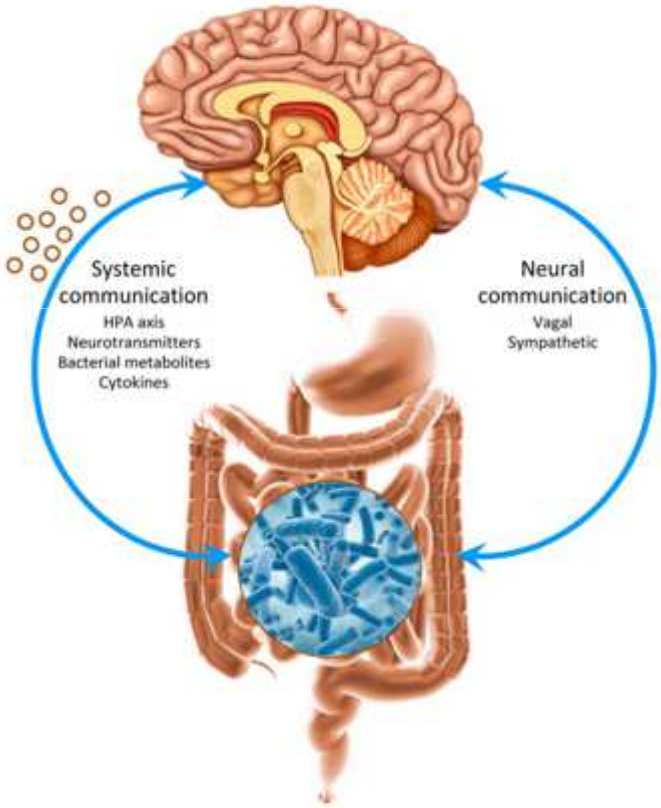
Phenolic Compounds

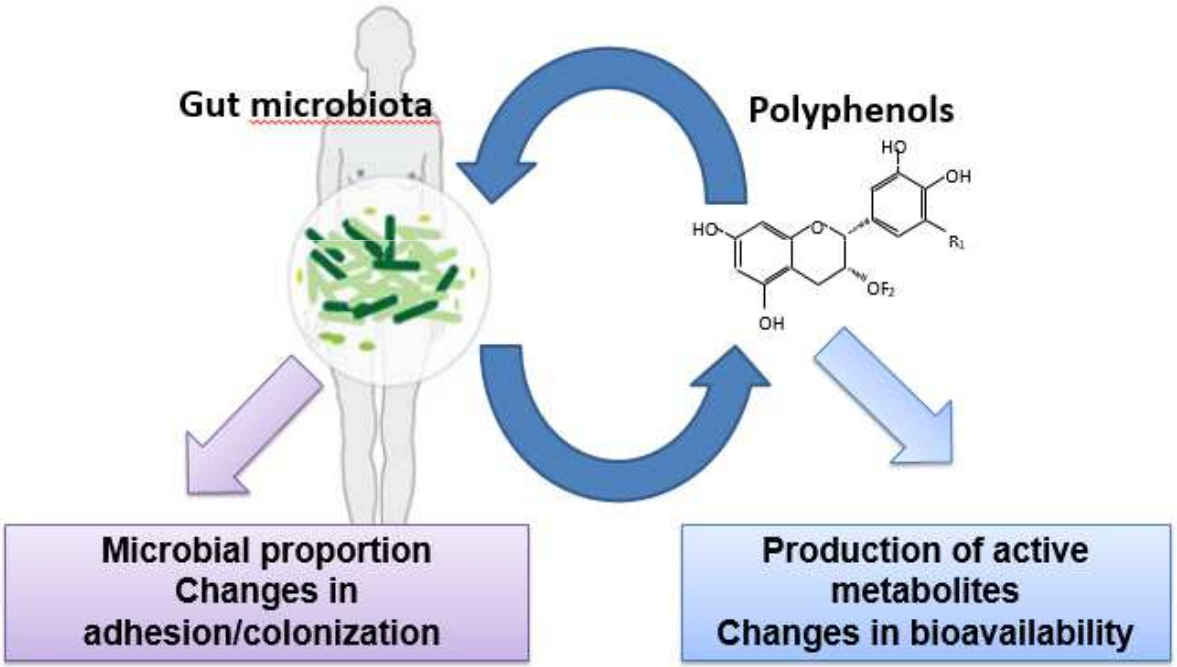


Gut–brain link grabs neuroscientists

13 NOVEMBER 2014 | VOL 515 | NATURE | 175

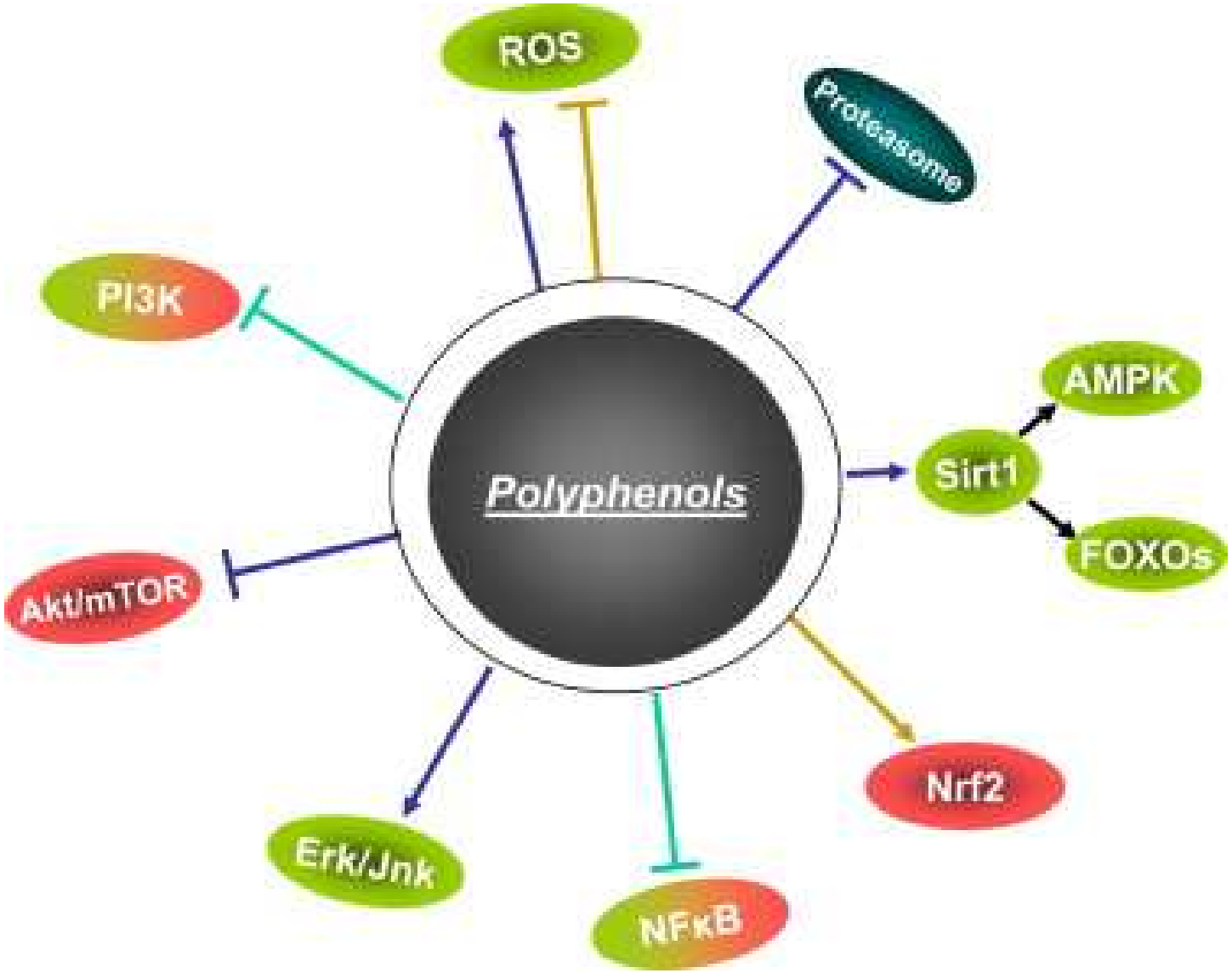
Idea that intestinal bacteria affect mental health gains ground.



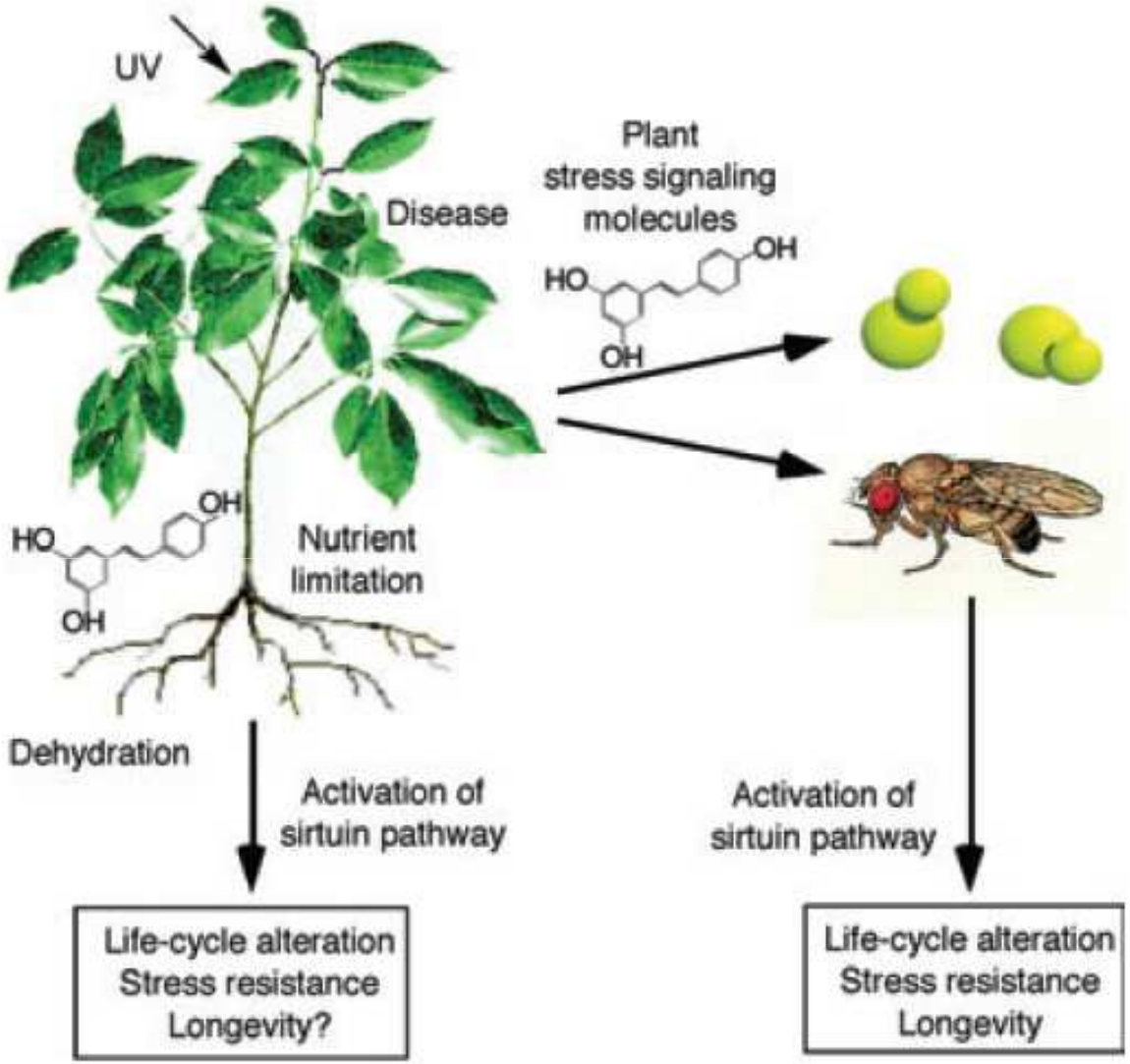


Bidirectional communication channels between the gut microbiome, the gut, and the brain.

Major pathways activated by polyphenols



“ The xenohormesis hypothesis”: organisms have evolved to respond to stress signaling molecules produced by other species in their environment.



Lamming DW, Wood JG, Sinclair DA. Small molecules that regulate lifespan: evidence for xenohormesis. Molecular Microbiology (2004)

1998-2001

Azienda Sanitaria Firenze
Servizio Sanitario della Toscana

Journals of Gerontology: Medical Sciences
cite as: *J Gerontol A Biol Sci Med Sci*, 2015, Vol. 70, No. 9, 1141–1147

The Relationship Between Urinary Total Polyphenols and the Frailty Phenotype in a Community-Dwelling Older Population: The InCHIANTI Study

Mireia Urpi-Sarda,[1,2] Cristina Andres-Lacueva,[1,2] Montserrat Rabassa,[1,2] Carmelinda Ruggiero,[3] Raul Zamora-Ros,[4] Stefania Bandinelli,[5] Luigi Ferrucci,[6] and Antonio Cherubini[7]

The Journal of Nutrition
Nutritional Epidemiology
J. Nutr. 143: 1445–1450, 2013

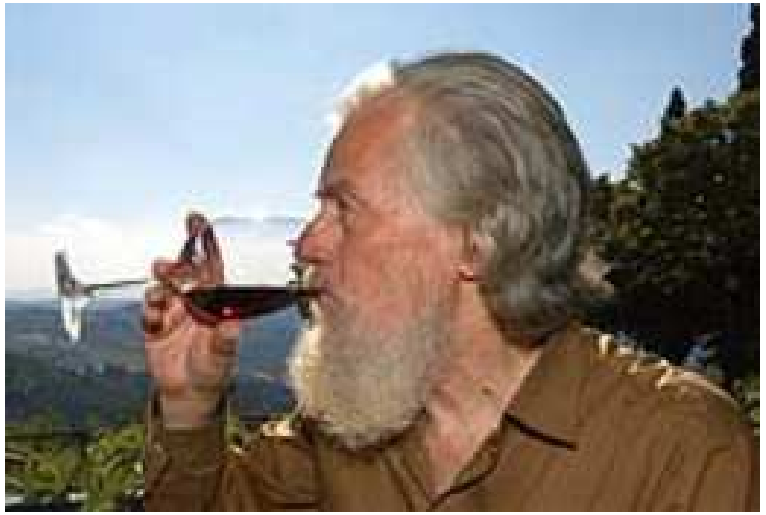
High Concentrations of a Urinary Biomarker of Polyphenol Intake Are Associated with Decreased Mortality in Older Adults[1,2]

Raul Zamora-Ros,[3,4] Montserrat Rabassa,[3] Antonio Cherubini,[5,6]* Mireia Urpí-Sardà,[3] Stefania Bandinelli,[7] Luigi Ferrucci,[8] and Cristina Andres-Lacueva[3]

JAGS 63:938–946, 2015

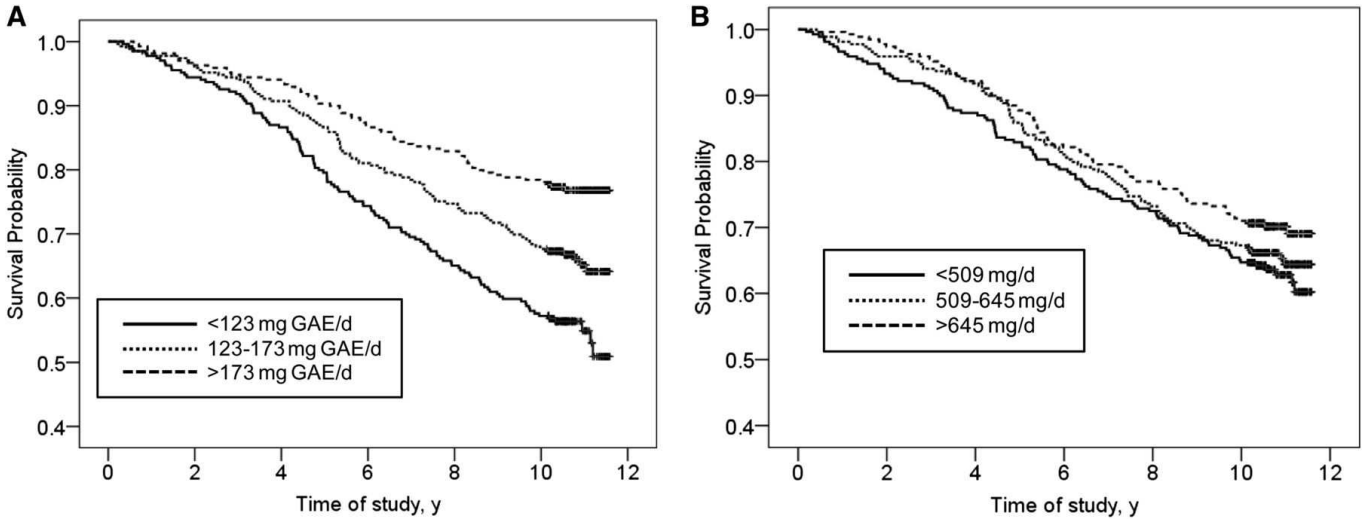
Low Levels of a Urinary Biomarker of Dietary Polyphenol Are Associated with Substantial Cognitive Decline over a 3-Year Period in Older Adults: The Invecchiare in Chianti Study

Montserrat Rabassa, MSc, Antonio Cherubini, MD, PhD,† Raul Zamora-Ros, PhD,‡ Mireia Urpi-Sarda, DPharm, PhD,* Stefania Bandinelli, MD,§ Luigi Ferrucci, MD, PhD,‖ and Cristina Andres-Lacueva, DPharm, PhD**



High Concentrations of a Urinary Biomarker of Polyphenol Intake are Associated with Decreased Mortality in Older Adults

Kaplan-Meier plots of all-cause mortality for 12 y of follow-up in the InCHIANTI study



The overall survival curves of participants by TUP (total urinary polyphenol) (**A**) or TDP (total dietary polyphenol) (**B**). Participants in the highest TUP tertile experienced lower all-cause mortality than those in the lowest TUP tertile.

J Nutr. 2013;143(9):1445-50

JAGS 63:938–946, 2015

Low Levels of a Urinary Biomarker of Dietary Polyphenol Are Associated with Substantial Cognitive Decline over a 3-Year Period in Older Adults: The Invecchiare in Chianti Study

Montserrat Rabassa, MSc, Antonio Cherubini, MD, PhD,† Raul Zamora-Ros, PhD,‡ Mireia Urpi-Sarda, DPharm, PhD,* Stefania Bandinelli, MD,§ Luigi Ferrucci, MD, PhD,‖ and Cristina Andres-Lacueva, DPharm, PhD**

Table 2. Logistic Regression Models Describing the Association Between Total Urinary Polyphenol (TUP) Tertile and 3-Year Substantial Cognitive Decline in Older Adults

	MMSE			TMT-A			TMT-B		
Model	Cutoff mg GAE/d	Cases n	OR (95% CI)	Cutoff mg GAE/d	Cases n	OR (95% CI)	Cutoff mg GAE/d	Cases n	OR (95% CI)
A[a]									
Tertile 1	<126.4	80	1 (reference)	<133.2	46	1 (reference)	<135.8	74	1 (reference)
Tertile 2	126.4–175.5	71	0.82 (0.55–1.21)	133.2–183.7	33	0.56 (0.32–0.97)	135.8–186.8	76	0.99 (0.60–1.64)
Tertile 3	>175.5	52	0.53 (0.35–0.80)	>183.7	24	0.50 (0.28–0.89)	>186.8	71	0.90 (0.54–1.49)
P trend[b]			.003			.02			.67
Continuous (log_2)		203	0.69 (0.52–0.92)		103	0.60 (0.41–0.90)		221	1.03 (0.71–1.50)
B[c]									
Tertile 1	<126.4	80	1 (reference)	<133.2	46	1 (reference)	<135.8	74	1 (reference)
Tertile 2	126.4–175.5	71	0.79 (0.51–1.22)	133.2–183.7	33	0.55 (0.31–0.99)	135.8–186.8	76	1.08 (0.63–1.84)
Tertile 3	>175.5	52	0.53 (0.34–0.85)	>183.7	24	0.52 (0.28–0.96)	>186.8	71	0.95 (0.56–1.62)
P trend[b]			.008			.03			.84
Continuous (log_2)		203	0.71 (0.51–0.97)		103	0.65 (0.42–0.99)		221	1.11 (0.73–1.67)

OR = odds ratio; CI = confidence interval; GAE = gallic acid equivalents.

Substantial cognitive decline was defined as ≥3 points on the Mini-Mental State Examination (MMSE) from baseline to 3 years later and worst 10% of the distribution of subtracting baseline from 3-year follow-up scores in seconds or test discontinued at follow-up for the Trail-Making Test Parts A (TMT-A) and B (TMT-B).

[a] Adjusted for baseline cognitive score only.

[b] Obtained by assigning the median of each tertile as scores.

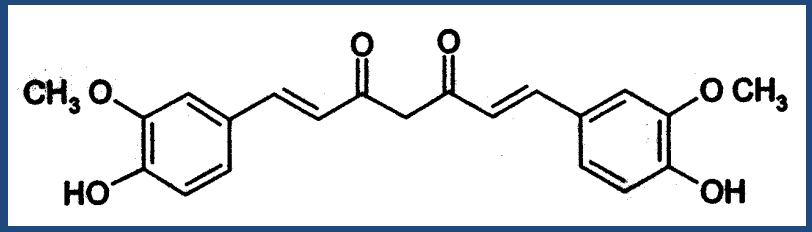
[c] Adjusted for baseline cognitive score, sex, age, education, body mass index, total energy intake, physical activity, total cholesterol, impaired renal function, smoking status, congestive heart failure, cancer, stroke, diabetes mellitus, and depressive symptoms.

Scapagnini G, Colombrita C, Amadio M, D'Agata V, Arcelli E, Sapienza M, Quattrone A, Calabrese V.

Curcumin activates defensive genes and protects neurons against oxidative stress.

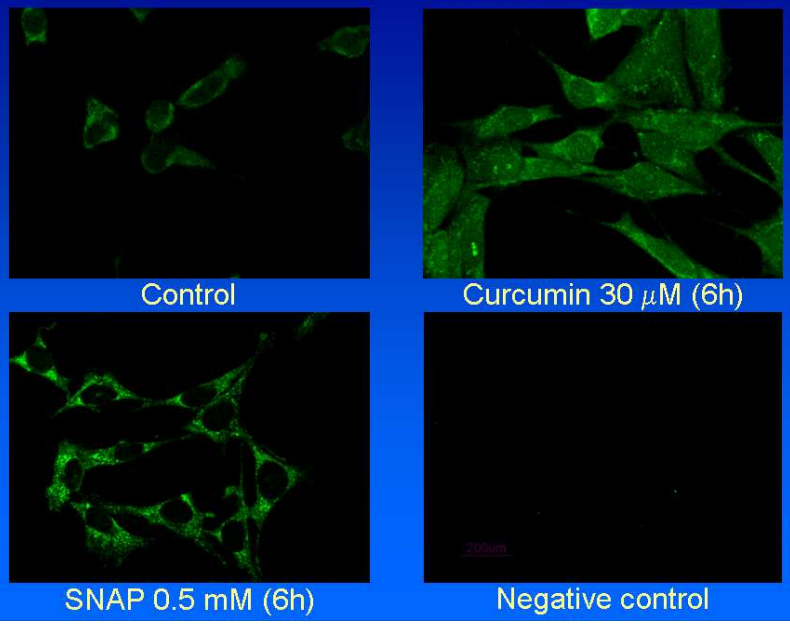
Antioxid Redox Signal. 2006 Mar-Apr;8(3-4):395-403.

Institute of Neurological Sciences, National Research Council (CNR), Catania, Italy.,
Blanchette Rockefeller Neurosciences Institute, West Virginia University, Rockville, Maryland.

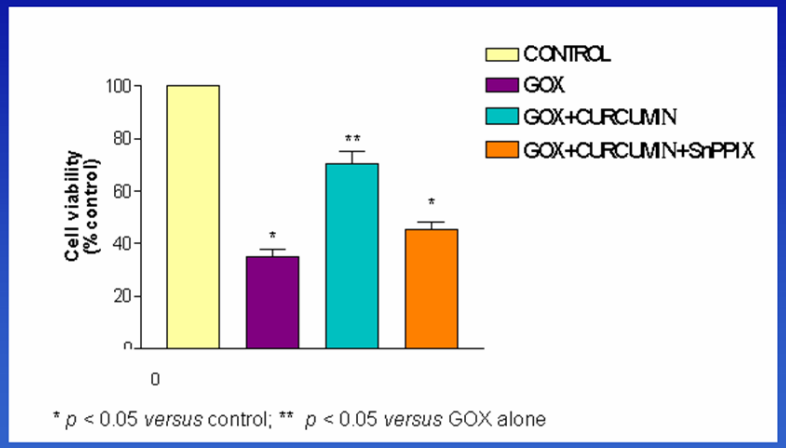


CURCUMIN

Effect of curcumin and SNAP on HO-1 protein expression in astrocytes



Effect of curcumin on glucose oxidase (GOX) mediated cellular injury in cortical neurons



jbc THE JOURNAL OF BIOLOGICAL CHEMISTRY

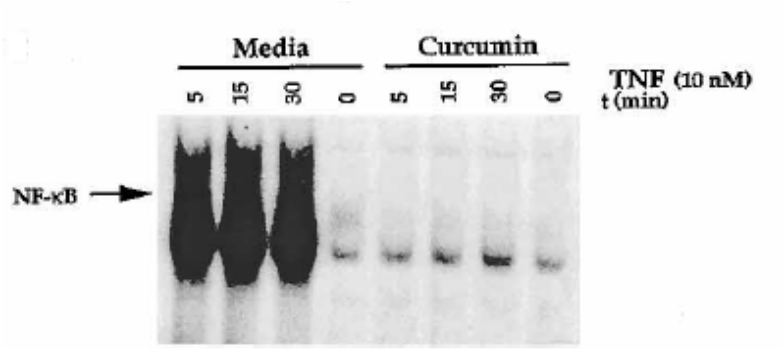
THE JOURNAL OF BIOLOGICAL CHEMISTRY
Vol. 270, No. 42, Issue of October 20, pp. 24995–25000, 1995
Printed in U.S.A.

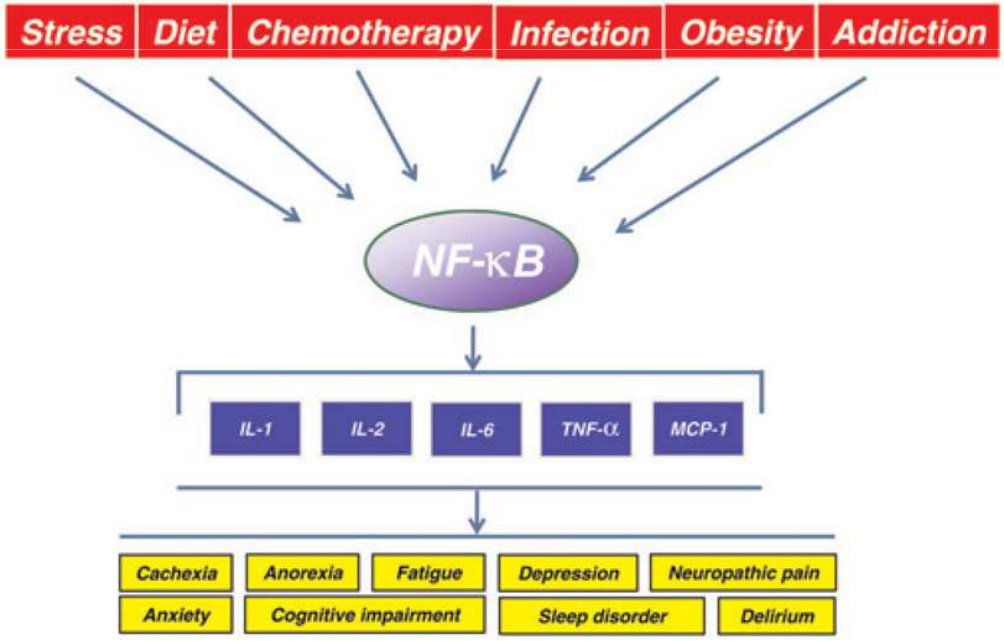
Activation of Transcription Factor NF-κB Is Suppressed by Curcumin (Diferulolylmethane)*

(Received for publication, July 13, 1995, and in revised form, August 11, 1995)

Sanjaya Singh and Bharat B. Aggarwal‡

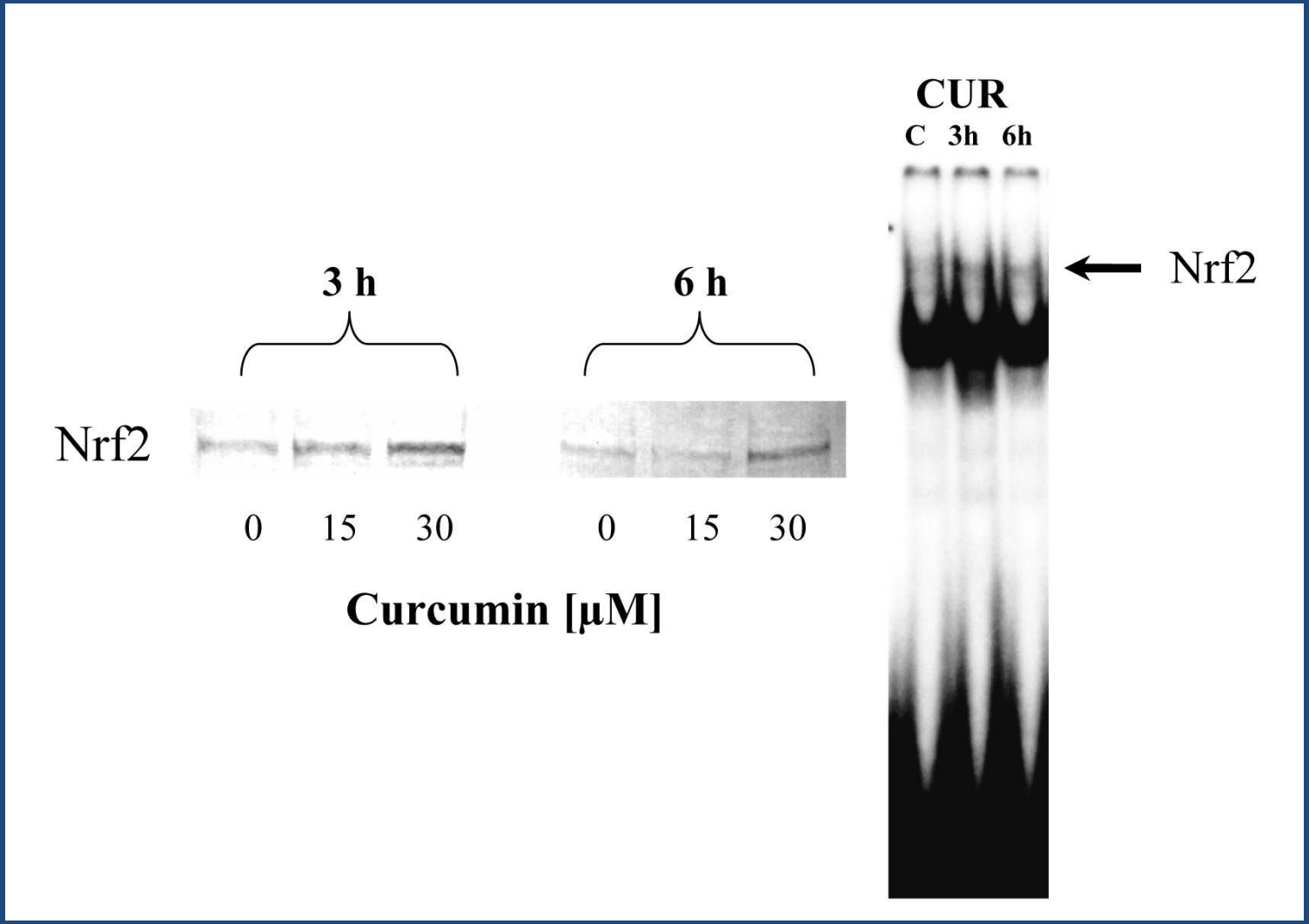
From the Cytokine Research Laboratory, Department of Molecular Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, Texas 77030



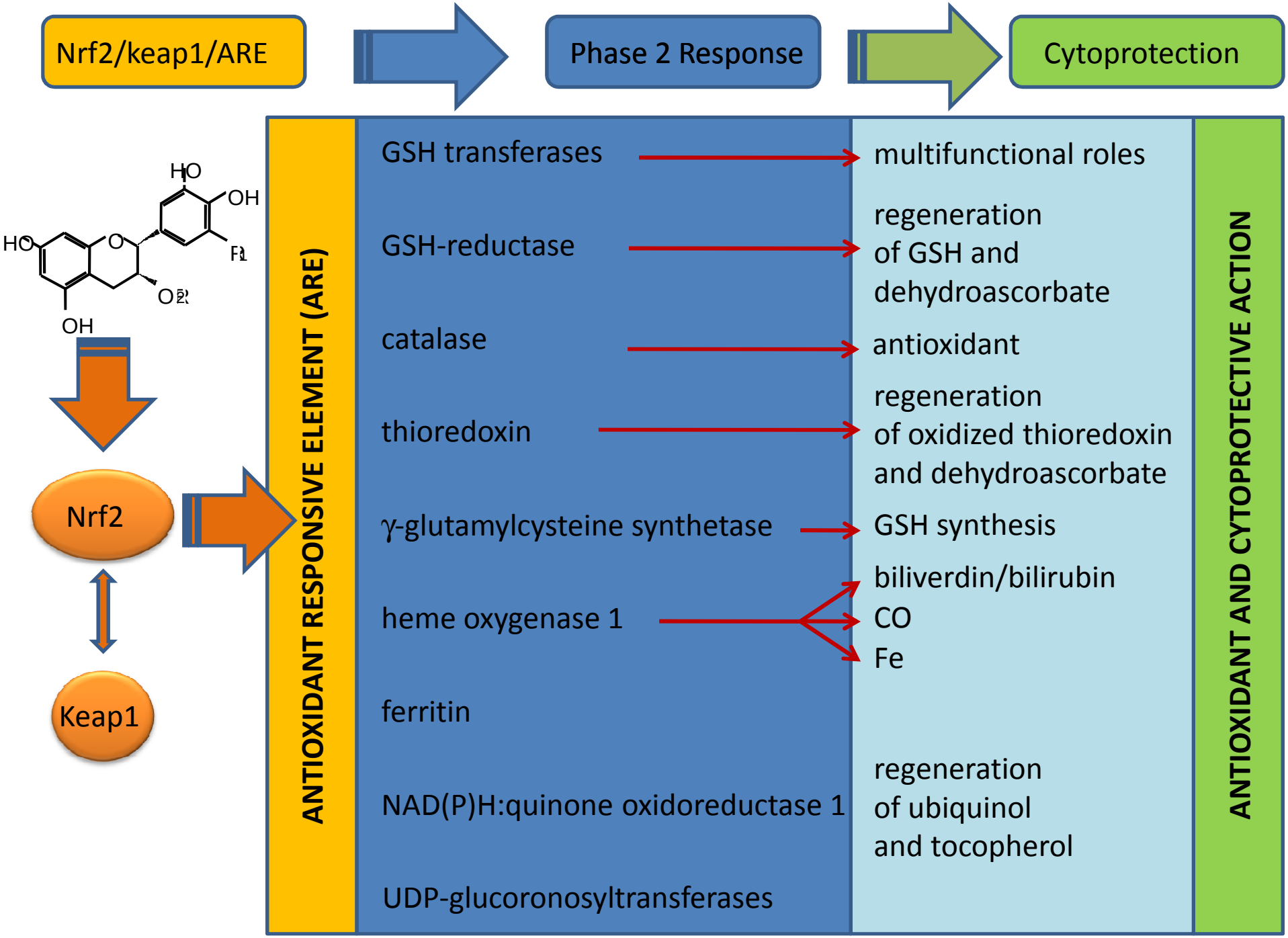


Regulation of inflammatory cytokines through activation of NF-κB

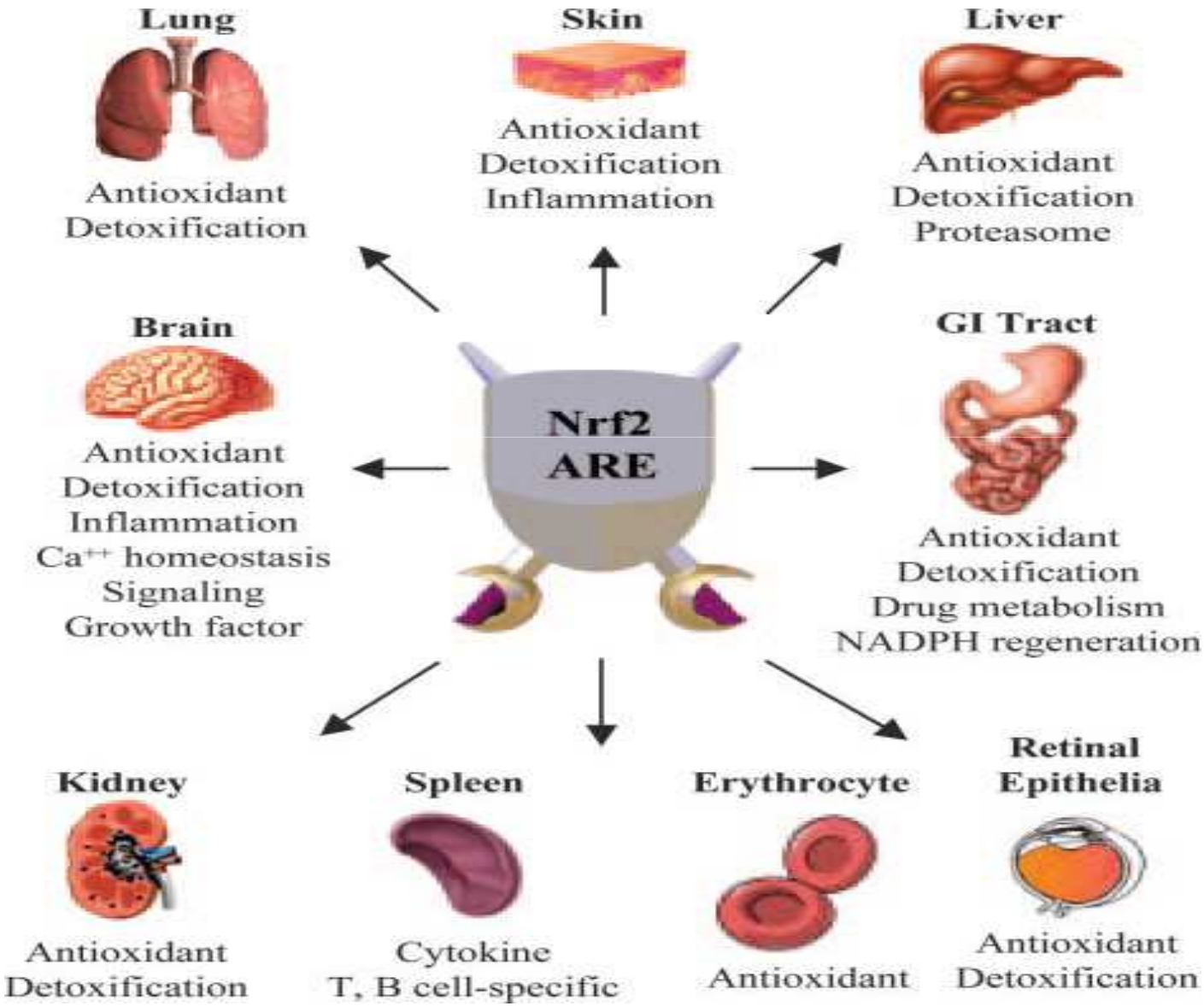
Curcumin activates Nrf2 expression and stimulates ARE-binding activity



Motterlini R. et al. Biochem J. 2003


Nrf2/keap1/ARE
Phase 2 Response
Cytoprotection
HO
OH
HO
O
OH
OH
Nrf2
Keap1
ANTIOXIDANT RESPONSIVE ELEMENT (ARE)
GSH transferases
GSH-reductase
catalase
thioredoxin
γ-glutamylcysteine synthetase
heme oxygenase 1
ferritin
NAD(P)H:quinone oxidoreductase 1
UDP-glucoronosyltransferases
multifunctional roles
regeneration of GSH and dehydroascorbate
antioxidant
regeneration of oxidized thioredoxin and dehydroascorbate
GSH synthesis
biliverdin/bilirubin
CO
Fe
regeneration of ubiquinol and tocopherol
ANTIOXIDANT AND CYTOPROTECTIVE ACTION

Multi-organ protection by the Nrf2 pathway

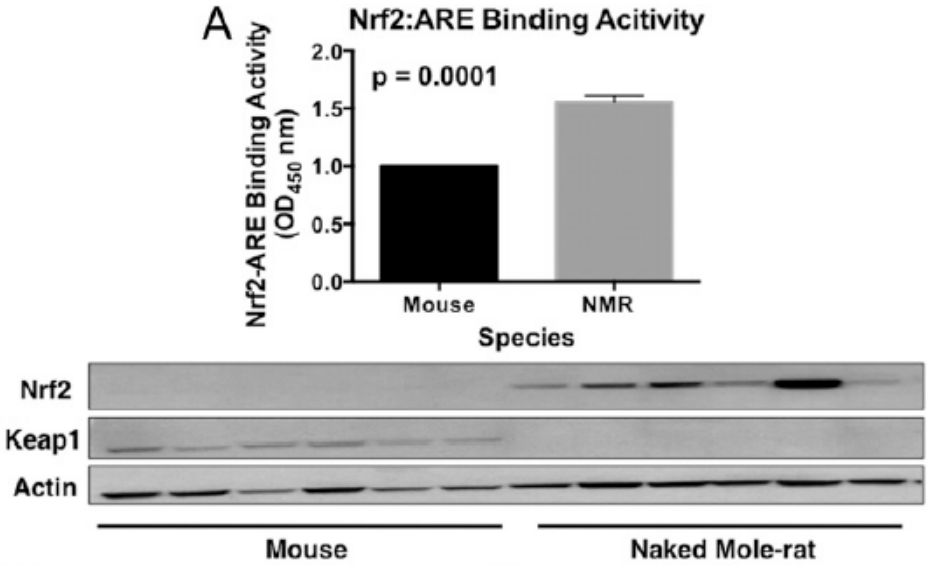


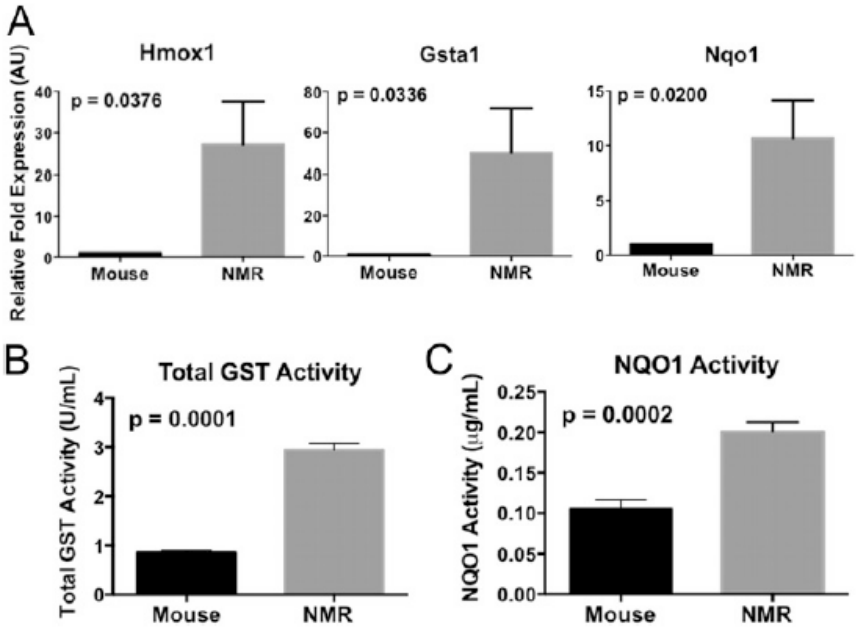
Regulation of Nrf2 signaling and longevity in naturally long-lived rodents

Kaitlyn N. Lewis[a,b], Emily Wason[c], Yael H. Edrey[b,c], Deborah M. Kristan[d], Eviatar Nevo[e], and Rochelle Buffenstein[a,b,c,1]

[a]Departments of Cellular and Structural Biology and [c]Physiology and [b]Barshop Institute for Longevity and Aging Studies, University of Texas Health Science Center at San Antonio, San Antonio, TX 78229; [d]Department of Biological Sciences, California State University, San Marcos, CA 92096; and [e]Institute of Evolution, University of Haifa, Haifa 31905, Israel

3722–3727 | PNAS | March 24, 2015 | vol. 112 | no. 12

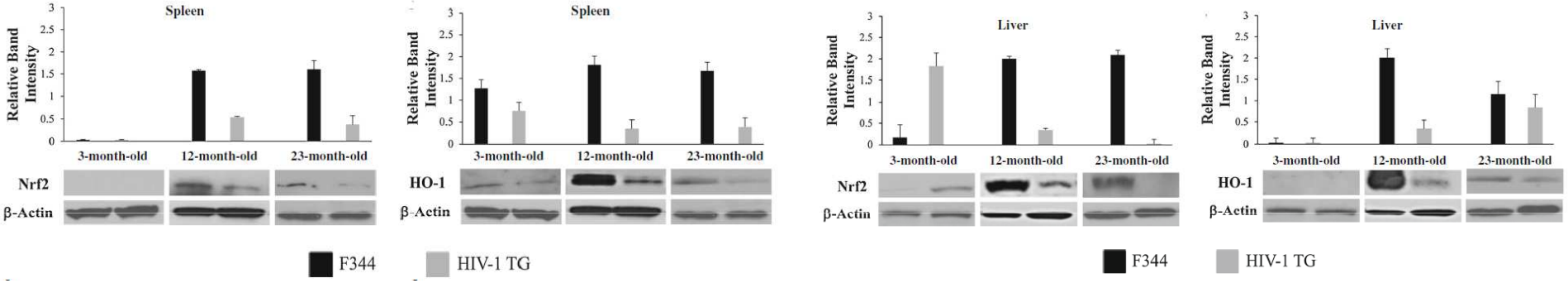


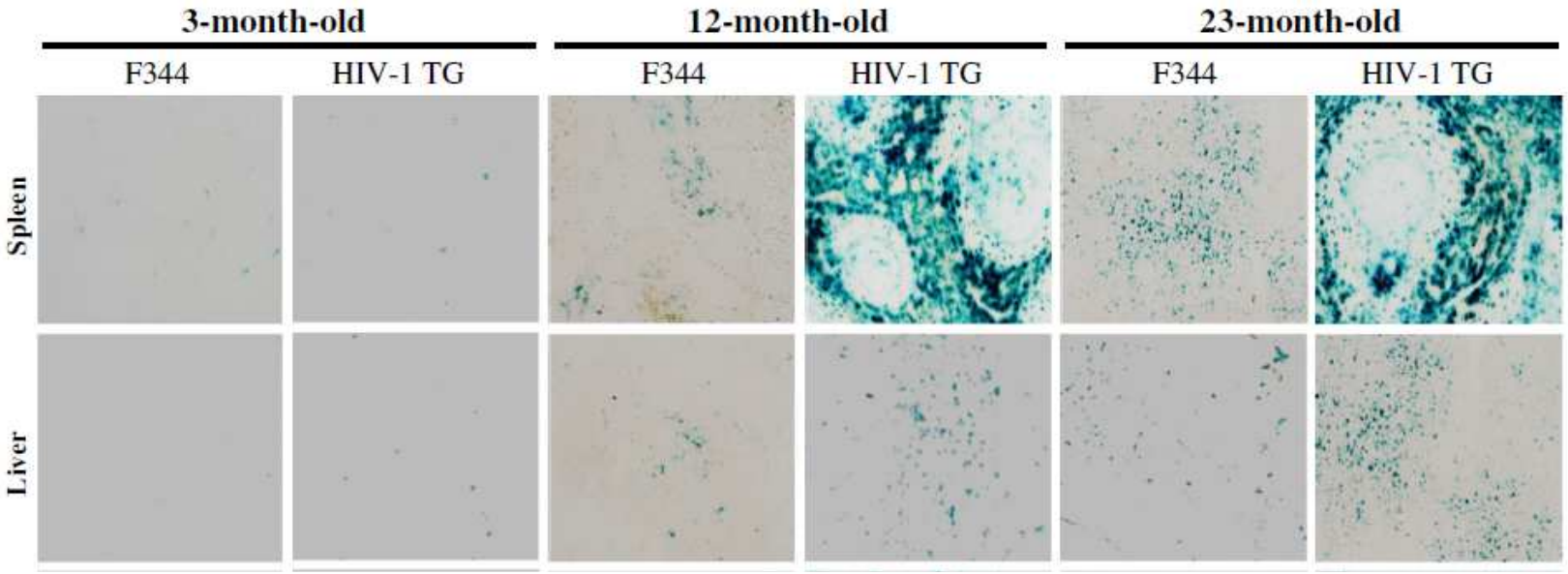


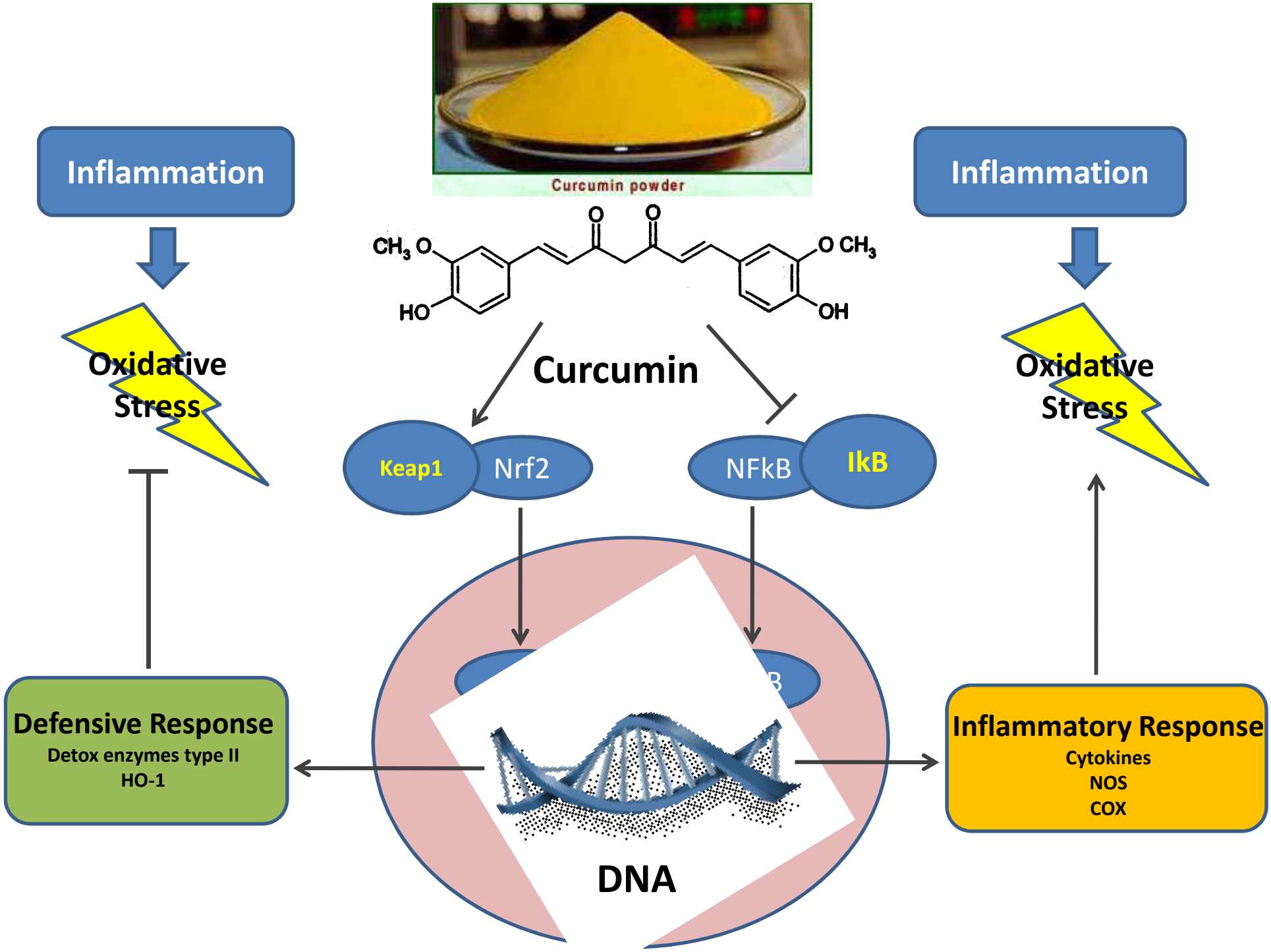
Altered expression pattern of Nrf2/HO-1 axis during accelerated-senescence in HIV-1 transgenic rat

Biogerontology Received: 25 January 2014 / Accepted: 23 June 2014

Sergio Davinelli · Giovanni Scapagnini · Frank Denaro · Vittorio Calabrese · Francesca Benedetti · Selvi Krishnan · Sabrina Curreli · Joseph Bryant · Davide Zella






Curcumin powder
Inflammation
Inflammation
Oxidative Stress
Oxidative Stress
Curcumin
Keap1
Nrf2
NFkB
IkB
Defensive Response
Detox enzymes type II
HO-1
Inflammatory Response
Cytokines
NOS
COX
DNA

Epidemiological studies showed that in India, where curcumin is widely used in daily diet, there is a reduced age-adjusted prevalence of AD (in patients between 70 and 79 years of age is 4.4 fold less than that of the United States), as well as a lower prevalence of Parkinson's disease.

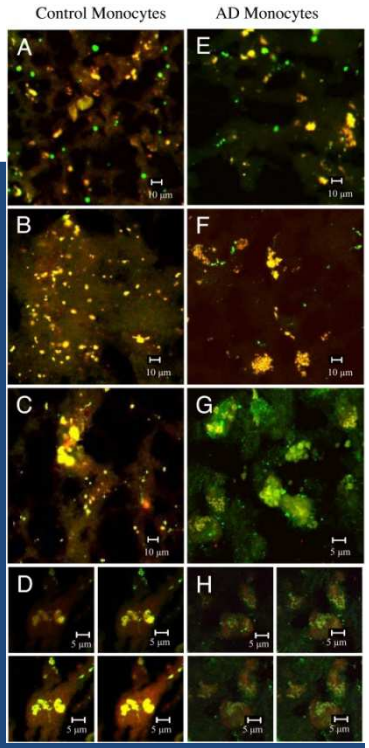
Chandra V, Pandav R, Dodge HH, Johnston JM, Belle SH, DeKosky ST, and Ganguli M. **Incidence of Alzheimer's disease in a rural community in India: the Indo-US study.** *Neurology* 57: 985-989, 2001.

Muthane U, Yasha TC, and Shankar SK. **Low numbers and no loss of melanized nigral neurons with increasing age in normal human brains from India.** *Ann Neurol* 43: 283-287, 1998.

Ng TP, Chiam PC, Lee T, Chua HC, Lim L, Kua EH. **Curry consumption and cognitive function in the elderly.** *Am J Epidemiol* 164(9):898-9, 2006

PNAS

Proceedings of the National Academy of Sciences of the United States of America



Proc Natl Acad Sci U S A. 2007 July 31; 104(31): 12849–12854.

Innate immunity and transcription of MGAT-III and Toll-like receptors in Alzheimer's disease patients are improved by bisdemethoxycurcumin

Fiala M. et al.

Department of Medicine, Greater Los Angeles Veteran's Affairs Medical Center

J Clin Psychopharmacol. 2008 Feb;28(1):110-3.

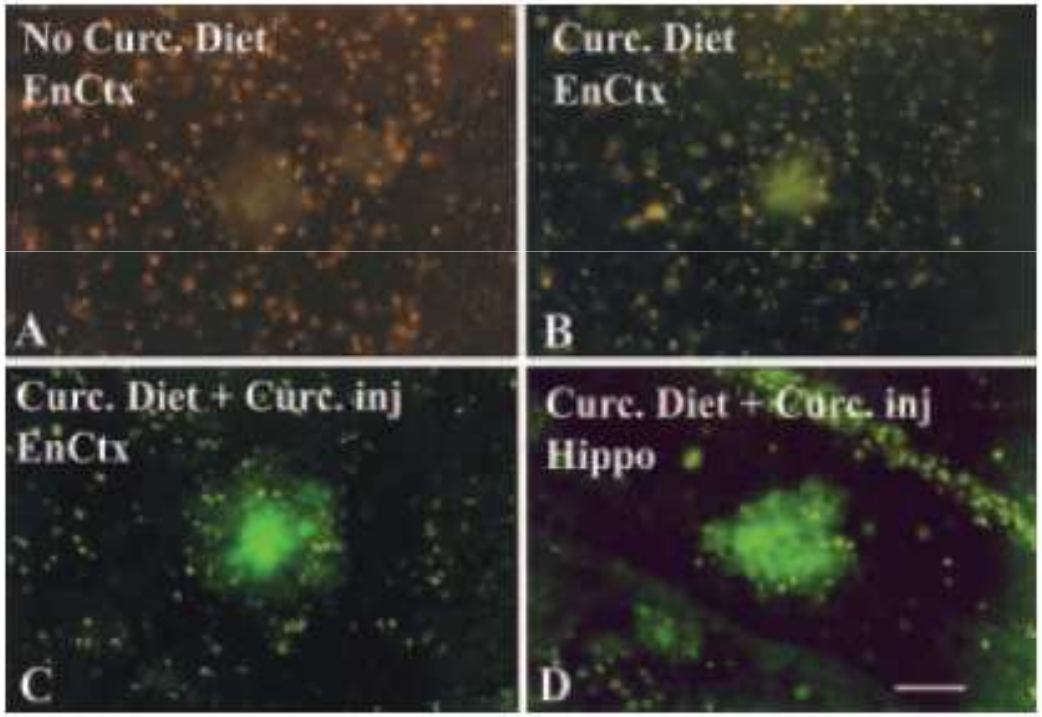
Six-month randomized, placebo-controlled, double-blind, pilot clinical trial of curcumin in patients with Alzheimer disease.

Baum L. et al

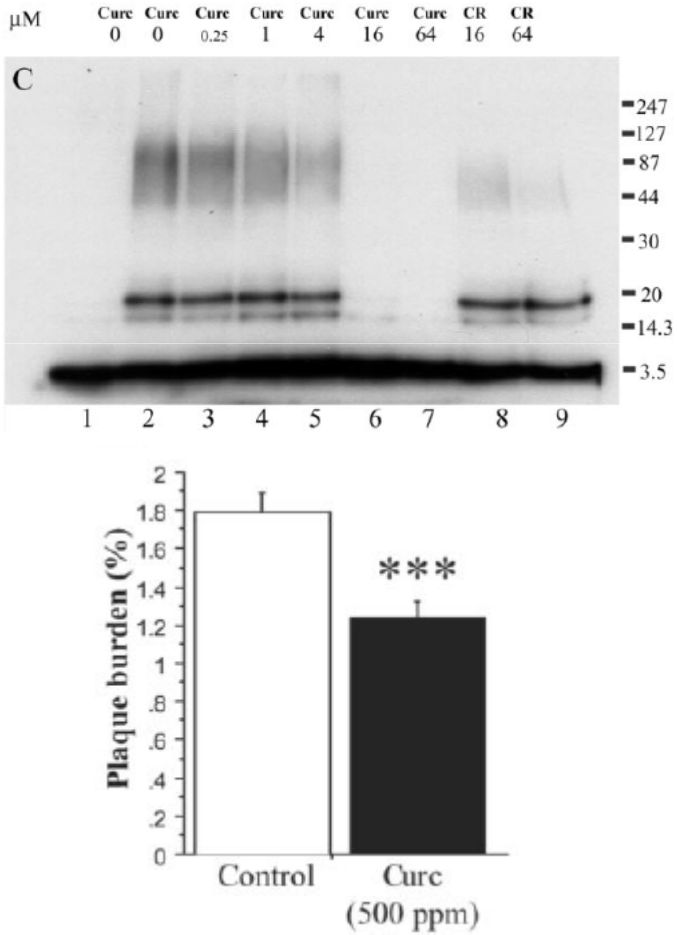
THE JOURNAL OF BIOLOGICAL CHEMISTRY Vol. 280, No. 7, Issue of February 18, pp. 5892–5901, 2005

Curcumin Inhibits Formation of Amyloid β Oligomers and Fibrils, Binds Plaques, and Reduces Amyloid *in Vivo**

Fusheng Yang‡§, Giselle P. Lim‡§, Aynun N. Begum‡§, Oliver J. Ubeda‡§, Mychica R. Simmons‡§, Surendra S. Ambegaokar‡§, Pingping Chen‡§, Rakez Kayed¶, Charles G. Glabe¶, Salley A. Frautschy‡§‖, and Gregory M. Cole‡§‖**



Curcumin crosses the blood-brain barrier and binds to plaques *in vivo in* Tg2576 mice

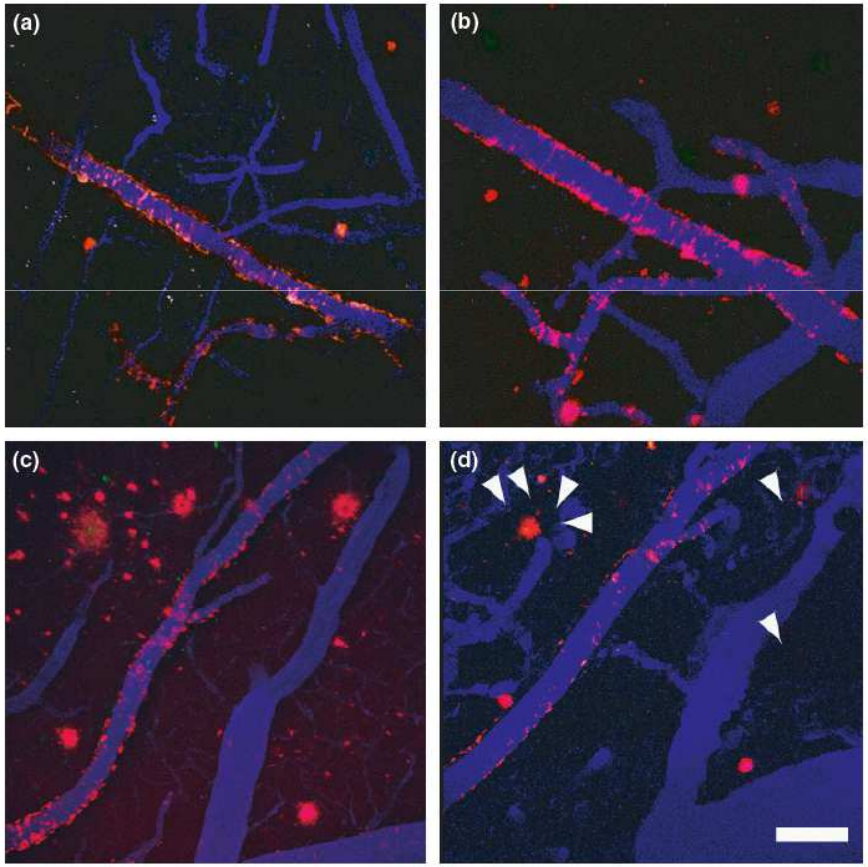


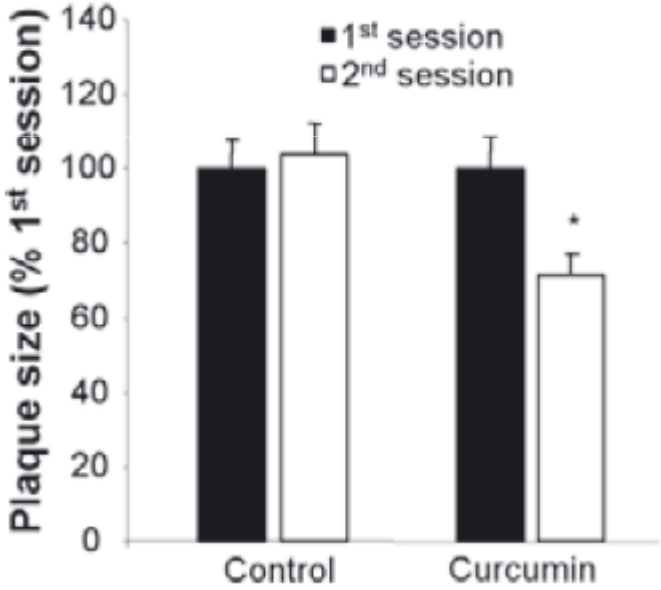
Curcumin inhibits formation of Aβ oligomers.

Journal of Neurochemistry, 2007, **102**, 1095–1104

Curcumin labels amyloid pathology *in vivo*, disrupts existing plaques, and partially restores distorted neurites in an Alzheimer mouse model

M. Garcia-Alloza, L. A. Borrelli, A. Rozkalne, B. T. Hyman and B. J. Bacskai





Representative longitudinal imaging of plaques with multiphoton microscopy before and after curcumin treatment in an APPswe/PS1dE9 mouse.

Alzheimer

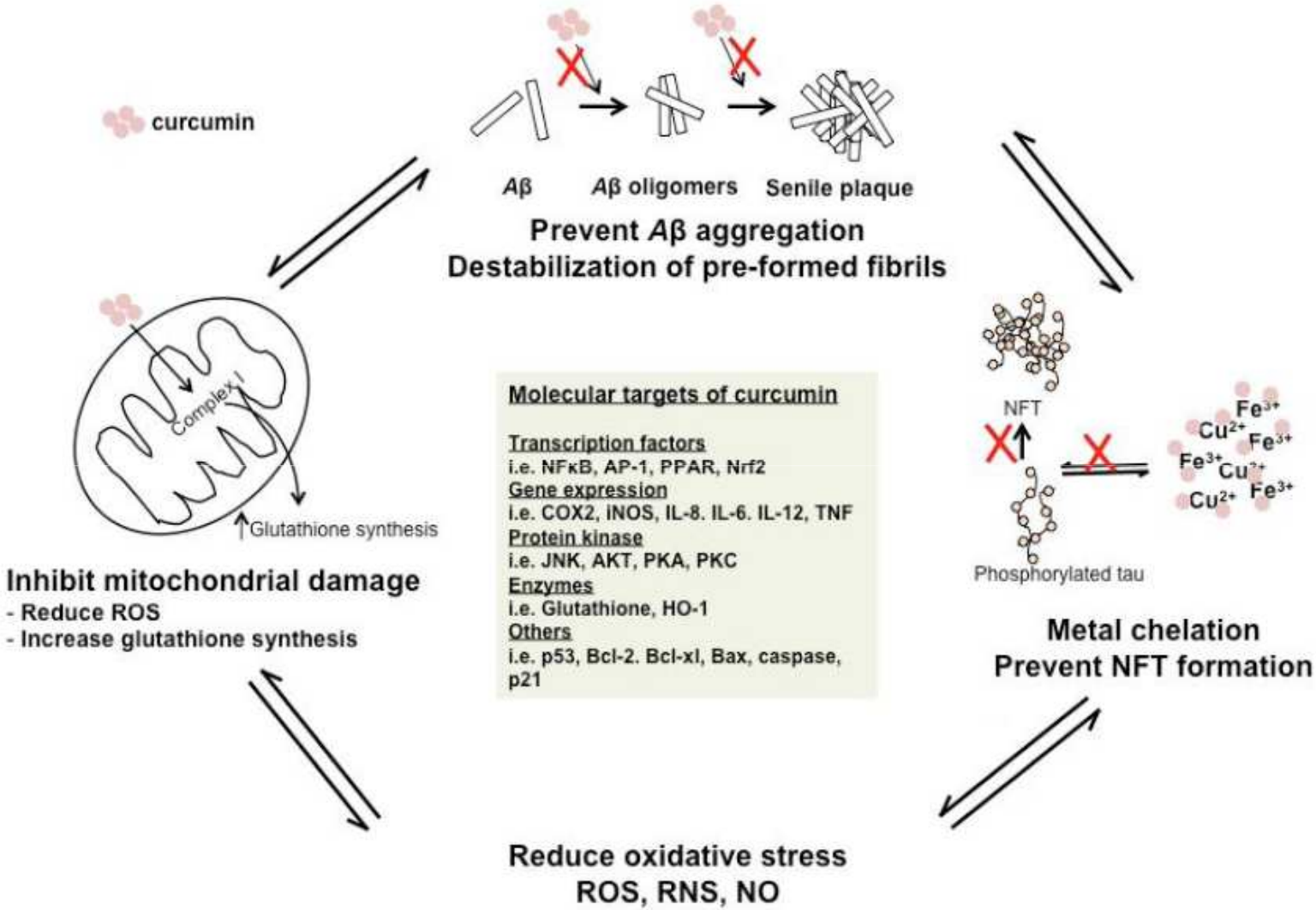


Fig. (6). Proposed molecular targets of curcumin against AD. Curcumin is known to prevent Aβ aggregation and destabilizes pre-formed fibrils. In addition, curcumin protects from mitochondrial dysfunction by decreasing the load of ROS and increases the synthesis of glutathione. Curcumin also prevents neuronal loss from oxidative damage by scavenging NO-based radicals; which thus neutralizes ROS and RNS-based radicals. Furthermore, curcumin is a potent metal-chelator and inhibits the formation of NFT.

The “Alzheimer's disease signature”: potential perspectives for novel biomarkers.

Immunity & Ageing 2011, 8:7
http://www.immunityageing.com/content/8/1/7/

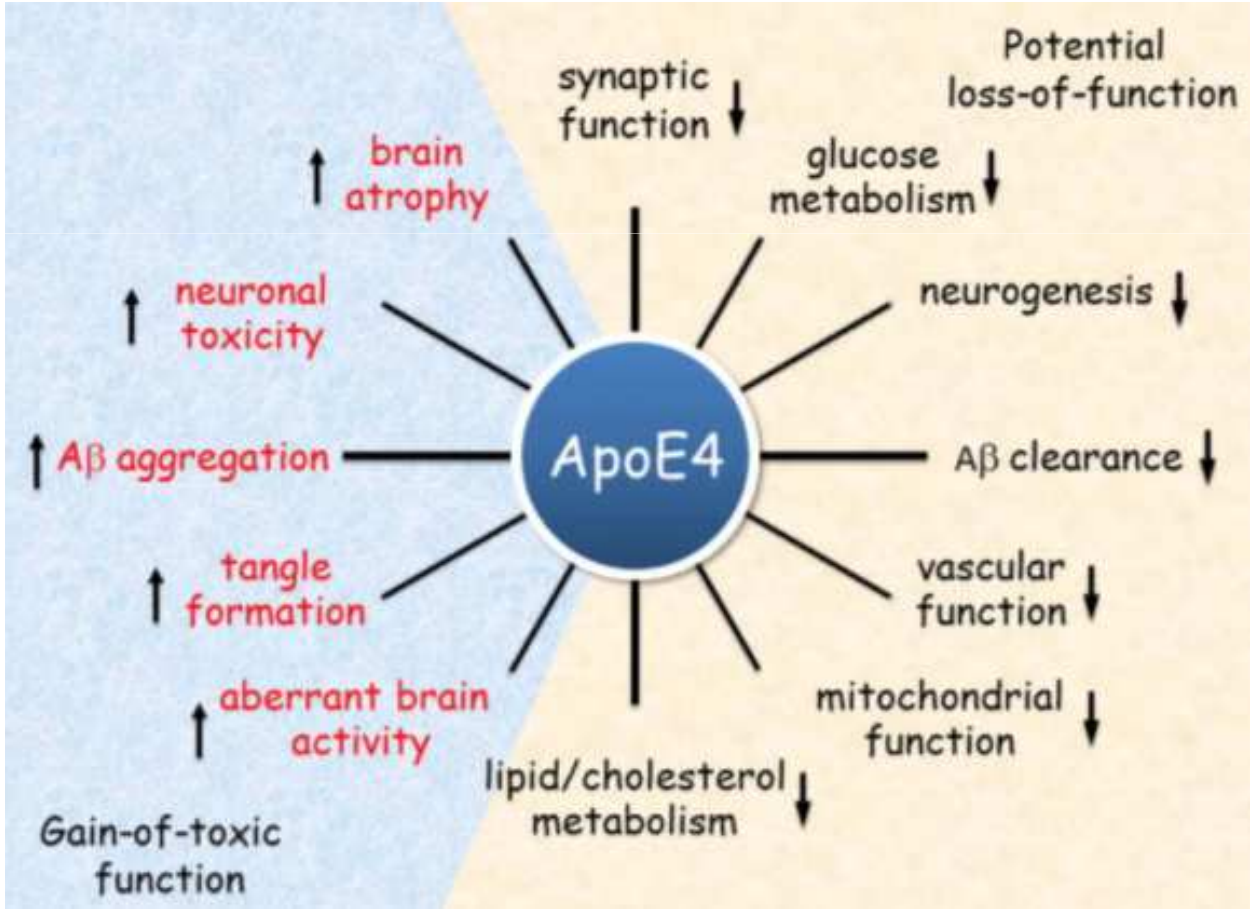
Sergio Davinelli[1], Mariano Intrieri[1], Claudio Russo[1], Alfonso Di Costanzo[1], Davide Zella[2], Paolo Bosco[3], Giovanni Scapagnini[1]

Schematic Overview of Major Alzheimer’s Disease (AD) Gene

Familial Genes	Locus	Functions
APP	21q21.3	APP gene encodes a membrane protein cleaved by secretase. Mutations in App locus causes autosomal dominant early onset AD and cerebroarterial amyloidosis.
PS1	14q24.2	PS1 is involved in APP processing and mutations can interfere the production of Aβ42 and to form plaques. Numerous alternatively spliced transcript variants encoding different isoforms have been identified for this gene.
PS2	1q42.13	Regulate APP processing as a part of the α-secretase complex. Familial mutations can change the production of Aβ42.
Risk Genes		
APOE	19q13.32	ApoE regulates the normal catabolism of triglyceride-rich lipoprotein constituents. APOE binds Aβ and it is involved in Aβ clearance. Subjects carrying the E4 allele have an increased amyloid burden.
TAU	17q21.31	The transcript undergoes complex alternative splicing and tau exists as six splice isoforms. The mutations can alter microtubule binding efficacy.
DYRK1A	21q22.13	DYRK1A is localized in the critical region of chromosome 21 and is involved in tau and APP phosphorylation. Firstly the activity is upregulated by Aβ and APP phosphorylation result in increased amyloidogenic processing with BACE interaction.
GSK3β	3q13.33	The overexpression of this gene may be relevant for AD. GSK-3 phosphorylates tau and presenilin-1, which are involved in the development of AD. The phosphorylation of tau leads to tangle formation and APP cleavage products can activate GSK3β resulting increased tau phosphorylation.

The role of Apolipoprotein E4 in Alzheimer disease pathogenesis

Genotype	E2/E2	E2/E3	E2/E4	E3/E3	E3/E4	E4/E4
Disease Risk	40% less likely	40% less likely	2.6 times more likely	Average risk	3.2 times more likely	14.9 times more likely



RESEARCH ARTICLE

The oral bioavailability of curcumin from micronized powder and liquid micelles is significantly increased in healthy humans and differs between sexes

Christina Schiborr[1], *Alexa Kocher*[1], *Dariush Behnam*[2], *Josef Jandasek*[3], *Simone Toelstede*[3] *and Jan Frank*[1]

[1] Institute of Biological Chemistry and Nutrition, University of Hohenheim, Stuttgart, Germany
[2] AQUANOVA AG, Darmstadt, Germany
[3] Raps GmbH & Co. KG, Kulmbach, Germany

Scope: Curcumin revealed various health-beneficial properties in numerous studies. However its bioavailability is low due to its limited intestinal uptake and rapid metabolism. The aim of our project was to develop novel curcumin formulations with improved oral bioavailability and to study their safety as well as potential sex-differences.

Methods and results: In this crossover study, healthy subjects (13 women, 10 men) took, in random order, a single oral dose of 500 mg curcuminoids as native powder, micronized powder, or liquid micelles. Blood and urine samples were collected for 24 h and total curcuminoids and safety parameters were quantified. Based on the area under the plasma concentration–time curve (AUC), the micronized curcumin was 14-, 5-, and 9-fold and micellar curcumin 277-, 114- and 185-fold better bioavailable than native curcumin in women, men, and all subjects, respectively. Thus, women absorbed curcumin more efficiently than men. All safety parameters remained within the reference ranges following the consumption of all formulations.

Conclusion: Both, the micronized powder and in particular the liquid micellar formulation of curcumin significantly improved its oral bioavailability without altering safety parameters and may thus be ideally suited to deliver curcumin in human intervention trials. The observed sex differences in curcumin absorption warrant further investigation.

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Revised: November 8, 2013
Accepted: November 17, 2013

Keywords:
Bioavailability / *Curcuma longa* / Curcumin / Healthy humans / Safety / Sex differences

Journal of Psychopharmacology

J Psychopharmacol May 2015 29:642-651

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

Cox KH[1], Pipingas A[1], Scholey AB[2].

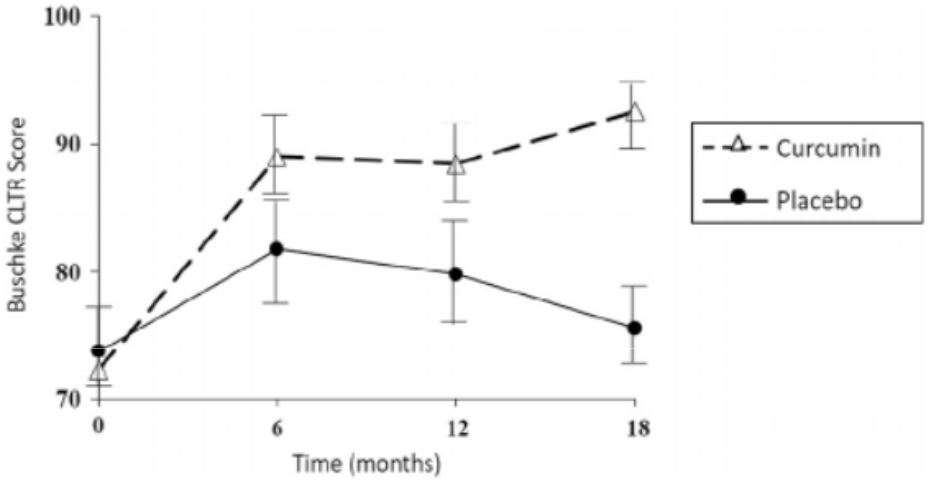
[1]Centre for Human Psychopharmacology, Swinburne University of Technology, Melbourne, VIC, Australia.
[2]Centre for Human Psychopharmacology, Swinburne University of Technology, Melbourne, VIC, Australia

Curcumin possesses many properties which may prevent or ameliorate pathological processes underlying age-related cognitive decline, dementia or mood disorders. These benefits in preclinical studies have not been established in humans. This randomized, double-blind, placebo-controlled trial examined the acute (1 and 3 h after a single dose), chronic (4 weeks) and acute-on-chronic (1 and 3 h after single dose following chronic treatment) effects of solid lipid curcumin formulation (400 mg as Longvida®) on cognitive function, mood and blood biomarkers in 60 healthy adults aged 60–85. One hour after administration curcumin significantly improved performance on sustained attention and working memory tasks, compared with placebo. Working memory and mood (general fatigue and change in state calmness, contentedness and fatigue induced by psychological stress) were significantly better following chronic treatment. A significant acute-on-chronic treatment effect on alertness and contentedness was also observed. Curcumin was associated with significantly reduced total and LDL cholesterol and had no effect on hematological safety measures. To our knowledge this is the first study to examine the effects of curcumin on cognition and mood in a healthy older population or to examine any acute behavioral effects in humans. Results highlight the need for further investigation of the potential psychological and cognitive benefits of curcumin in an older population.

Am J Geriatr Psychiatry 26:3, March 2018

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

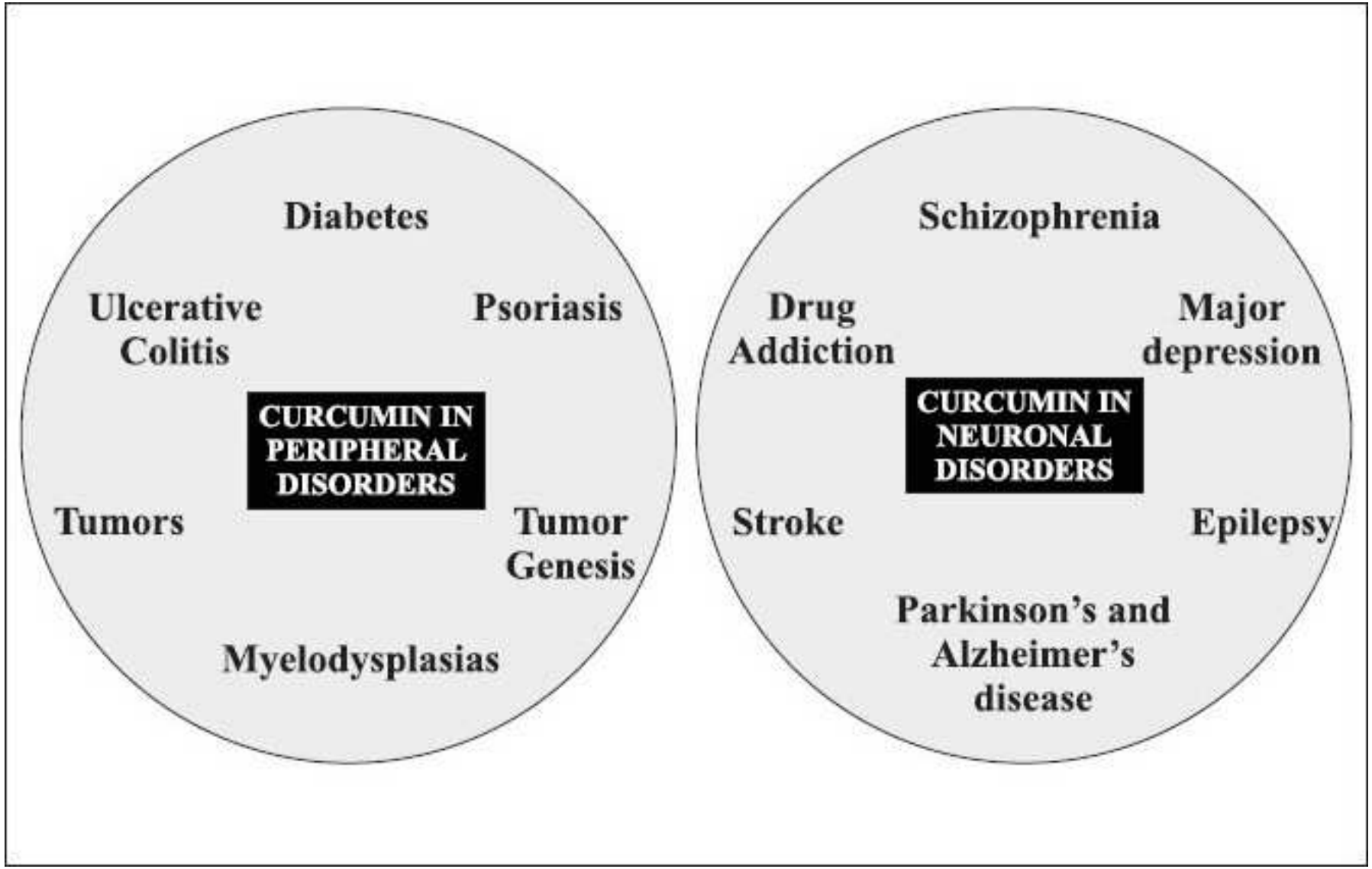
Gary W. Small, et al.



Conclusions: Daily oral curcumin may lead to improved memory and attention in non-demented adults. The FDDNP-PET findings suggest that symptom benefits are associated with decreases in amyloid and tau accumulation in brain regions modulating mood and memory.

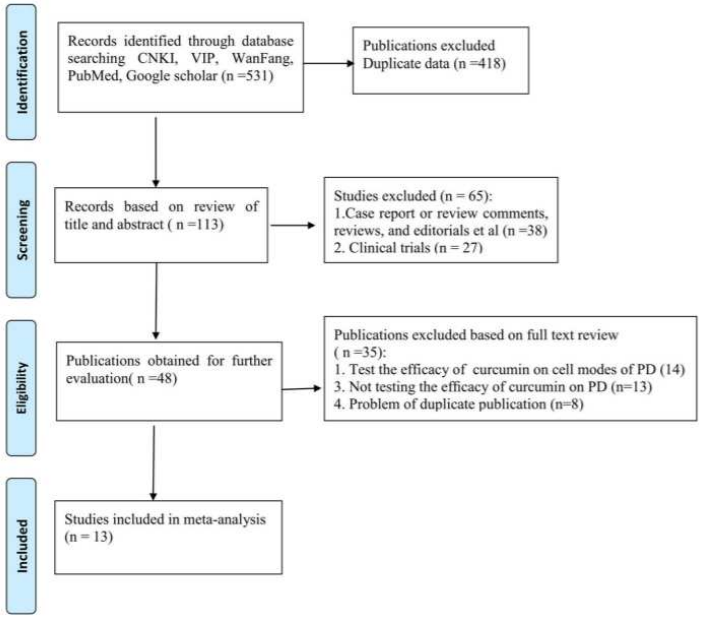
TABLE 3. Baseline and 18-Month Regional FDDNP Binding Levels, Percent Changes, and Effect Sizes

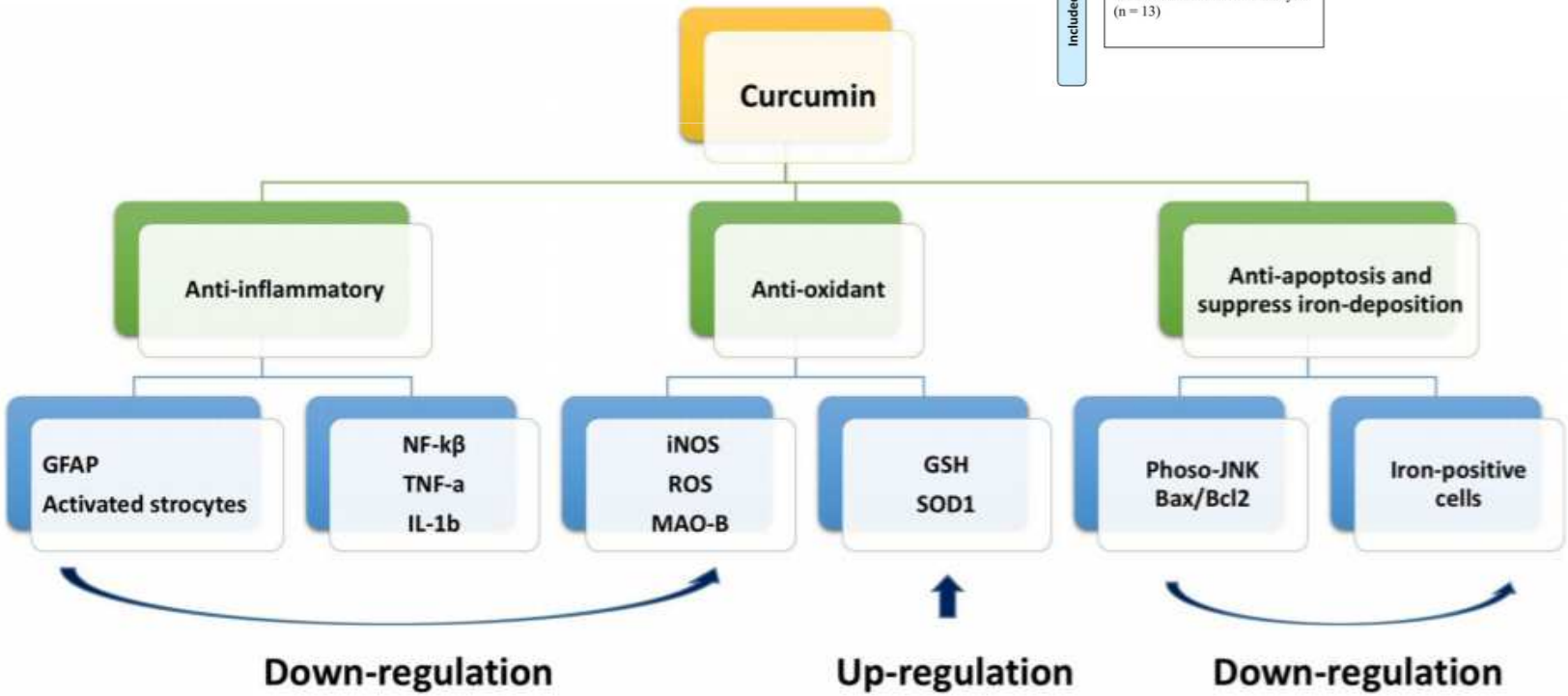
	Curcumin			Placebo			Effect Size		
Regions	Baseline	18-Month	% Change	Baseline	18-Month	% Change	Within Curcumin	Within Placebo	Between Group
Frontal	1.11 (0.05)	1.10 (0.06)	−0.63	1.15 (0.08)	1.13 (0.08)	−1.52	−0.13	−0.22	−0.10
Parietal	1.04 (0.06)	1.06 (0.06)	1.38	1.07 (0.05)	1.07 (0.05)	−0.51	0.24	−0.11	−0.35
Lat Temp	1.11 (0.05)	1.12 (0.05)	0.64	1.13 (0.08)	1.14 (0.07)	0.50	0.14	0.08	−0.06
Med Temp	1.16 (0.06)	1.17 (0.07)	0.52	1.18 (0.07)	1.19 (0.06)	1.31	0.09	0.23	0.14
Post Cingul	1.13 (0.06)	1.12 (0.05)	−0.88	1.14 (0.08)	1.14 (0.06)	−0.17	−0.19	−0.03	0.16
Ant Cingul	1.18 (0.06)	1.18 (0.05)	−0.16	1.22 (0.09)	1.20 (0.08)	−1.50	−0.04	−0.21	−0.17
Amygdala[a]	1.29 (0.06)	1.26 (0.06)	−2.05	1.31 (0.11)	1.32 (0.10)	0.62	−0.41	0.08	0.48
Hypothalamus[b]	1.42 (0.06)	1.40 (0.06)	−1.31	1.42 (0.14)	1.46 (0.13)	2.52	−0.30	0.26	0.55


Diabetes
Ulcerative Colitis
Psoriasis
CURCUMIN IN PERIPHERAL DISORDERS
Tumors
Tumor Genesis
Myelodysplasias
Schizophrenia
Drug Addiction
Major depression
CURCUMIN IN NEURONAL DISORDERS
Stroke
Epilepsy
Parkinson's and Alzheimer's disease

Neuroprotective properties of curcumin in toxin-base animal models of Parkinson's disease: a systematic experiment literatures review

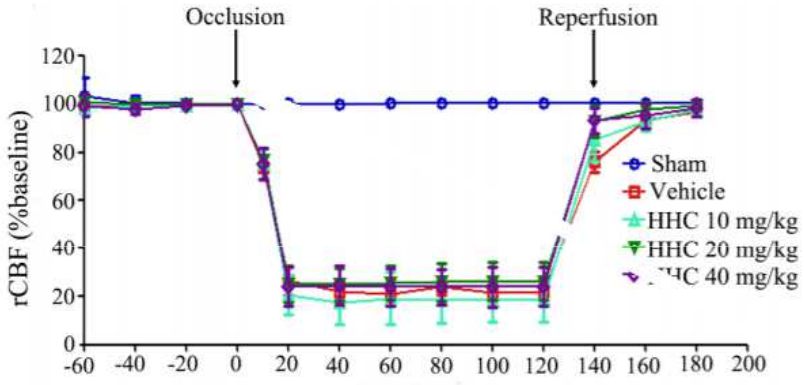
Xin-Shi Wang[1†], Zeng-Rui Zhang[1†], Man-Man Zhang[1], Miao-Xuan Sun[3], Wen-Wen Wang[2*] and Cheng-Long Xie[1*]

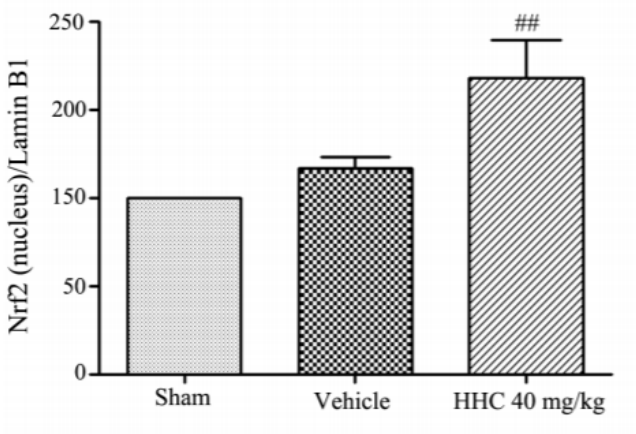


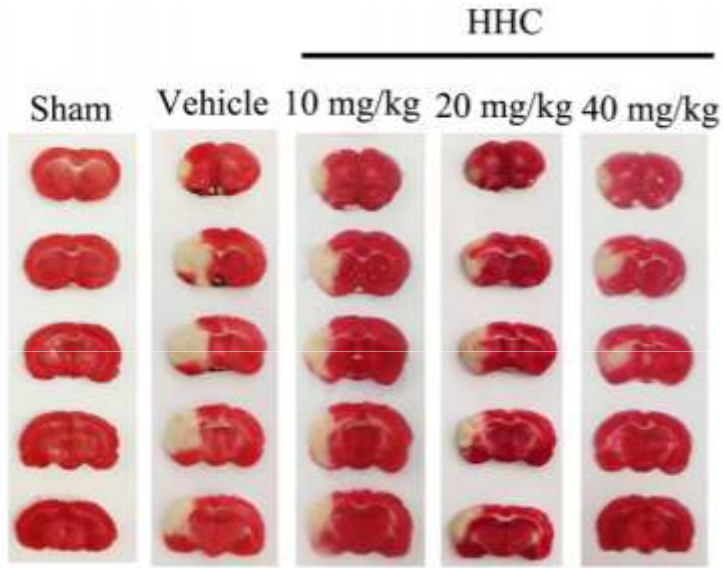


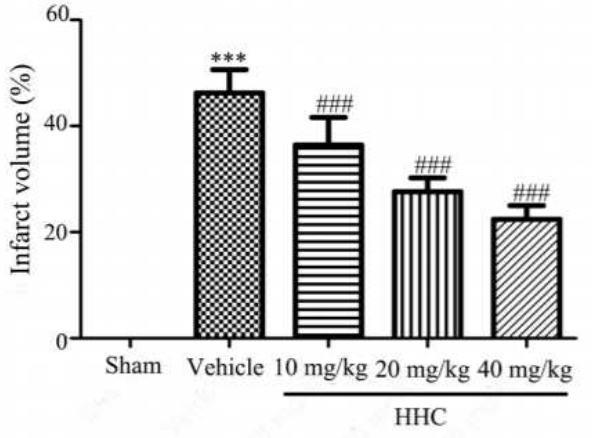
Hexahydrocurcumin protects against cerebral ischemia/reperfusion injury, attenuates inflammation, and improves antioxidant defenses in a rat stroke model

Wicha P. et al



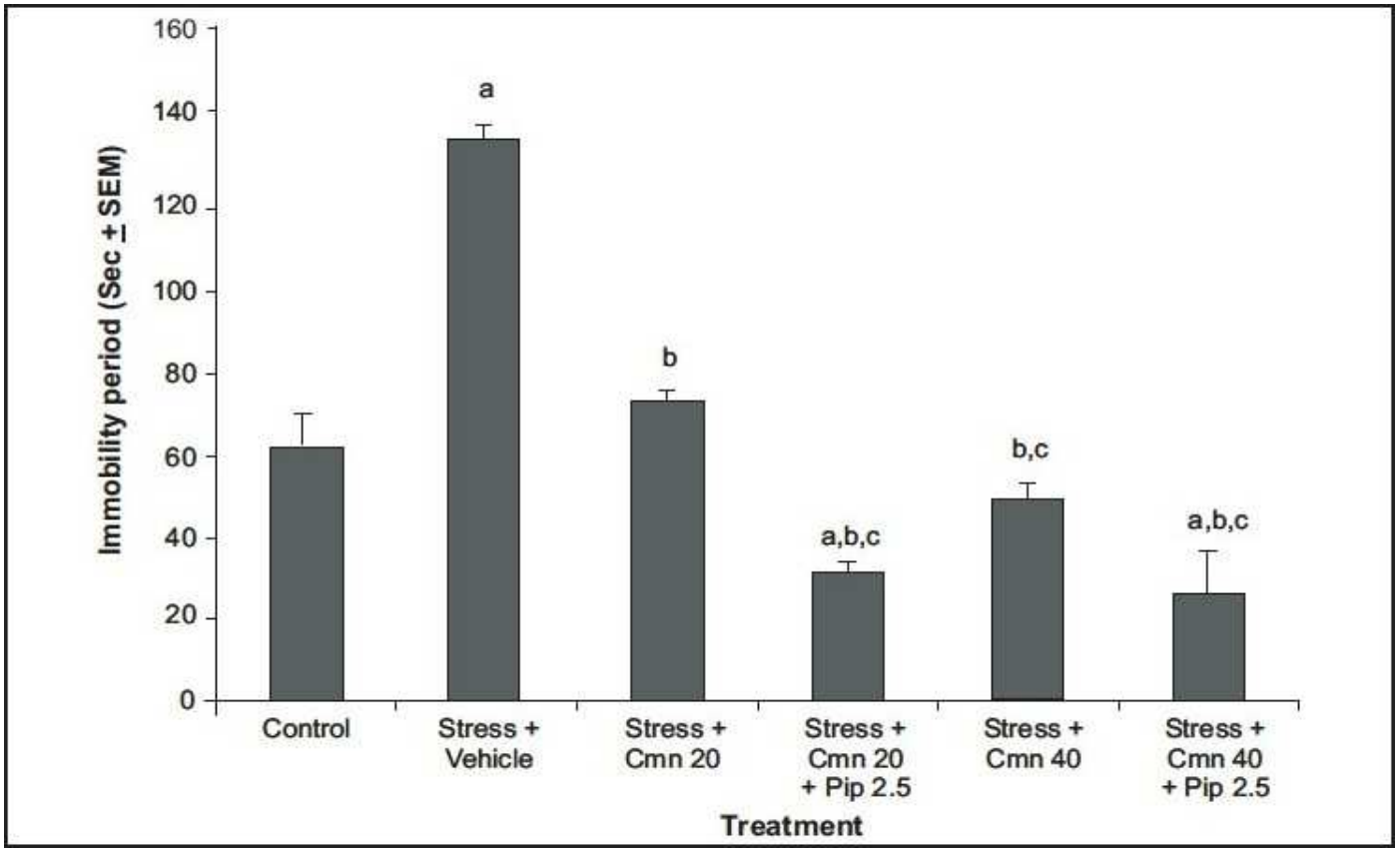






Pharmacology, Biochemistry and Behavior

Anti-depressant like effect of curcumin and its combination with piperine in unpredictable chronic stress-induced behavioral, biochemical and neurochemical changes. Bhutani MK et al. 2009



Effect of curcumin and its combination with piperine on forced swim-induced immobility period in rats. ap≤0.05 as compared with control group; bp≤0.05 as compared with stress (S)+vehicle group, cp≤0.05 as compared with stress (S)+ curcumin (20).

BRAIN RESEARCH

Curcumin reverses impaired hippocampal neurogenesis and increases serotonin receptor 1A mRNA and brain-derived neurotrophic factor expression in chronically stressed rats. Xu Y et al. 2007

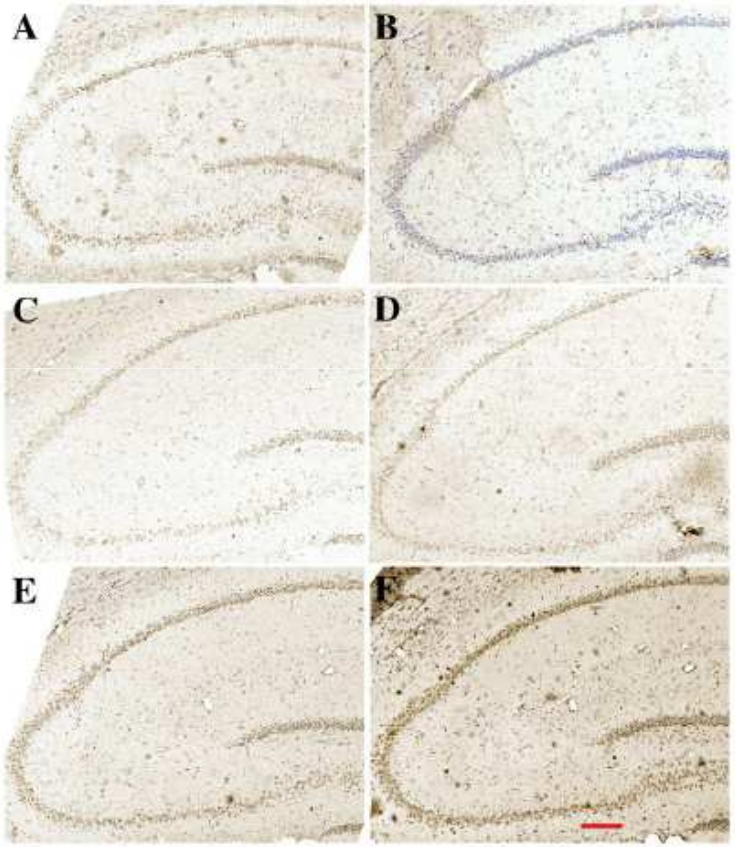


Table 1 – The effects of curcumin on 5-HT$_{1A}$ receptor mRNA expression in stressed rats

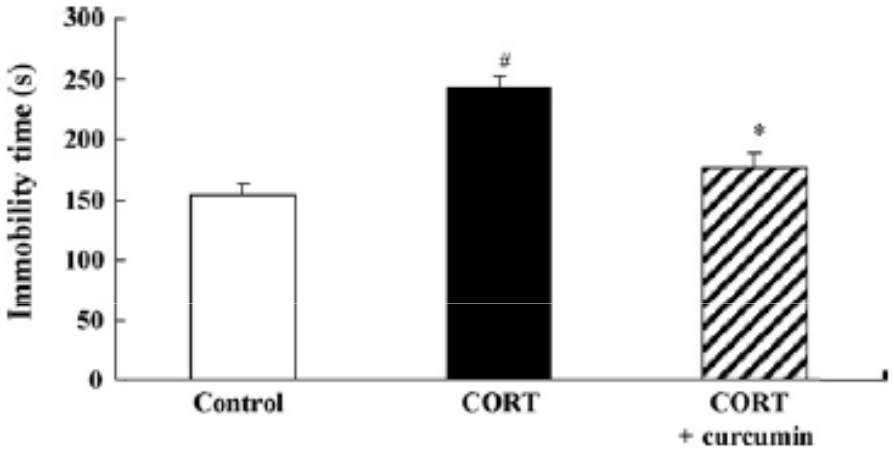
Group	Dose (mg/kg)	Brain region 5-HT$_{1A}$ receptor mRNA expression		
		CA1	CA3	DG
Control		100.0±2.2	100.0±1.9	100.0±1.5
Stress+vehicle		60.7±2.1**	77.5±0.7	57.2±1.3**
Curcumin	5	72.9±1.9	73.8±1.4	66.8±1.2
	10	80.1±1.7*	79.1±1.2	77.1±1.7*
	20	85.7±0.9*	81.2±0.8	84.5±1.1*
Imipramine	10	91.4±1.3**	85.6±1.3	89.1±2.1**

Values are mean±S.E.M. and expressed as a percentage of the control group (n=5–6). **$p<0.01$, compared with control group; *$p<0.05$, **$p<0.01$, compared with stress+vehicle group.

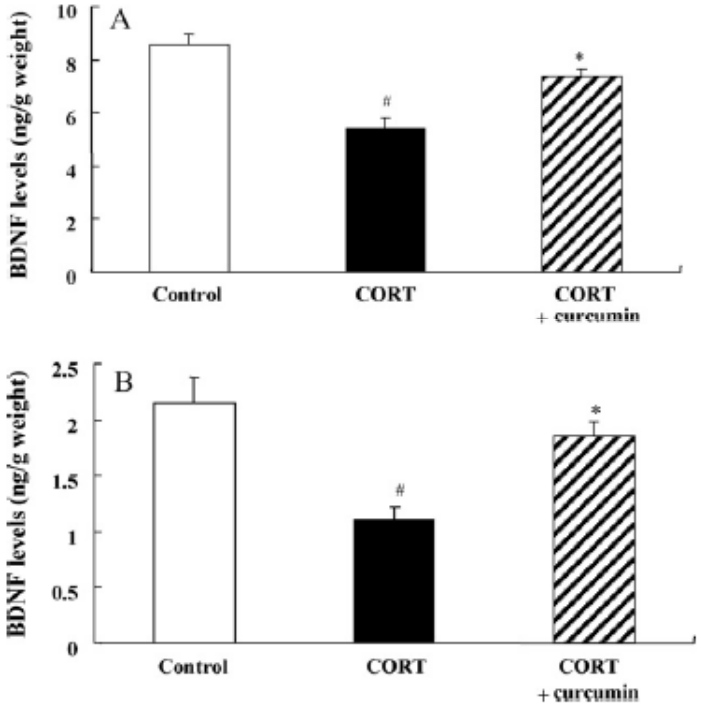
The effects of curcumin on BDNF immunoreactivity in hippocampal neurons of stressed rats. (A) Control group. (B) Stress+vehicle group. (C) 5 mg/kg curcumin. (D) 10 mg/kg curcumin. (E) 20 mg/kg curcumin. (F) 10 mg/kg imipramine.

Neuroscience Letters

Curcumin reverses corticosterone-induced depressive-like behavior and decrease in brain BDNF levels in rats. Huang Z et al. 2011



Effect of curcumin on the immobility time of CORT-treated rats in the forced swim test. The rats were administered with CORT (40 mg/kg, s.c.) once daily for 21 days, and curcumin (20 mg/kg, p.o.) was given to the animals 30 min prior to the CORT injection. Values are given as mean±SEM (n = 8). #p < 0.01 compared with the control group; *p < 0.01 compared with the CORT group.



Effect of curcumin on brain-derived neurotrophic factor (BDNF) protein levels in the hippocampus (A) and frontal cortex (B) of CORT-treated rats.

Contents lists available at ScienceDirect

Journal of Affective Disorders

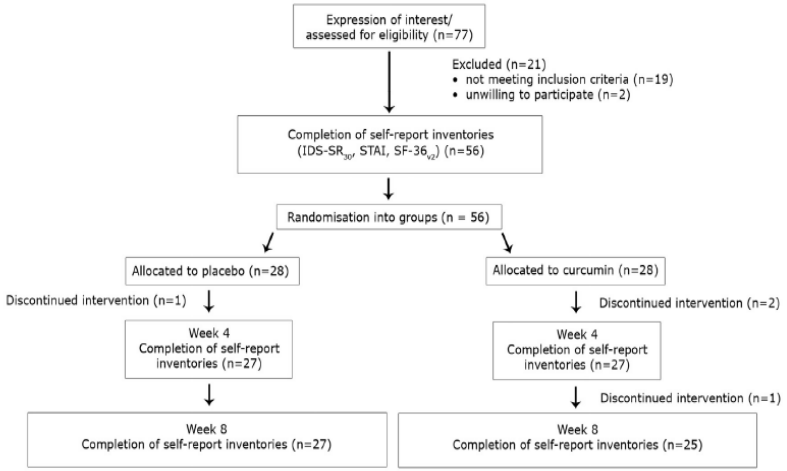
journal homepage: www.elsevier.com/locate/jad

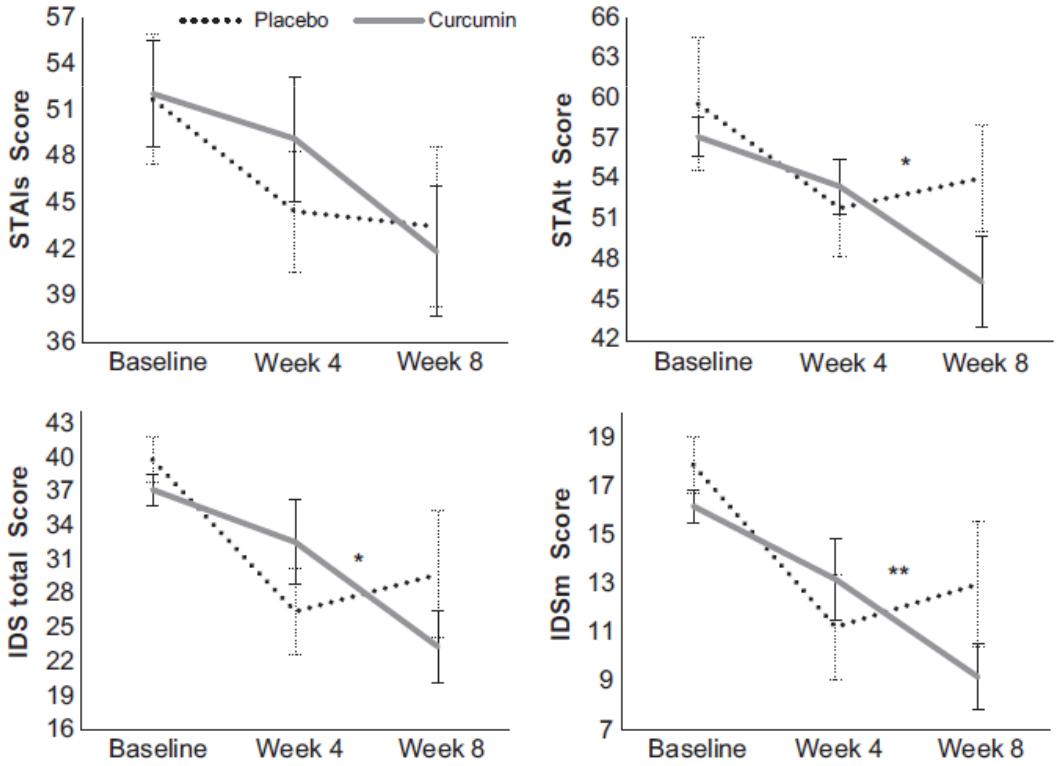
Research report

Journal of Affective Disorders 167 (2014) 368–375

Curcumin for the treatment of major depression: A randomised, double-blind, placebo controlled study

Adrian L. Lopresti [a,*], Michael Maes [b,c], Garth L. Maker [d], Sean D. Hood [e], Peter D. Drummond [a]





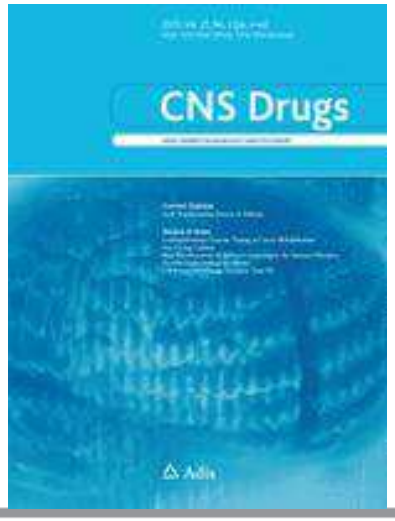
MECHANISMS PROPOSED FOR ANTIDEPRESSANT ACTIVITY OF CURCUMIN

Monoamine oxidase (MAO) inhibitory property of curcumin

Modulating the serotonin and dopamine neurotransmission in brain

Increasing the levels of neurotrophic factors, particularly brain derived neurotrophic factor (BDNF)

Antiinflammatory and antioxidant property



LEADING ARTICLE

CNS Drugs 2012; 26 (6): 477-490
1172-7047/12/0006-0477/$49.95/0

Antioxidants as Antidepressants

Fact or Fiction?

Giovanni Scapagnini,[1] *Sergio Davinelli*,[1] *Filippo Drago*,[2] *Antonino De Lorenzo*[3] and *Giovannangelo Oriani*[1]

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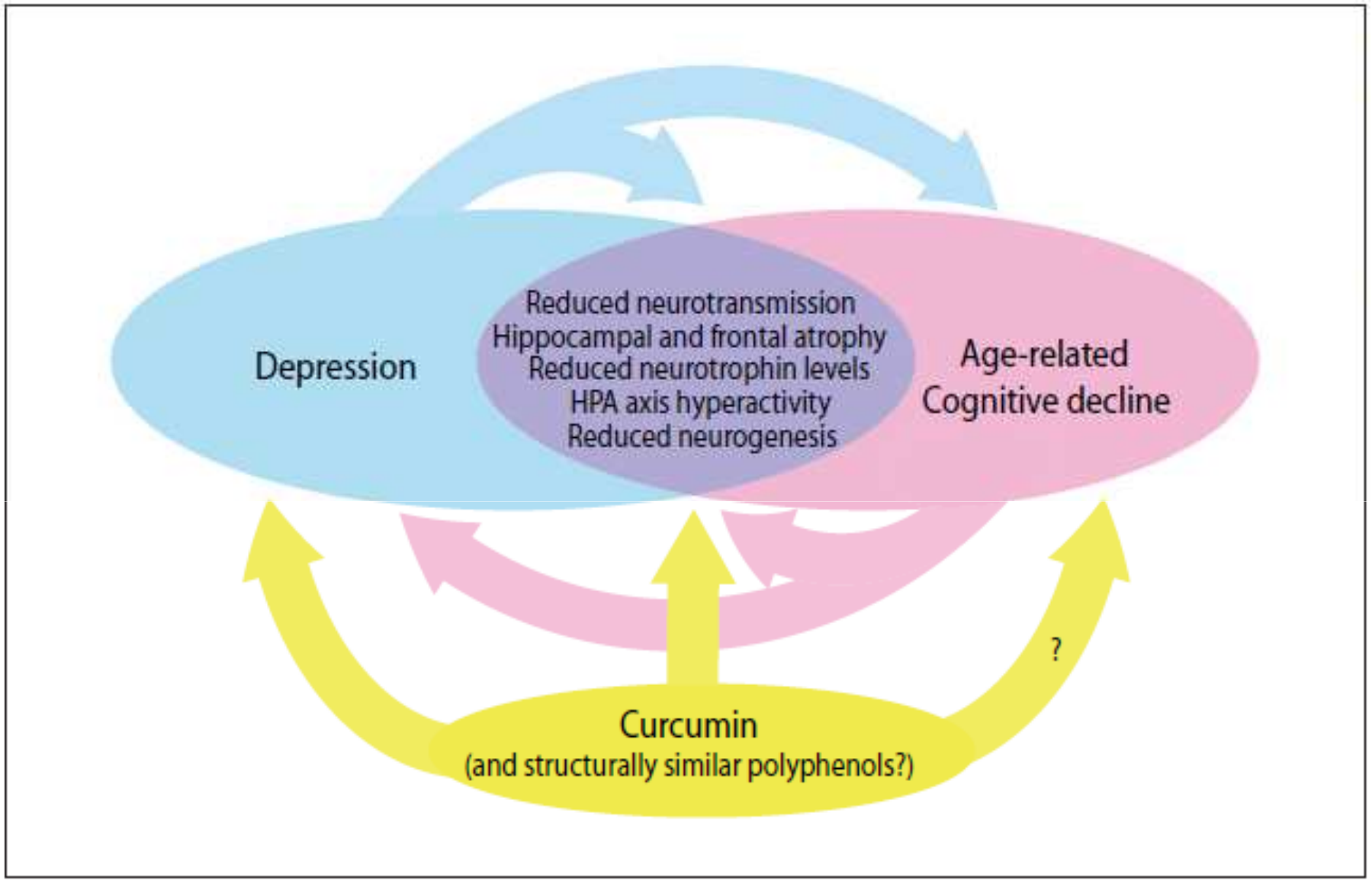
2 Department of Clinical and Molecular Biomedicine, Section of Pharmacology and Biochemistry, University of Catania, Catania, Italy
3 Department of Neuroscience, Division of Human Nutrition, University of Rome Tor Vergata, Rome, Italy

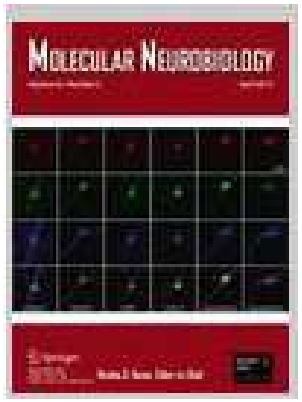


Ogle WO et al. Potential of Treating Age-Related Depression and Cognitive Decline with Nutraceutical Approaches. Gerontology 2013;59:23–31

Modulation of Nrf2/ARE pathway by food polyphenols: a nutritional neuroprotective strategy for cognitive and neurodegenerative disorders.

Scapagnini G, Vasto S, Abraham NG, Caruso C, Zella D, Galvano F.

Mol Neurobiol. 2011 Oct;44(2):192-201.



Received: 30 November 2010 / Accepted: 4 April 2011

Abstract In recent years, there has been a growing interest, supported by a large number of experimental and epidemiological studies, for the beneficial effects of some phenolic substances, contained in commonly used spices and herbs, in preventing various age-related pathologic conditions, ranging from cancer to neurodegenerative diseases. Although the exact mechanisms by which polyphenols promote these effects remain to be elucidated, several reports have shown their ability to stimulate a general xenobiotic response in the target cells, activating multiple defense genes. Data from our and other laboratories have previously demonstrated that curcumin, the yellow pigment of curry, strongly induces heme-oxygenase-1 (HO-1) expression and activity in different brain cells via the activation of *heterodimers of NF-E2-related factors 2* (Nrf2)/antioxidant responsive element (ARE) pathway. Many studies clearly demonstrate that activation ofNrf2 target genes, and particularly HO-1, in astrocytes and neurons is strongly protective against inflammation, oxidative damage, and cell death. In the central nervous system, the HO system has been reported to be very active, and its modulation seems to play a crucial role in the pathogenesis of neurodegenerative disorders. Recent and unpublished data from our group revealed that low concentrations of epigallocatechin-3-gallate, the major green tea catechin, induces HO-1 by ARE/Nrf2 pathway in hippocampal neurons, and by this induction, it is able to protect neurons against different models of oxidative damages. Furthermore, we have demonstrated that other phenolics, such as caffeic acid phenethyl ester and ethyl ferulate, are also able to protect neurons via HO-1 induction. These studies identify a novel class of compounds that could be used for therapeutic purposes as preventive agents against cognitive decline.

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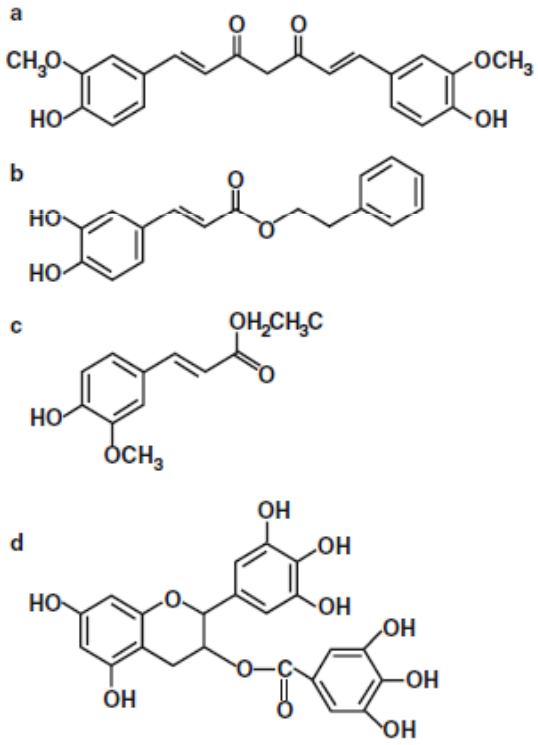
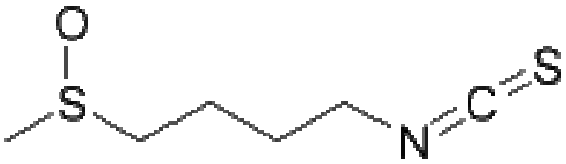


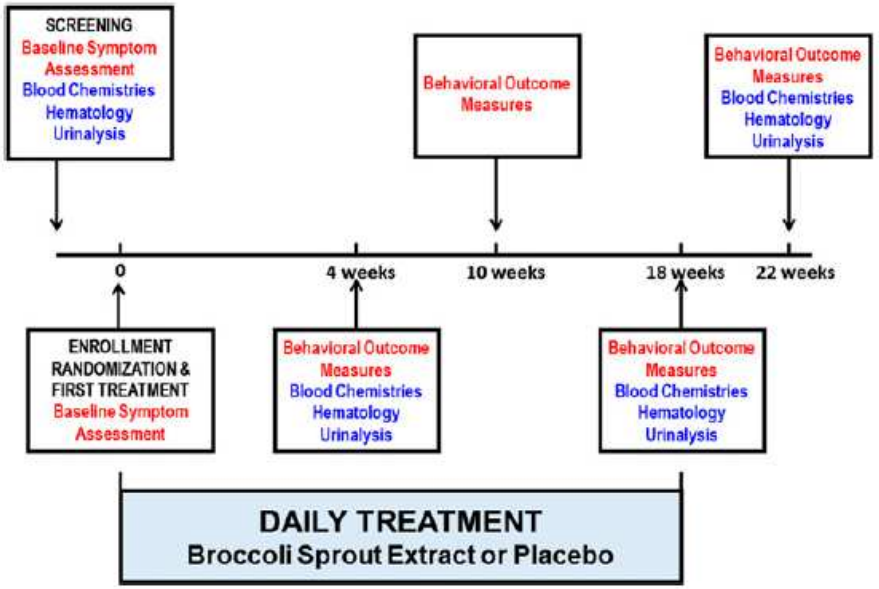
Fig. 1 The chemical structures of curcumin (**a**), CAPE (**b**), EFE (**c**), (−)-EGCG (**d**)

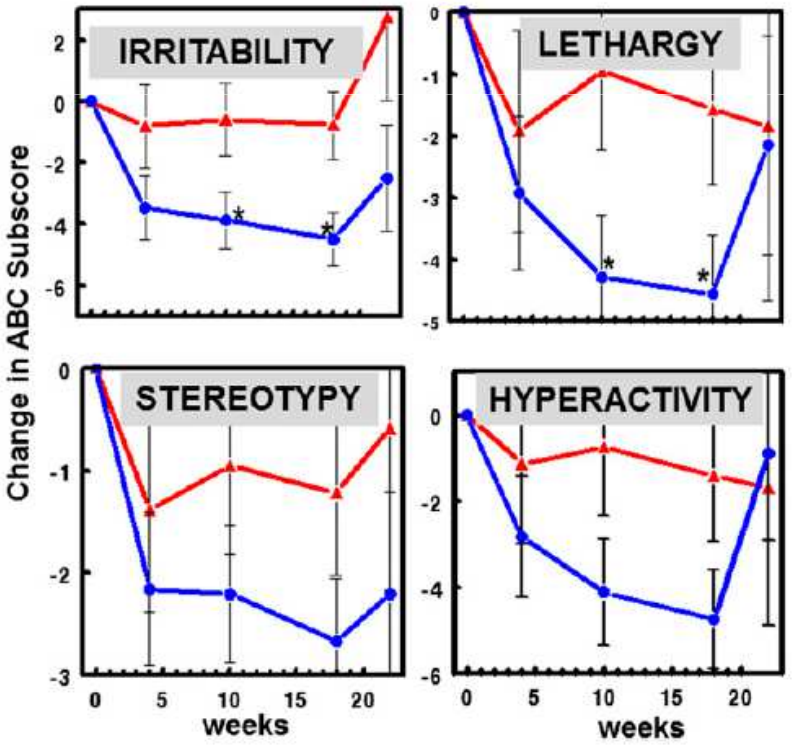
Sulforaphane treatment of autism spectrum disorder (ASD)

PNAS | October 28, 2014 | vol. 111 | no. 43

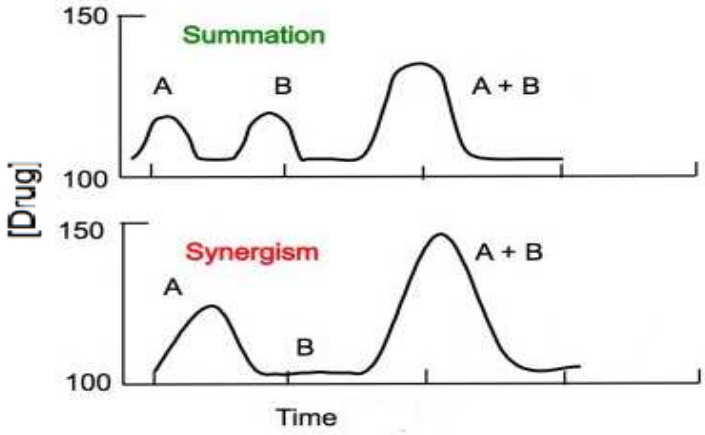
Kanwaljit Singh[a,b], Susan L. Connors[a], Eric A. Macklin[c], Kirby D. Smith[d], Jed W. Fahey[e], Paul Talalay[e,1], and Andrew W. Zimmerman[a,b,1]

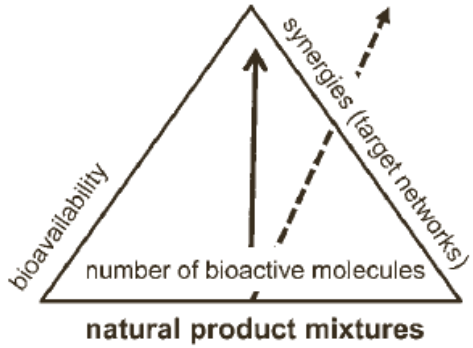






Synergy research: Approaching a new generation of nutraceuticals

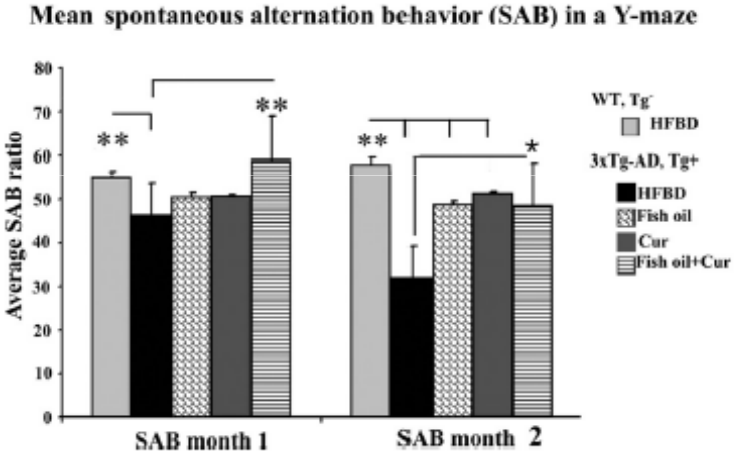




β-Amyloid Oligomers Induce Phosphorylation of Tau and Inactivation of Insulin Receptor Substrate via c-Jun N-Terminal Kinase Signaling: Suppression by Omega-3 Fatty Acids and Curcumin

The Journal of Neuroscience, July 15, 2009 · 29(28):9078–9089

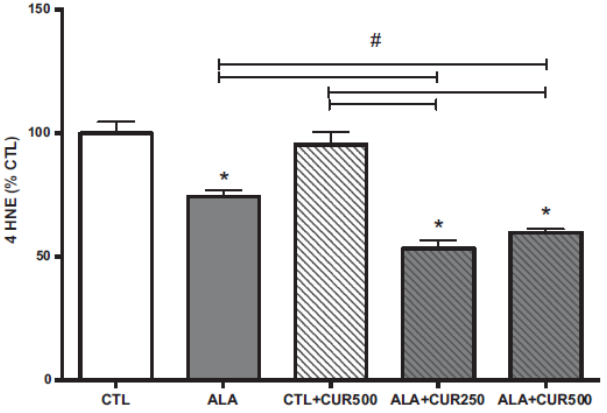
Qiu-Lan Ma,[1,4] Fusheng Yang,[1,4] Emily R. Rosario,[1,4] Oliver J. Ubeda,[1,4] Walter Beech,[1,4] Dana J. Gant,[1,4] Ping Ping Chen,[1,4] Beverly Hudspeth,[1,4] Cory Chen,[1,4] Yongle Zhao,[1,4] Harry V. Vinters,[2,3] Sally A. Frautschy,[1,2,4] and Greg M. Cole[1,2,4]



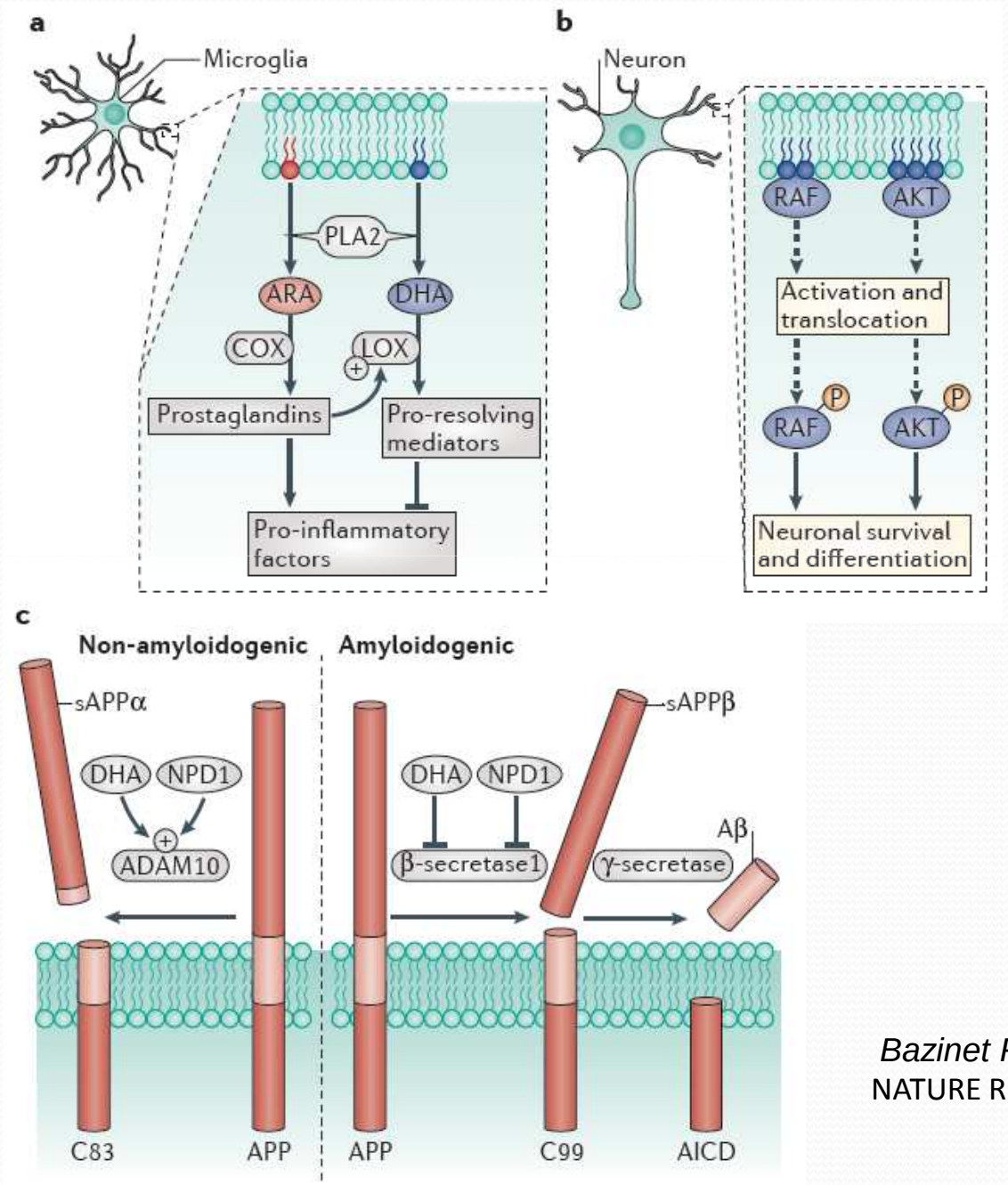
Curcumin boosts DHA in the brain: Implications for the prevention of anxiety disorders

Biochimica et Biophysica Acta (2014)

AiguoWu a, Emily E. Noble a, Ethika Tyagi a, Zhe Ying a, Yumei Zhuang a, Fernando Gomez-Pinilla



Roles of PUFAs in the brain



Bazinet RP and Layé S, 2014
NATURE REVIEWS **NEUROSCIENCE** 15

Red blood cell omega-3 fatty acid levels and markers of accelerated brain aging

Neurology 78 February 28, 2012

Z.S. Tan, MD, MPH
W.S. Harris, PhD
A.S. Beiser, PhD
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J.J. Himali, MS
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ABSTRACT

Objective: Higher dietary intake and circulating levels of docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) have been related to a reduced risk for dementia, but the pathways underlying this association remain unclear. We examined the cross-sectional relation of red blood cell (RBC) fatty acid levels to subclinical imaging and cognitive markers of dementia risk in a middle-aged to elderly community-based cohort.

Methods: We related RBC DHA and EPA levels in dementia-free Framingham Study participants (n = 1,575; 854 women, age 67 ± 9 years) to performance on cognitive tests and to volumetric brain MRI, with serial adjustments for age, sex, and education (model A, primary model), additionally for *APOE* ϵ4 and plasma homocysteine (model B), and also for physical activity and body mass index (model C), or for traditional vascular risk factors (model D).

Results: Participants with RBC DHA levels in the lowest quartile (Q1) when compared to others (Q2–4) had lower total brain and greater white matter hyperintensity volumes (for model A: $\beta \pm$ SE = −0.49 ± 0.19; $p = 0.009$, and 0.12 ± 0.06; $p = 0.049$, respectively) with persistence of the association with total brain volume in multivariable analyses. Participants with lower DHA and ω-3 index (RBC DHA+EPA) levels (Q1 vs Q2–4) also had lower scores on tests of visual memory ($\beta \pm$ SE = −0.47 ± 0.18; $p = 0.008$), executive function ($\beta \pm$ SE = −0.07 ± 0.03; $p = 0.004$), and abstract thinking ($\beta \pm$ SE = −0.52 ± 0.18; $p = 0.004$) in model A, the results remaining significant in all models.

Conclusion: Lower RBC DHA levels are associated with smaller brain volumes and a "vascular" pattern of cognitive impairment even in persons free of clinical dementia. ***Neurology*® 2012;78:658–664**

REVIEW SCIENTIFICA
SULL'INTEGRAZIONE ALIMENTARE:
STATO DELL'ARTE ALLA LUCE
DELLE EVIDENZE SCIENTIFICHE

23 Giugno 2016
Prima edizione

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INTEGRATORI ITALIA
Associazione Italiana Industrie Prodotti Alimentari

Integratori e loro ruolo nella fisiologia dell'invecchiamento cerebrale

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** Ricercatore, Dipartimento Scienze per la Salute, Università degli Studi del Molise

Cervello e invecchiamento

Il cervello è l'organo del corpo che invecchia più velocemente e in maniera più significativa rispetto a tutti gli altri tessuti dell'organismo.[1] Il motivo di questo fenomeno è intrinsecamente legato alla biochimica e alla funzione cerebrale. Infatti i neuroni, le cellule principali di cui è composto il cervello, sono post-mitotici, cioè non si duplicano né si rigenerano (lo fanno solo in aree limitate, mediante la neurogenesi, che però incide molto poco in termini di replacement). Di conseguenza, una volta morte, non vengono sostituite da nuove cellule. Inoltre, occorre ricordare che il cervello è una struttura ad alto metabolismo energetico. Infatti, il cervello utilizza grandi quantitativi di ossigeno (1/3 dell'ossigeno che respiriamo è usato dal cervello) e, quindi, produce molti radicali liberi, sostanze altamente reattive, in grado di procurare danni irreversibili a livello cellulare. Le membrane cellulari dei neuroni sono, inoltre, caratterizzate da un'alta concentrazione di acidi grassi polinsaturi, che rappresentano un substrato ideale per il danno ossidativo. Il cervello in alcune aree presenta poi un'alta concentrazione di ferro e rame, metalli che sono in grado di catalizzare la produzione di forme radicaliche molto dannose (reazione di Fenton). Inoltre, e questo rappresenta quasi un paradosso, il cervello ha una bassissima concentrazione di antiossidanti endogeni (proteici e non). Ad esempio i livelli di glutatione, di superossidodismutasi e di catalasi sono circa 1/5 rispetto a quelli del fegato. Di fatto, quindi, il cervello è per sua natura estremamente esposto allo stress ossidativo e di conseguenza invecchia più precocemente di altri tessuti.[2] È possibile attraverso adeguate strategie nutraceutiche supportare adeguatamente la fisiologia cerebrale, promuovere un mantenimento delle funzioni cognitive nel tempo, ridurre i danni ossidativi a livello neuronale ed evitare così un invecchiamento patologico del nostro cervello? Si tratta di un argomento estremamente rilevante, soprattutto nell'ottica di prevenire l'instaurarsi di patologie neurodegenerative collegate all'invecchiamento, che negli ultimi anni stanno aumentando in modo preoccupante a livello globale.

Declino cognitivo, difese naturali e dieta

Negli ultimi anni le patologie neurodegenerative, e in particolare la malattia di Alzheimer (AD), stanno aumentando in maniera esponenziale nei Paesi industrializzati, e anche in quelli in via di sviluppo. Gli ultimi dati presentati dall'Alzheimer Association parlano di una triplicazione dei casi di Alzheimer da