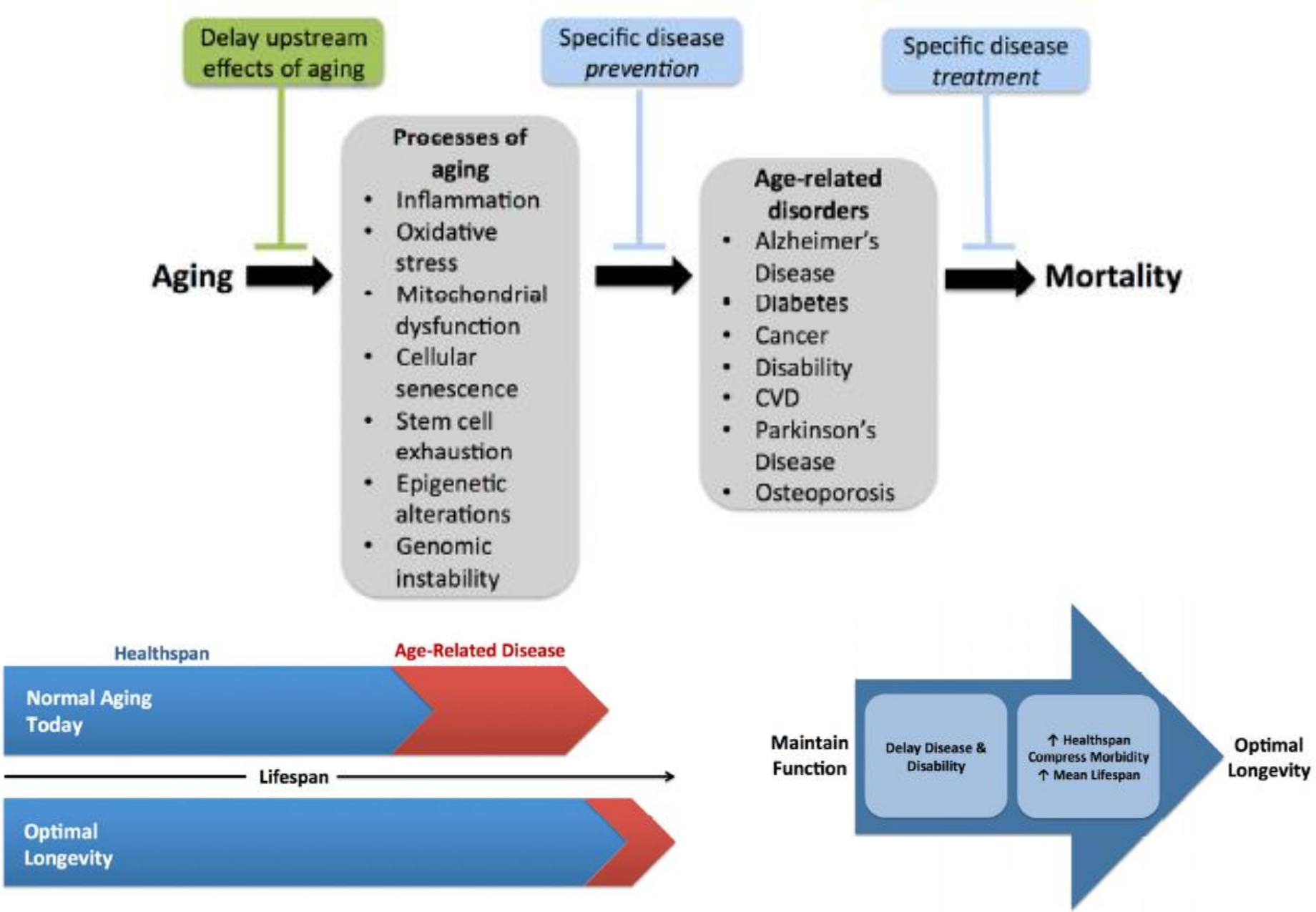
Università degli Studi del Molise
Via De Sanctis - 86100 Campobasso - Tel. +39 0874 4041

Blanchette Rockefeller Neurosciences Institute
West Virginia University

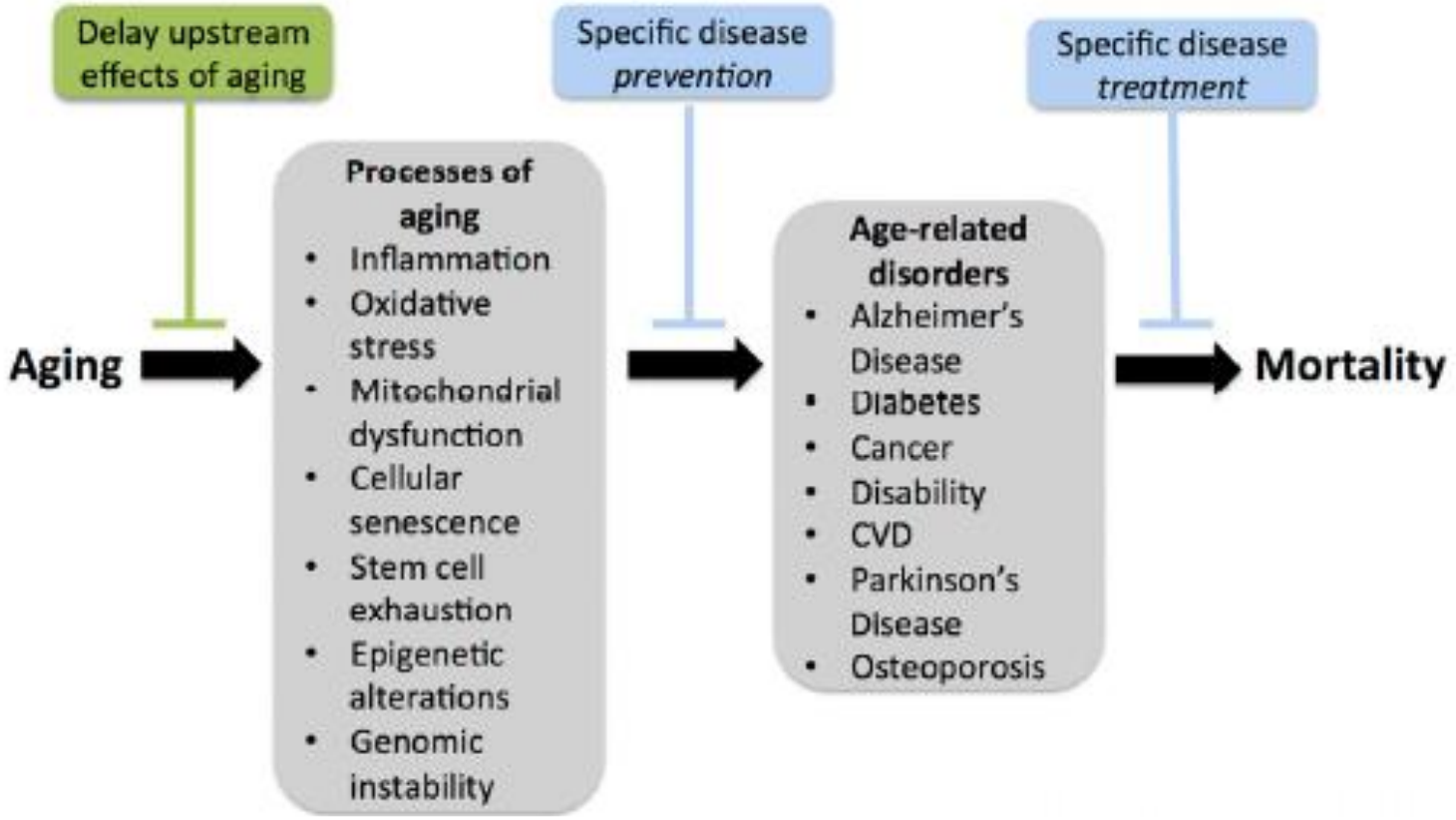
Consiglio Nazionale delle Ricerche
Istituto di Scienze Neurologiche

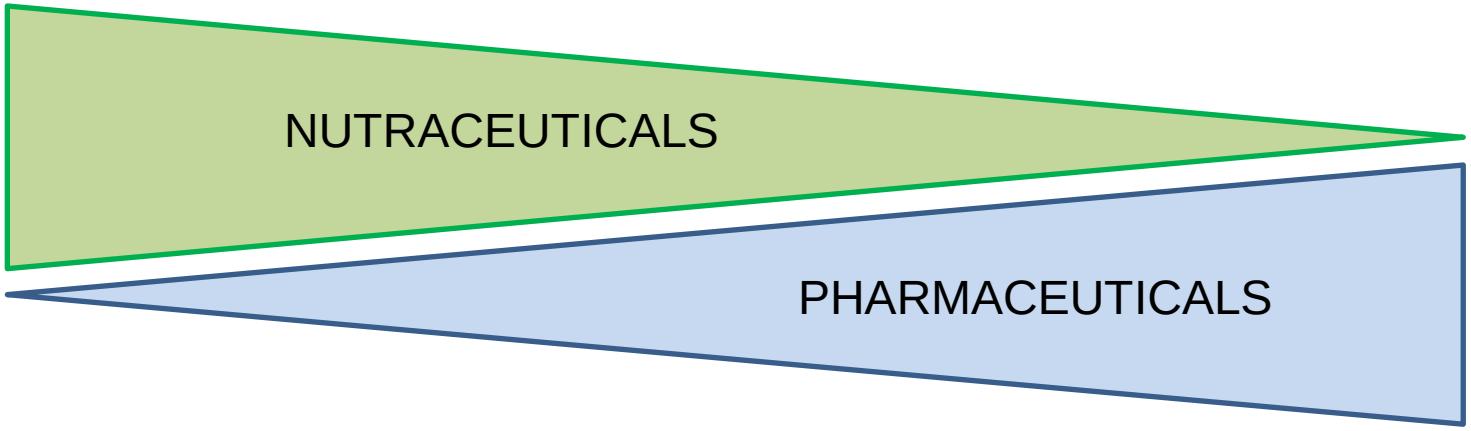
Estendere l'invecchiamento in salute: vie metaboliche sensibili ai nutrienti e popolazioni centenarie

Giovanni Scapagnini, MD, PhD

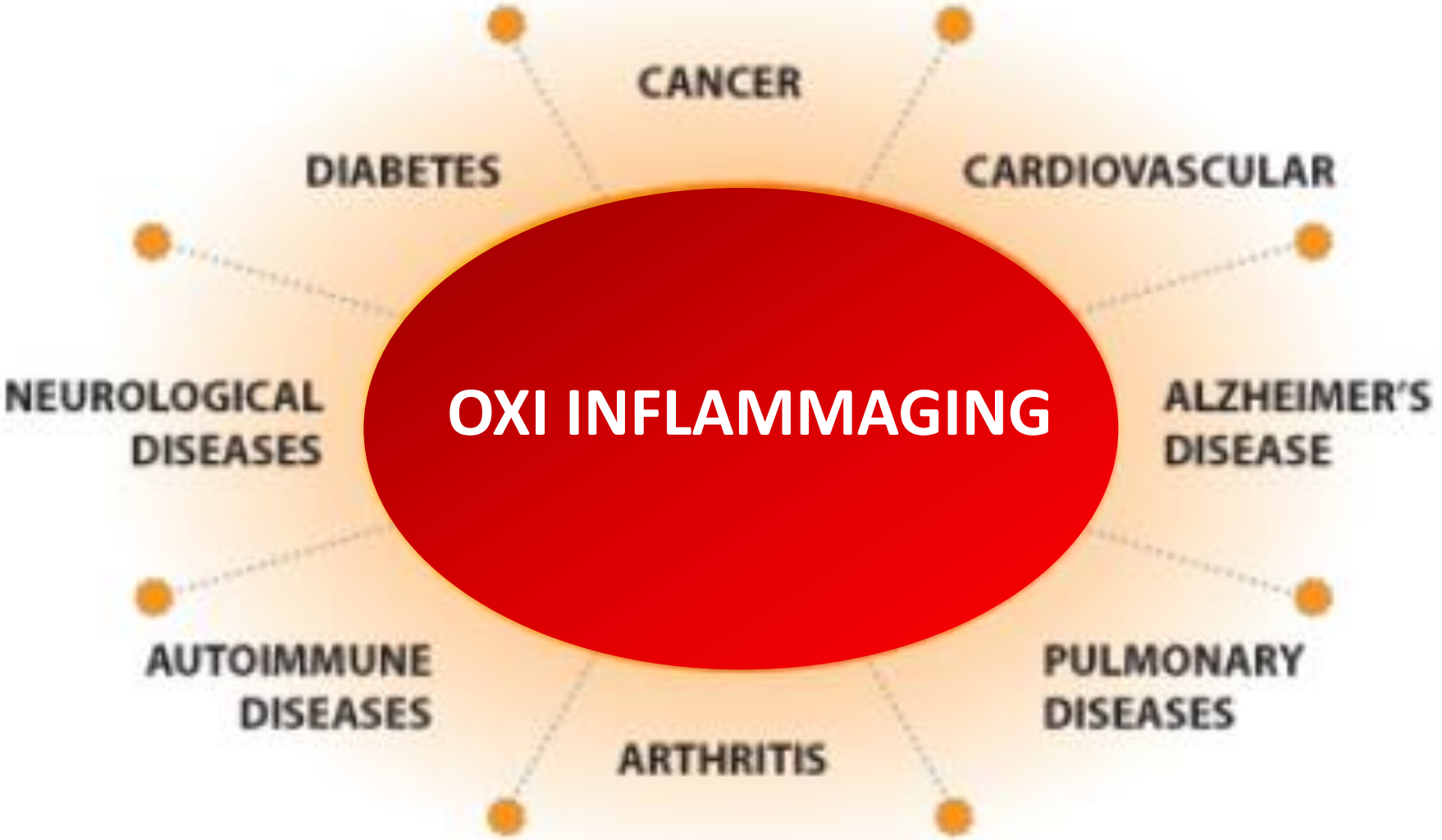


Seals DR and Melov S. Translational Geroscience: Emphasizing function to achieve optimal longevity. Aging 2014, 6: 718-730


Delay upstream effects of aging
Specific disease prevention
Specific disease treatment
Aging
Processes of aging
Inflammation
Oxidative stress
Mitochondrial dysfunction
Cellular senescence
Stem cell exhaustion
Epigenetic alterations
Genomic instability
Age-related disorders
Alzheimer's Disease
Diabetes
Cancer
Disability
CVD
Parkinson's Disease
Osteoporosis
Mortality


NUTRACEUTICALS
PHARMACEUTICALS

Oxidation and Inflammation
The link with age related chronic diseases



Contents lists available at SciVerse ScienceDirect

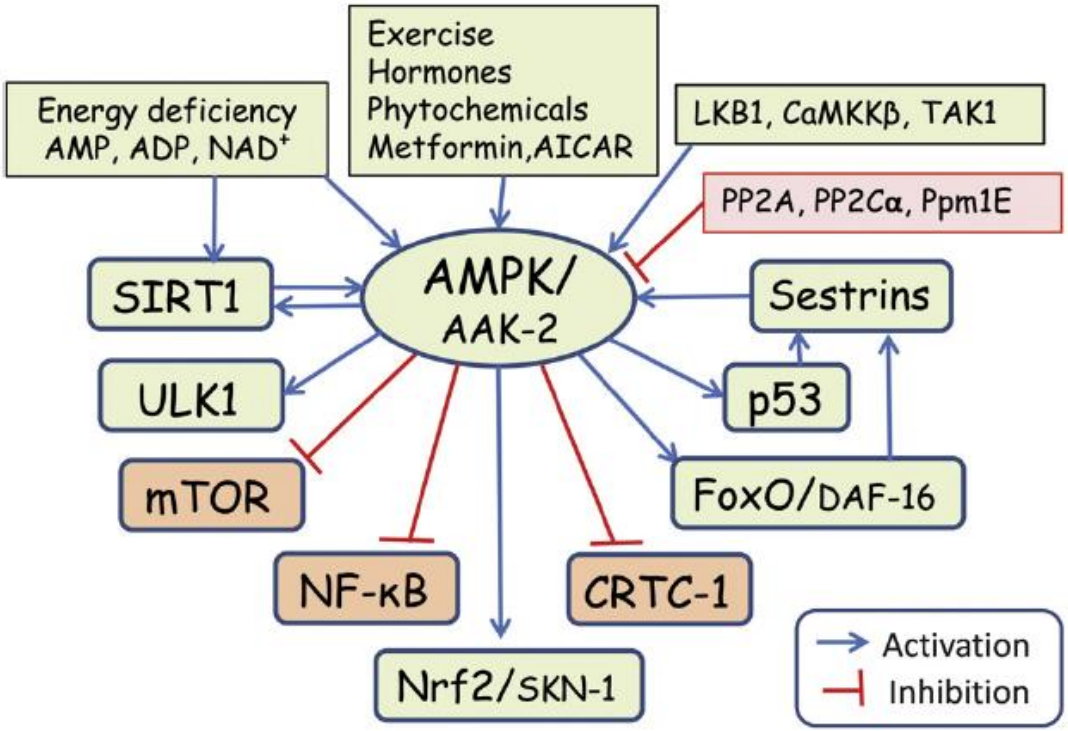
Ageing Research Reviews

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

AMP-activated protein kinase (AMPK) controls the aging process via an integrated signaling network

Ageing Research Reviews 11 (2012) 230– 241

Antero Salminen[a,b,*], Kai Kaarniranta[c,d]



Decline in AMPK activation with aging:

Decreases autophagy	Increases inflammation
Increases oxidative stress	Increases fat deposition
Increases endoplasmic stress	Induces hyperglycemia
Increases apoptotic resistance	Enhances metabolic syndrome

Dr. Nir Barzilai on the TAME Study

We hypothesize that delaying aging is the only effective way to delay age-related diseases and compress morbidity. TAME is a novel study that will recruit elderly subjects and, in a double-blind, placebo-control study, will test if metformin can delay the onset of multi-morbidities including cancer, CVD, T2DM, cognitive decline, and mortality. It is sponsored by the American Federation for Aging Research (AFAR), and I will serve as the PI. There is a wide range of involvement of gerontologists and intervention geriatricians in an executive committee and consensus committee as well as other investigators.

Metformin

Do we finally have an anti-aging drug?

Cell Cycle 12:22, 3483–3489; November 15, 2013;

Vladimir N Anisimov

Department of Carcinogenesis and Oncogerontology; N.N. Petrov Research Institute of Oncology; St. Petersburg, Russia

Nutrients acts as dietary signals

Nutritional factors

↓

Transcription factors

↓

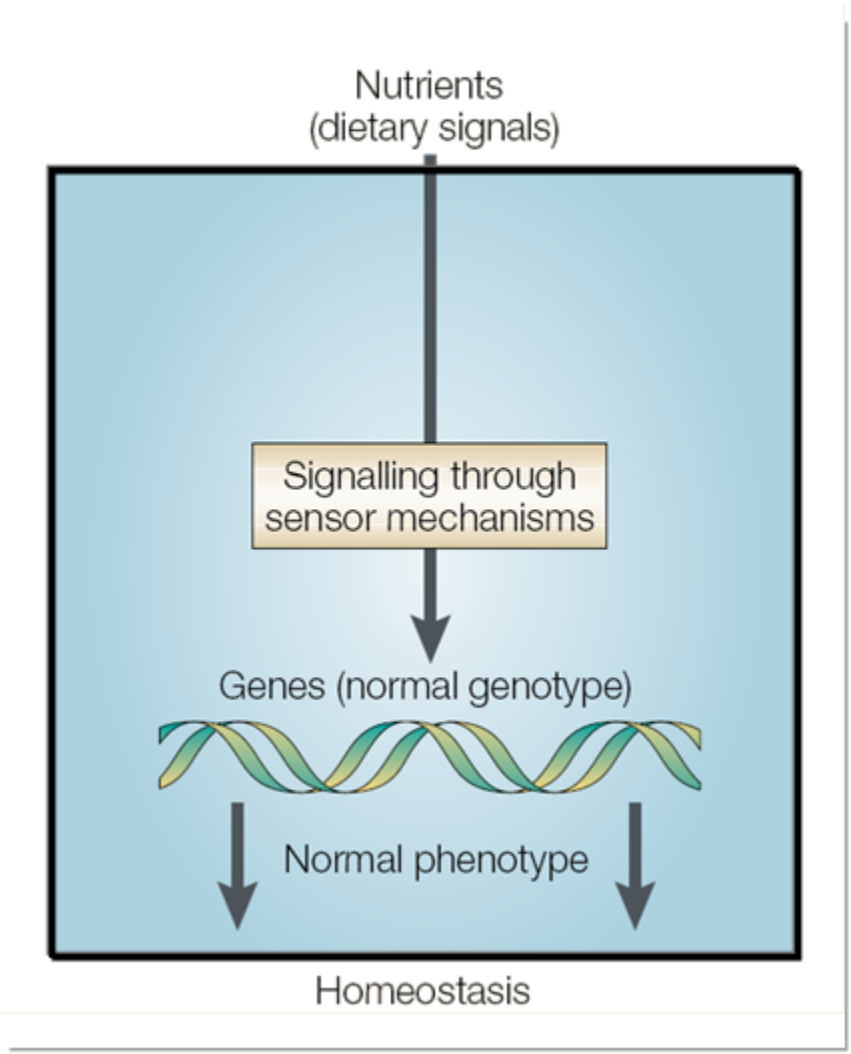
Gene transcription

↓

Energy homeostasis

Cell proliferation

Nutrient absorption



Aiello et al. Immunity & Ageing
DOI 10.1186/s12979-016-0071-2

Immunity & Ageing

EDITORIAL Open Access

Nutrigerontology: a key for achieving successful ageing and longevity

Anna Aiello[1], Giulia Accardi[1], Giuseppina Candore[1], Giuseppe Carruba[2], Sergio Davinelli[3], Giuseppe Passarino[4], Giovanni Scapagnini[3], Sonya Vasto[5] and Calogero Caruso[1*]

Abstract

During the last two centuries the average lifespan has increased at a rate of approximately 3 months/year in both sexes, hence oldest old people are becoming the population with the fastest growth in Western World. Although the average life expectancy is increasing dramatically, the healthy lifespan is not going at the same pace. This underscores the importance of studies on the prevention of age-related diseases, in order to satisfactorily decrease the medical, economic and social problems associated to advancing age, related to an increased number of individuals not autonomous and affected by invalidating pathologies. In particular, data from experimental studies in model organisms have consistently shown that nutrient signalling pathways are involved in longevity, affecting the prevalence of age-related loss of function, including age-related diseases. Accordingly, nutrigerontology is defined as the scientific discipline that studies the impact of nutrients, foods, macronutrient ratios, and diets on lifespan, ageing process, and age-related diseases. To discuss the potential relevance of this new science in the attainment of successful ageing and longevity, three original studies performed in Sicily with local foods and two reviews have been assembled in this series. Data clearly demonstrate the positive effects of nutraceuticals, functional foods and Mediterranean Diet on several biological parameters. In fact, they could represent a prevention for many age-related diseases, and, although not a solution for this social plague, at least a remedy to alleviate it. Thus, the possibility to create a dietary pattern, based on the combined strategy of the use of both nutraceuticals and functional foods should permit to create a new therapeutic strategy, based not only on a specific bioactive molecule or on a specific food but on a integrated approach that, starting from the local dietary habits, can be led to a "nutrafunctional diet" applicable worldwide.

Keywords: Ageing, Longevity, Mediterranean Diet, Nutraceuticals, Nutrigerontology, Phytochemicals

EMBO reports

EMBO reports VOL 13 | NO 3 | 2012

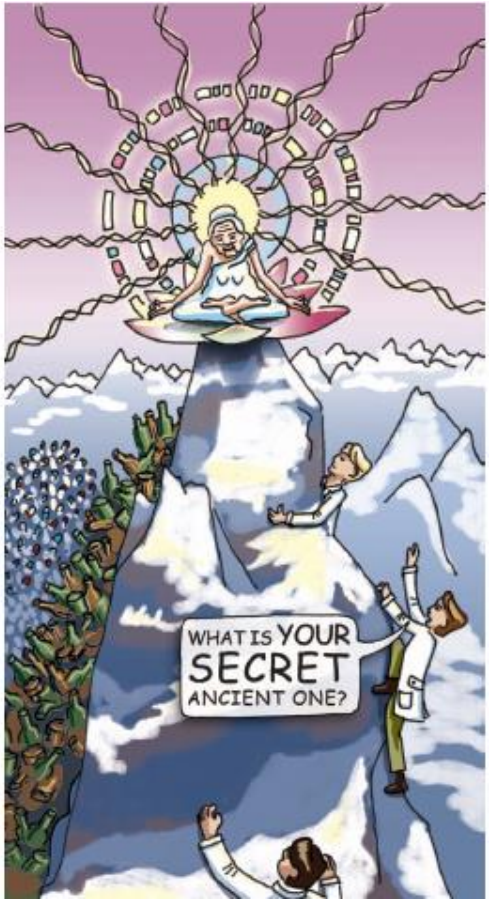
science & society

‘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**



Long living animals

Proteus anguinus Laurenti
> 100 years

Heterocephalus glaber
> 32 years

Short living animals

Notobranchius furzeri
< 12 weeks

HIV transgenic rat
< 1 year

Centenarians are a great model of Positive Biology
Study the escapers to keep their secret of long life

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]

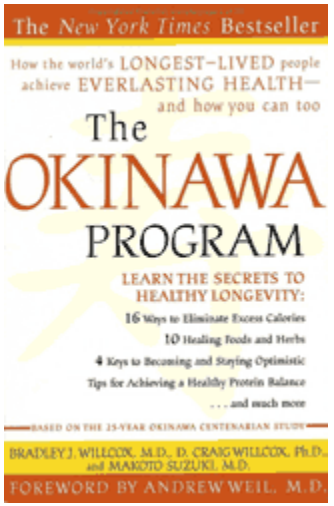
REJUVENATION RESEARCH
Volume 15, Number 2, 2012

DOI: 10.1089/rej.2011.1280

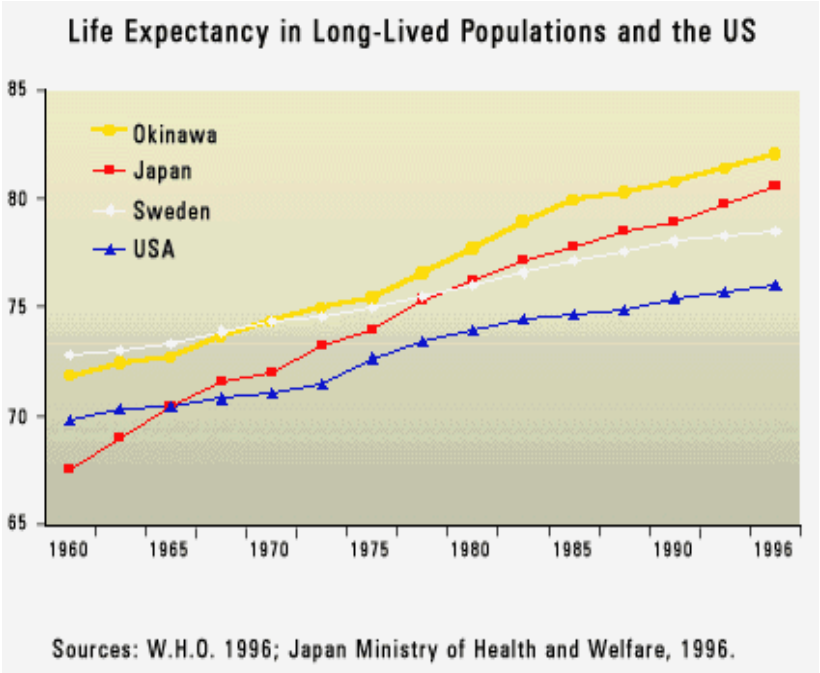
Mediterranean Diet and Longevity in Sicily: Survey in a Sicani Mountains Population

Sonya Vasto,[1] Giovanni Scapagnini,[2] Claudia Rizzo,[2] Roberto Monastero,[3] Antonio Marchese,[4] and Calogero Caruso[1]

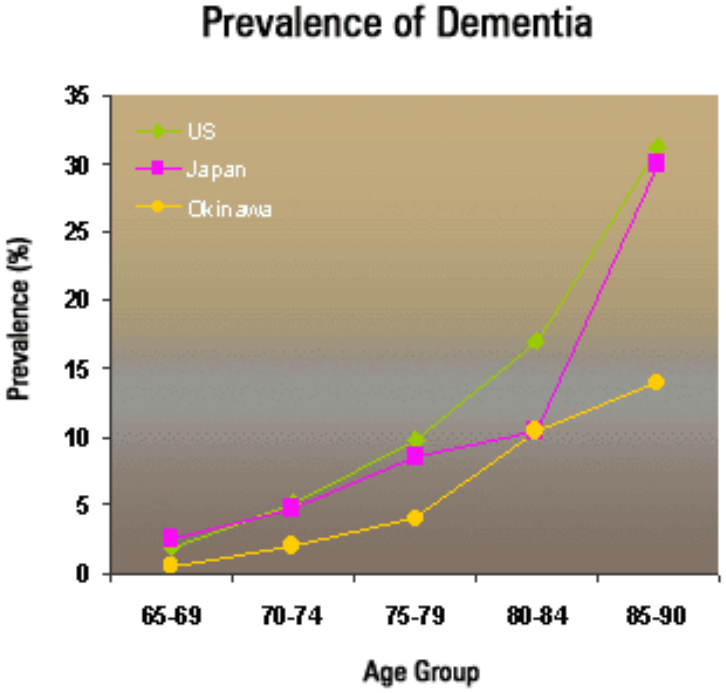

Sea of Japan
JAPAN
Tokyo
Pacific Ocean
Okinawa


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.

In Okinawa, centenarian ratios may be the world's highest at approximately 50 per 100,000 population

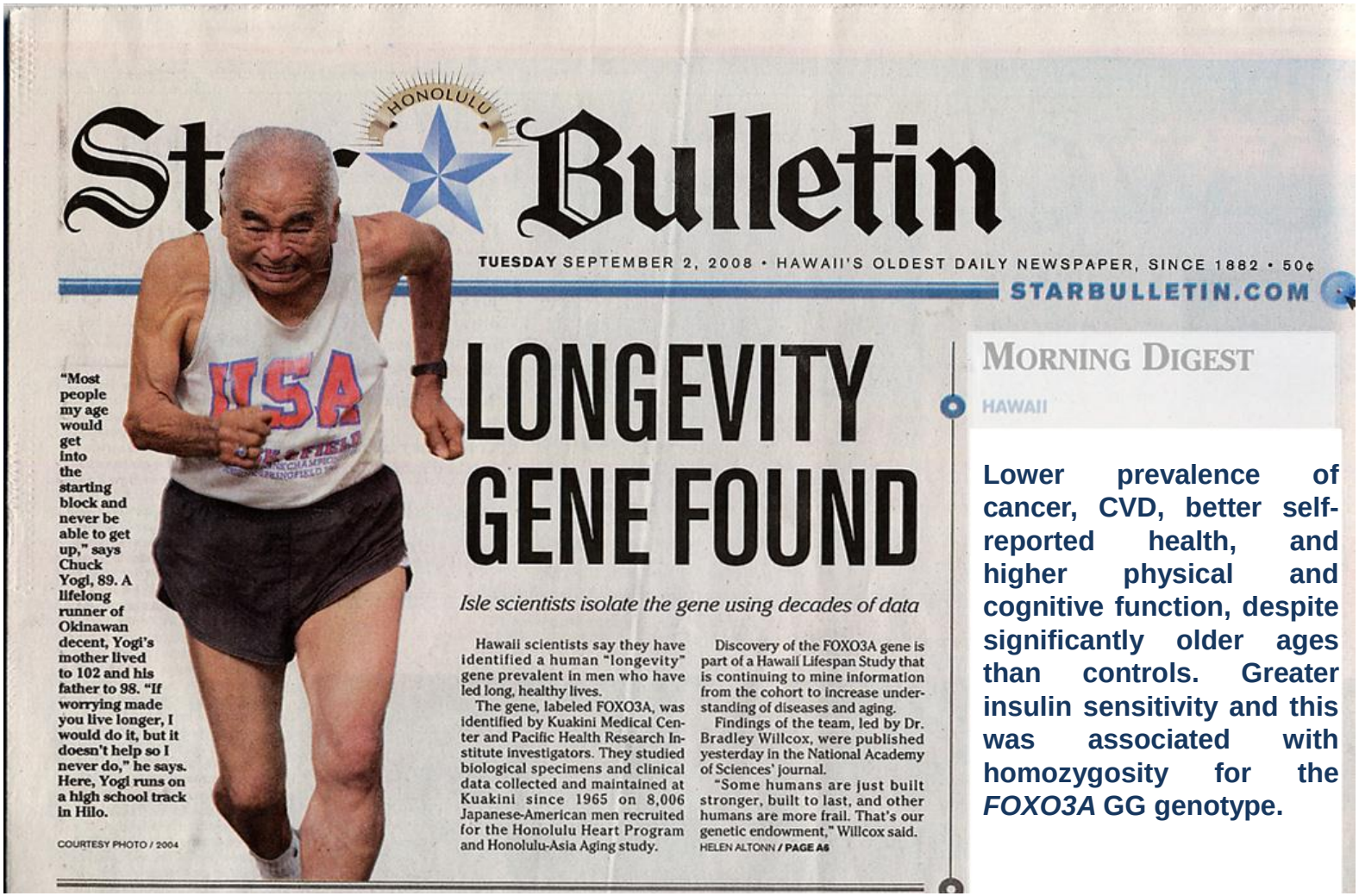


Almost 1000 Okinawan centenarians and numerous other elderly in their seventies, eighties, and nineties, have been studied from 1975



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.

Gene Varient in Insulin Signaling Pathway Strongly Associated with Healthy Aging and Longevity (Willcox et al. Proc Nat Acad Sci 2008)



HONOLULU Star-Bulletin

TUESDAY SEPTEMBER 2, 2008 • HAWAII'S OLDEST DAILY NEWSPAPER, SINCE 1882 • 50¢

STARBULLETIN.COM

"Most people my age would get into the starting block and never be able to get up," says Chuck Yogi, 89. A lifelong runner of Okinawan decent, Yogi's mother lived to 102 and his father to 98. "If worrying made you live longer, I would do it, but it doesn't help so I never do," he says. Here, Yogi runs on a high school track in Hilo.

COURTESY PHOTO / 2004

LONGEVITY GENE FOUND

Isle scientists isolate the gene using decades of data

Hawaii scientists say they have identified a human "longevity" gene prevalent in men who have led long, healthy lives.

The gene, labeled FOXO3A, was identified by Kuakini Medical Center and Pacific Health Research Institute investigators. They studied biological specimens and clinical data collected and maintained at Kuakini since 1965 on 8,006 Japanese-American men recruited for the Honolulu Heart Program and Honolulu-Asia Aging study.

Discovery of the FOXO3A gene is part of a Hawaii Lifespan Study that is continuing to mine information from the cohort to increase understanding of diseases and aging.

Findings of the team, led by Dr. Bradley Willcox, were published yesterday in the National Academy of Sciences' journal.

"Some humans are just built stronger, built to last, and other humans are more frail. That's our genetic endowment," Willcox said.

HELEN ALTONN / PAGE A6

MORNING DIGEST

HAWAII

Lower prevalence of cancer, CVD, better self-reported health, and higher physical and cognitive function, despite significantly older ages than controls. Greater insulin sensitivity and this was associated with homozygosity for the *FOXO3A* GG genotype.

Aging Cell (2016) pp1–8

The FoxO3 gene and cause-specific mortality

Bradley J. Willcox,[1,2] Gregory J. Tranah,[3] Randi Chen,[1] Brian J. Morris,[1,2,4] Kamal H. Masaki,[1,2] Qimei He,[1] D. Craig Willcox,[1,2,5] Richard C. Allsopp,[6] Stefan Moisyadi,[6] Leonard W. Poon,[7] Beatriz Rodriguez,[1,2] Anne B. Newman,[8] Tamara B. Harris,[9] Steven R. Cummings,[3] Yongmei Liu,[10] Neeta Parimi,[3] Daniel S. Evans,[3] Phil Davy,[6] Mariana Gerschenson[11] and Timothy A. Donlon[1]

Japanese (n = 3584)	Whites (n = 1794)	Blacks (n = 1281)

The G allele of the FOXO3 single nucleotide polymorphism (SNP) rs2802292 exhibits a consistently replicated genetic association with longevity in multiple populations worldwide. The aims of this study were to quantify the mortality risk for the longevity associated genotype and to discover the particular cause(s) of death associated with this allele. We found G allele carriers had a combined (Japanese, white, and black populations) risk reduction of 10% for total (all-cause) mortality (HR = 0.90; 95% CI, 0.84–0.95; P = 0.001). This effect size was consistent across populations and mostly contributed by 26% lower risk for CHD death (HR = 0.74; 95% CI, 0.64–0.86; P = 0.00004).

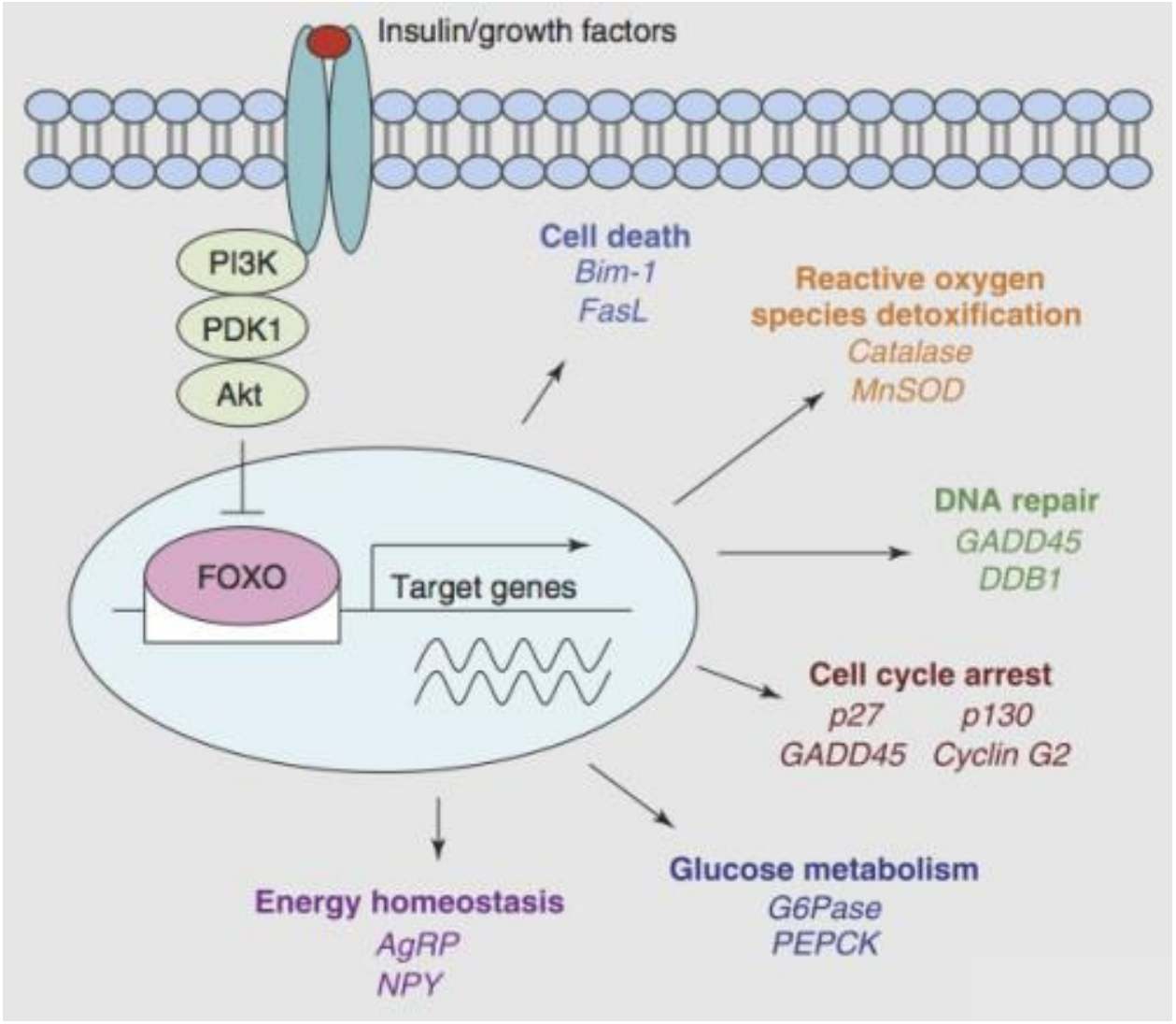
(A)

Cause of death	No. of deaths	HR* (95% CI)	*P*-value
Cancer	546	1.01 (0.85–1.19)	0.93
CHD (coronary heart disease)	524	0.75 (0.63–0.90)	0.001
Stroke	315	0.97 (0.77–1.21)	0.76
Dementia	221	1.01 (0.78–1.32)	0.93
Other cardiovascular disease (CVD)	213	0.85 (0.65–1.11)	0.23
Infectious disease	188	0.91 (0.68–1.21)	0.52
Chronic obstructive pulmonary disease (COPD)	117	0.83 (0.57–1.19)	0.31
Renal failure	45	0.86 (0.48–1.55)	0.61
GI (gastrointestinal disease)	39	1.22 (0.65–2.30)	0.54
Other deaths	480	0.86 (0.72–1.03)	0.09

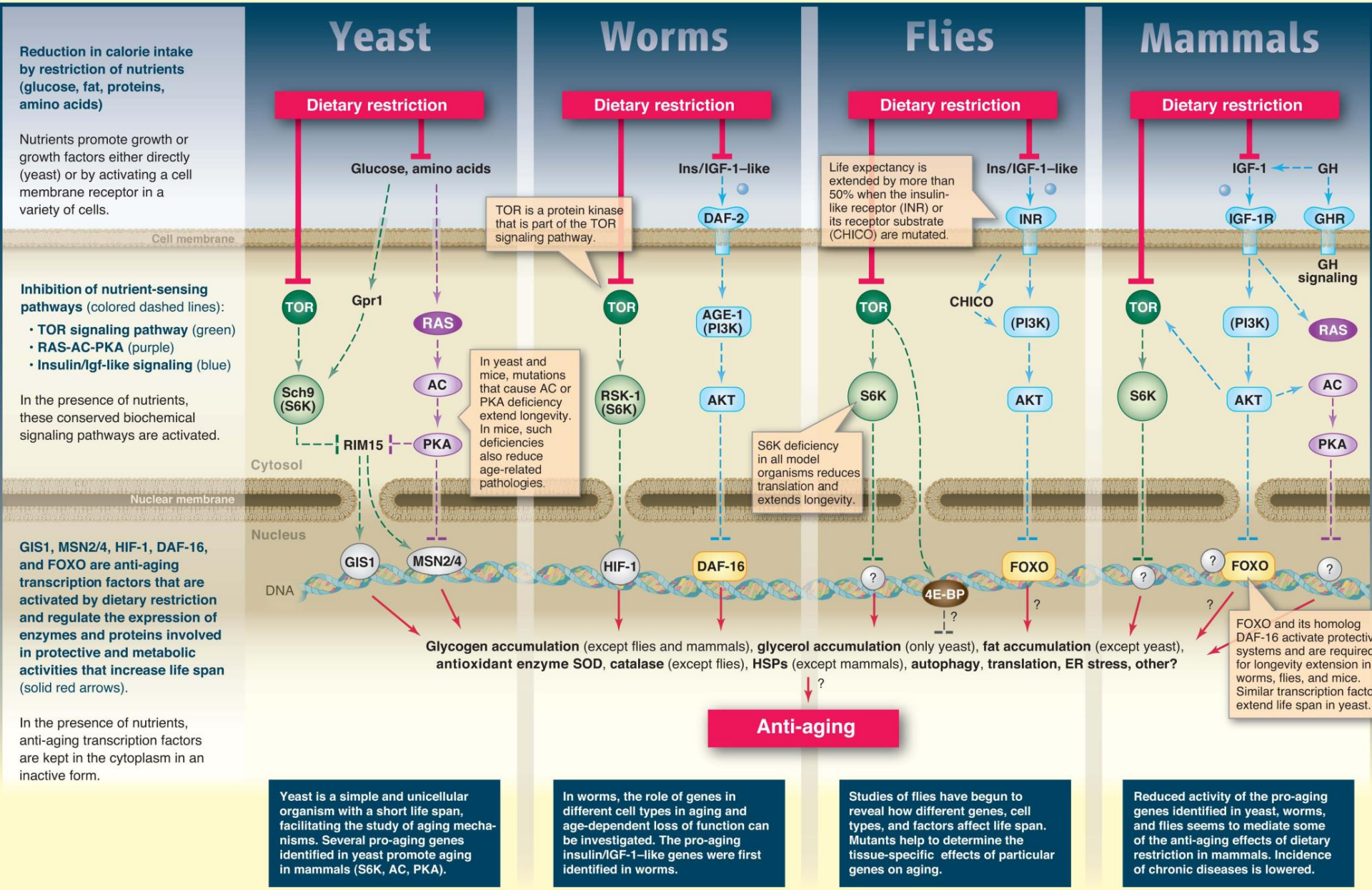
Aging Cell (2016) **15**, pp196–207 Doi: 10.1111/acel.12427

REVIEW

Long live FOXO: unraveling the role of FOXO proteins in aging and longevity



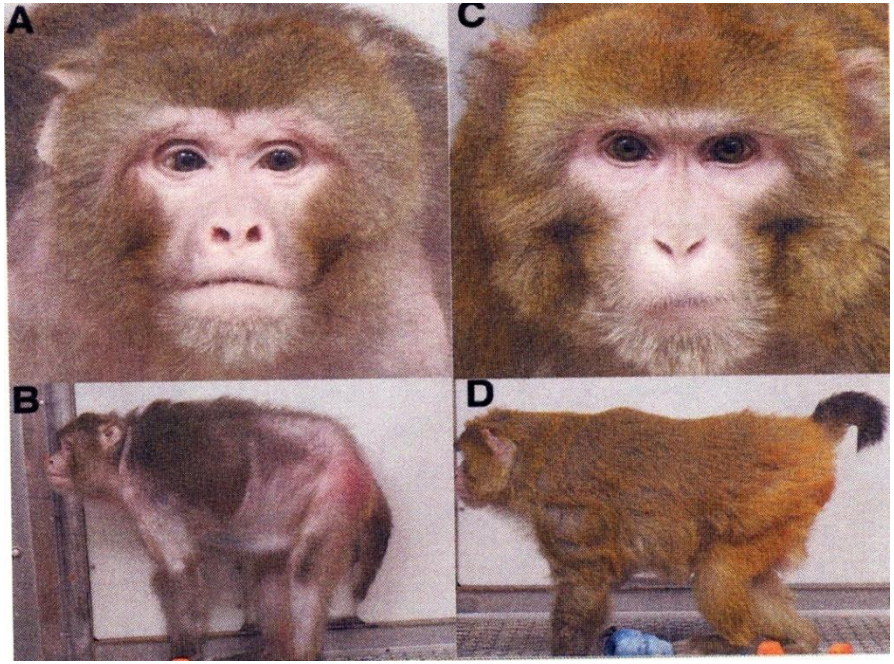
Conserved Nutrient Signaling Pathways Regulating Longevity



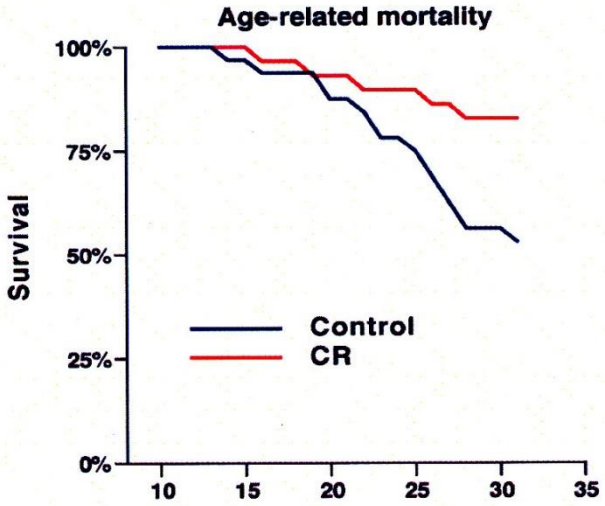
Fontana L et al. Science 2010

Caloric Restriction : Most Powerful Anti-Aging Intervention

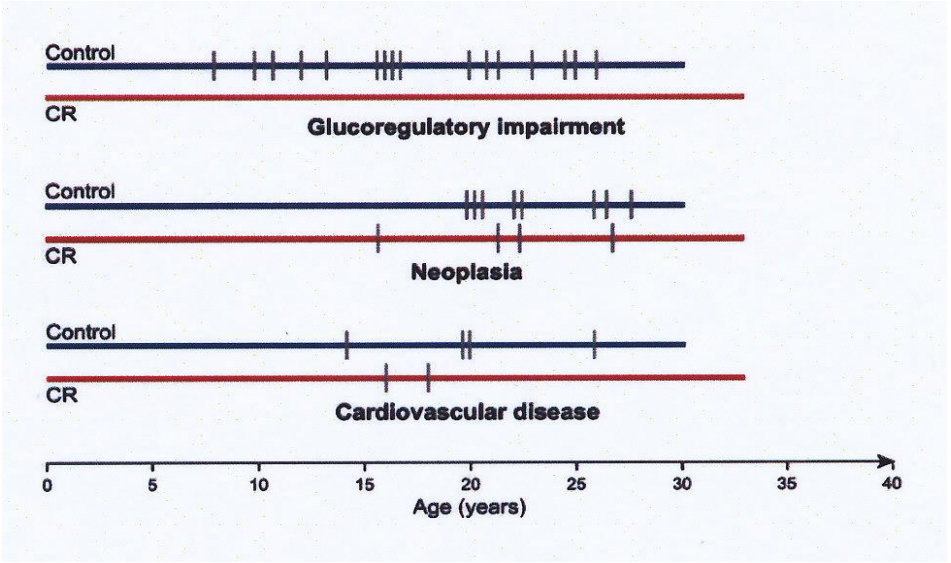
Caloric restriction reduces age-related and all-cause mortality in rhesus monkeys. Colman RJ, Beasley TM, Kemnitz JW, Johnson SC, Weindruch R, Anderson RM. Nat Commun. 2014 Apr 1;5:3557



Ad libitum **CR**



P = 0.03
HR = 3.0



Oxidative Stress and Longevity in Okinawa: An Investigation of Blood Lipid Peroxidation and Tocopherol in Okinawan Centenarians

Current Gerontology and Geriatrics Research
Volume 2010, Article ID 380460

Makoto Suzuki,[1,2,3] D. Craig Willcox,[1,2,4]
Matthew W. Rosenbaum,[1] and Bradley J. Willcox[1,4,5,6,7]

TABLE 1: Plasma lipid peroxide in young, middle-aged, and older age groups (mean and SD), nmol/ml. LPO levels were measured using the TBA method [21, 22].

	20s	30s	70s	80s	100s
Male	3.34 ± 1.79	4.06 ± 1.24	3.15 ± 0.70	2.92 ± 0.32	1.49 ± 0.51
(*n*)	(4)	(8)***	(11)***	(5)***	(30)
Female	3.18 ± 0.64	2.95 ± 0.53	3.56 ± 0.81	2.90 ± 0.46	1.72 ± 1.28
(*n*)	(4)*	(8)**	(18)***	(3)	(109)
Total	3.30 ± 1.25	3.51 ± 1.08	3.40 ± 0.79	2.91 ± 0.34	1.67 ± 1.16
(*n*)	(8)***	(16)***	(29)***	(8)***	(139)

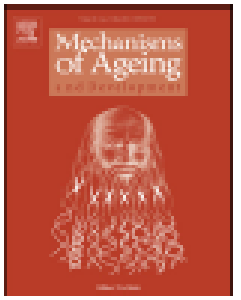
Significant difference between centenarians and particular age group: $*P < .05$, $**P < .01$, $***P < .001$.

Conclusions. The low plasma level of LPO in Okinawan centenarians, compared to younger controls, argues for protection against oxidative stress in the centenarian population and is consistent with the predictions of the Free Radical Theory of Aging.

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

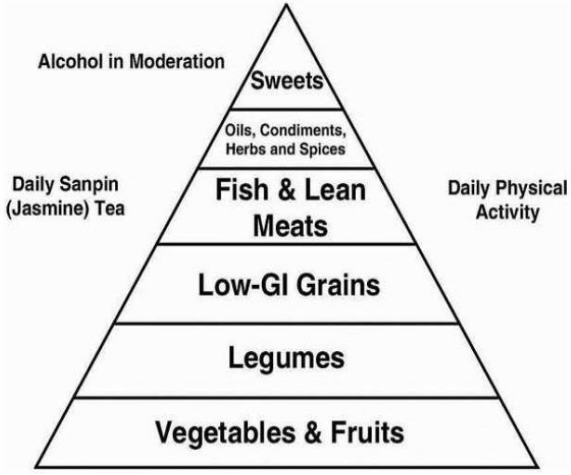
1) Low Caloric Density (plant-based, low fat, moderate protein from soy, fish, lean meats)

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

Extending healthy ageing: nutrient sensitive pathway and centenarian population

IMMUNITY & AGEING

Sergio Davinelli[1], D Craig Willcox[2], Giovanni Scapagnini[1]*

1 Department of Health Sciences, University of Molise, Campobasso, Italy
2 Department of Human Welfare, Okinawa International University, Ginowan, Japan
* Corresponding author

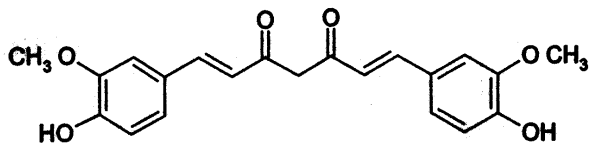
Abstract

Ageing is a challenge for any living organism and human longevity is a complex phenotype. With increasing life expectancy, maintaining long-term health, functionality and well-being during ageing has become an essential goal. To increase our understanding of how ageing works, it may be advantageous to analyze the phenotype of centenarians, perhaps one of the best examples of successful ageing. Healthy ageing involves the interaction between genes, the environment, and lifestyle factors, particularly diet. Besides evaluating specific gene-environment interactions in relation to exceptional longevity, it is important to focus attention on modifiable lifestyle factors such as diet and nutrition to achieve extension of health span. Furthermore, a better understanding of human longevity may assist in the design of strategies to extend the duration of optimal human health. In this article we briefly discuss relevant topics on ageing and longevity with particular focus on dietary patterns of centenarians and nutrient-sensing pathways that have a pivotal role in the regulation of life span. Finally, we also discuss the potential role of Nrf2 system in the pro-ageing signaling emphasizing its phytohormetic activation.

Davinelli et al. Immunity & Ageing 2012

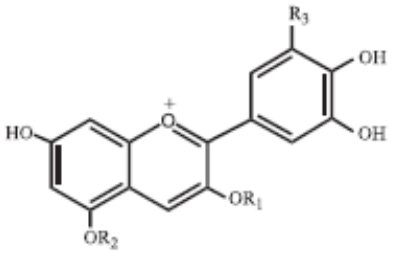
Healthy aging diets other than the Mediterranean: A focus on the Okinawan diet. Willcox DC, Scapagnini G, Willcox BJ. Mech Ageing Dev. 2014 Jan 21.

Curcuma longa



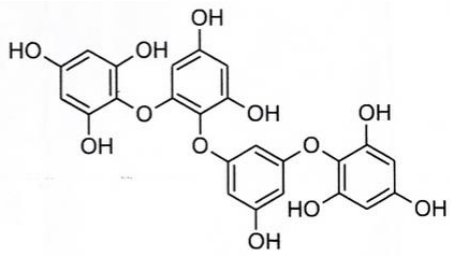
Curcumin

Ipomoera batatas cultivar Ayamurasaki



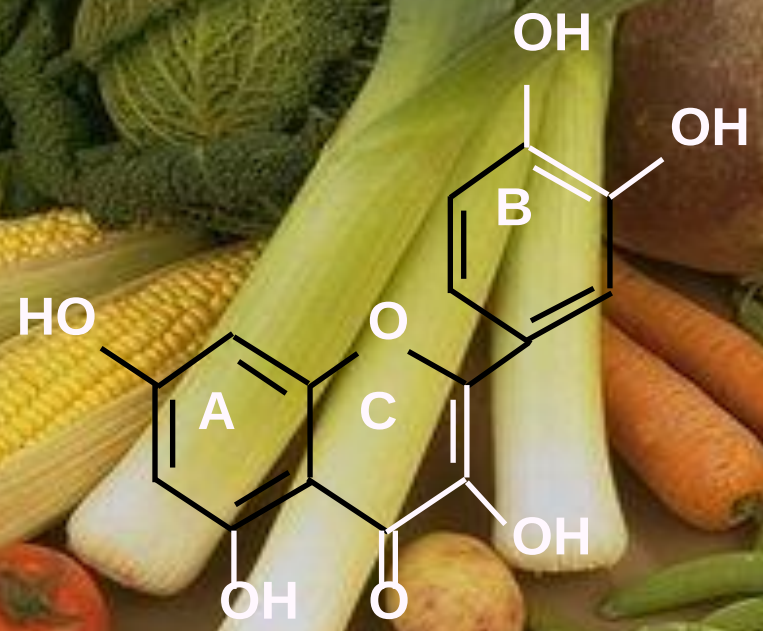
Anthocyanin

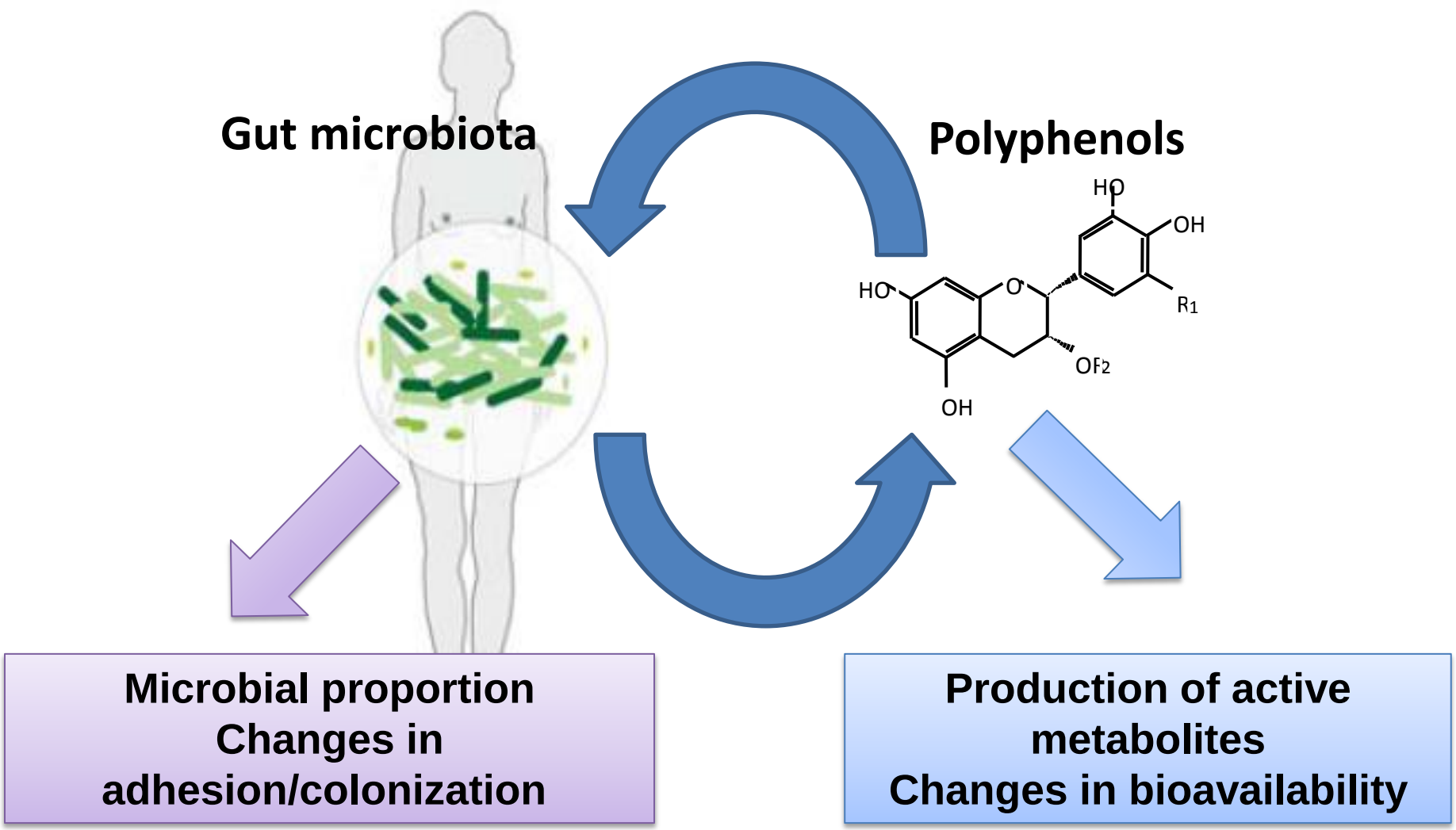
Wakame Undaria pinnatifida



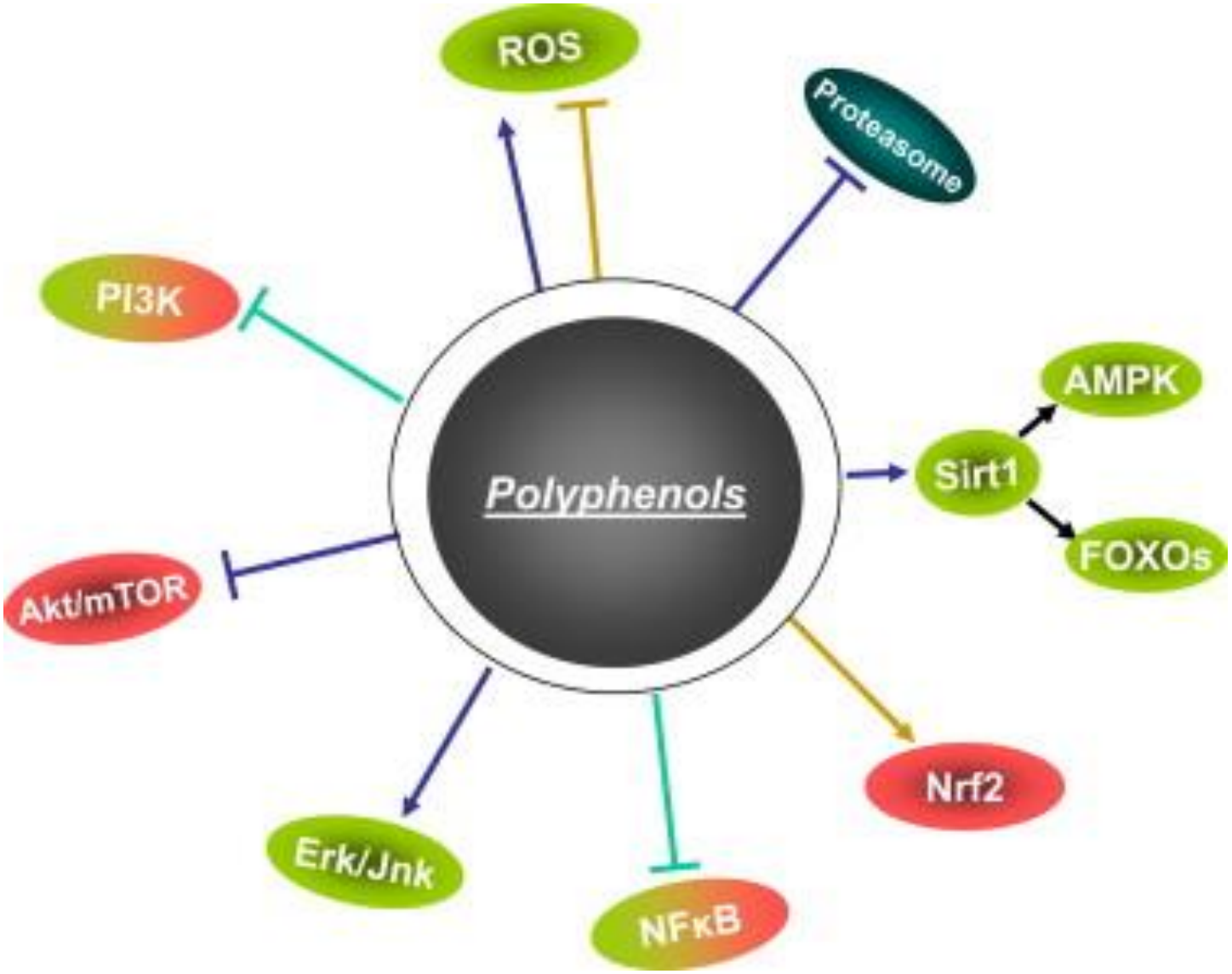
Phlorotannin

POLYPHENOLS

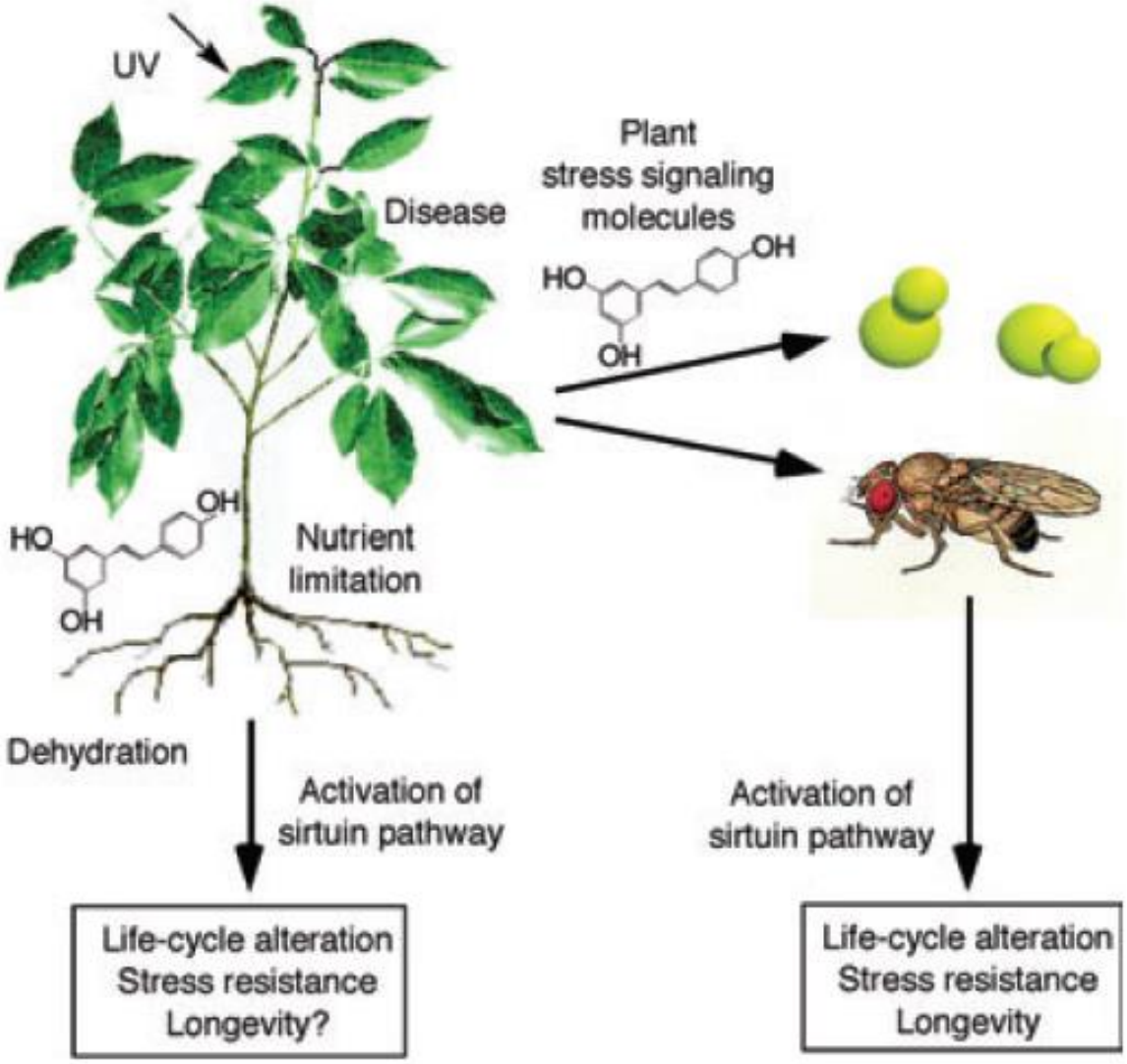



Gut microbiota
Polyphenols
HO
OH
HO
O
R1
OH2
OH
Microbial proportion
Changes in
adhesion/colonization
Production of active
metabolites
Changes in bioavailability

Major pathways activated by polyphenols



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

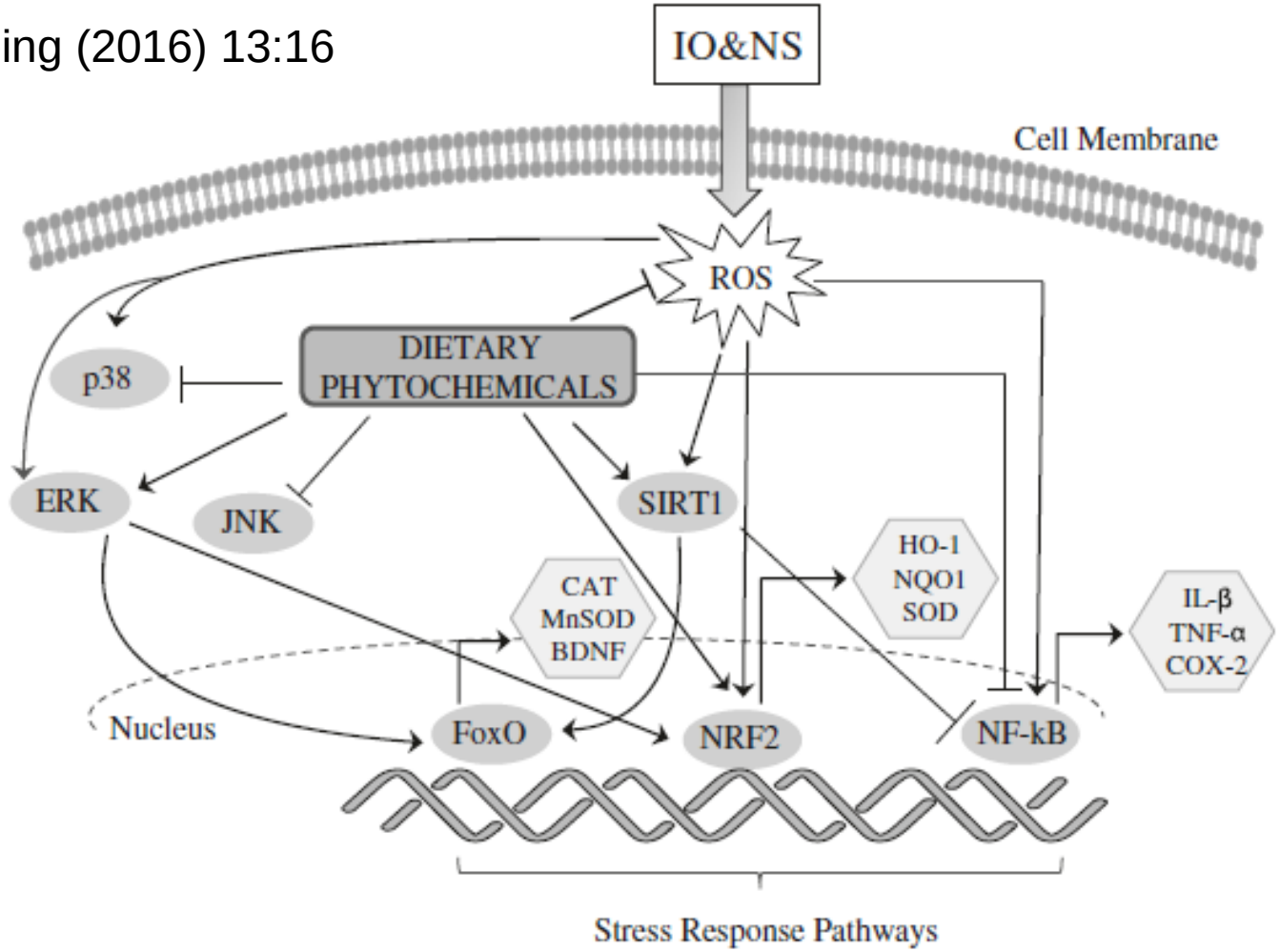


Lamming DW, Wood JG, Sinclair DA. Small molecules that regulate lifespan: evidence for xenohormesis. Molecular Microbiology (2004)

Dietary phytochemicals and neuro-inflammaging: from mechanistic insights to translational challenges

Sergio Davinelli[1*], Michael Maes[2,3], Graziamaria Corbi[1], Armando Zarrelli[4], Donald Craig Willcox[5,6] and Giovanni Scapagnini[1]

Immunity & Ageing (2016) 13:16

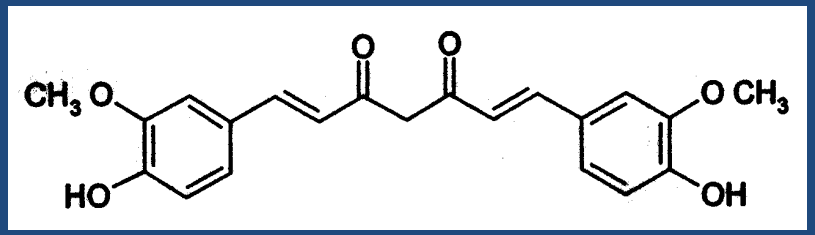


Scapagnini G, Colombrita C, Amadio M, D'Agata V, Arcelli E, Sapienza M, Quattrone A, Calabrese V.

Curcumin activates defensive genes and protects neurons against oxidative stress.

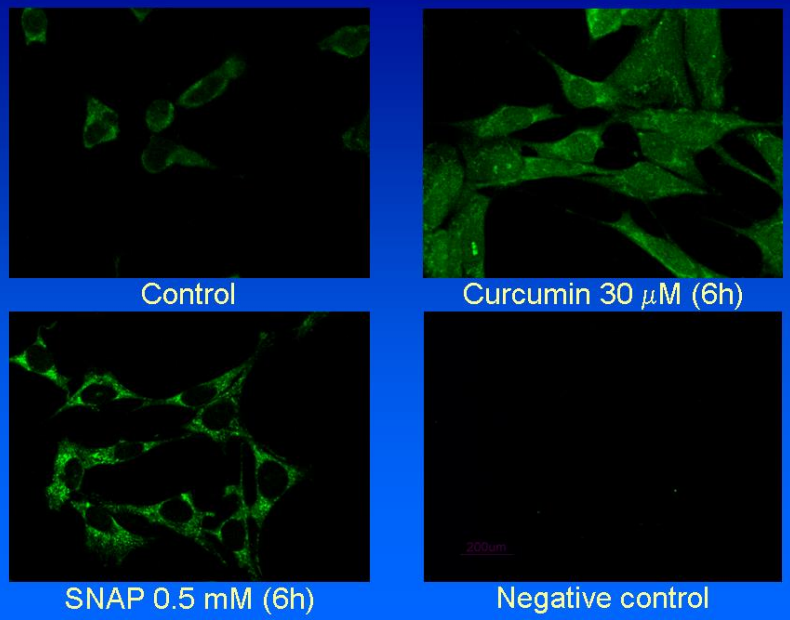
Antioxid Redox Signal. 2006 Mar-Apr;8(3-4):395-403.

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

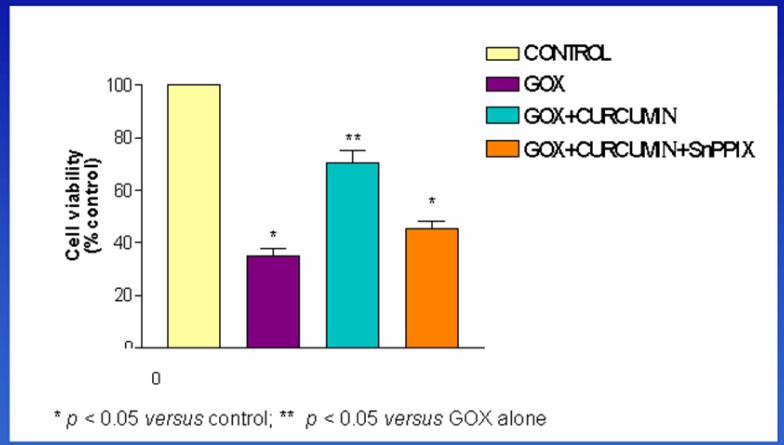


CURCUMIN

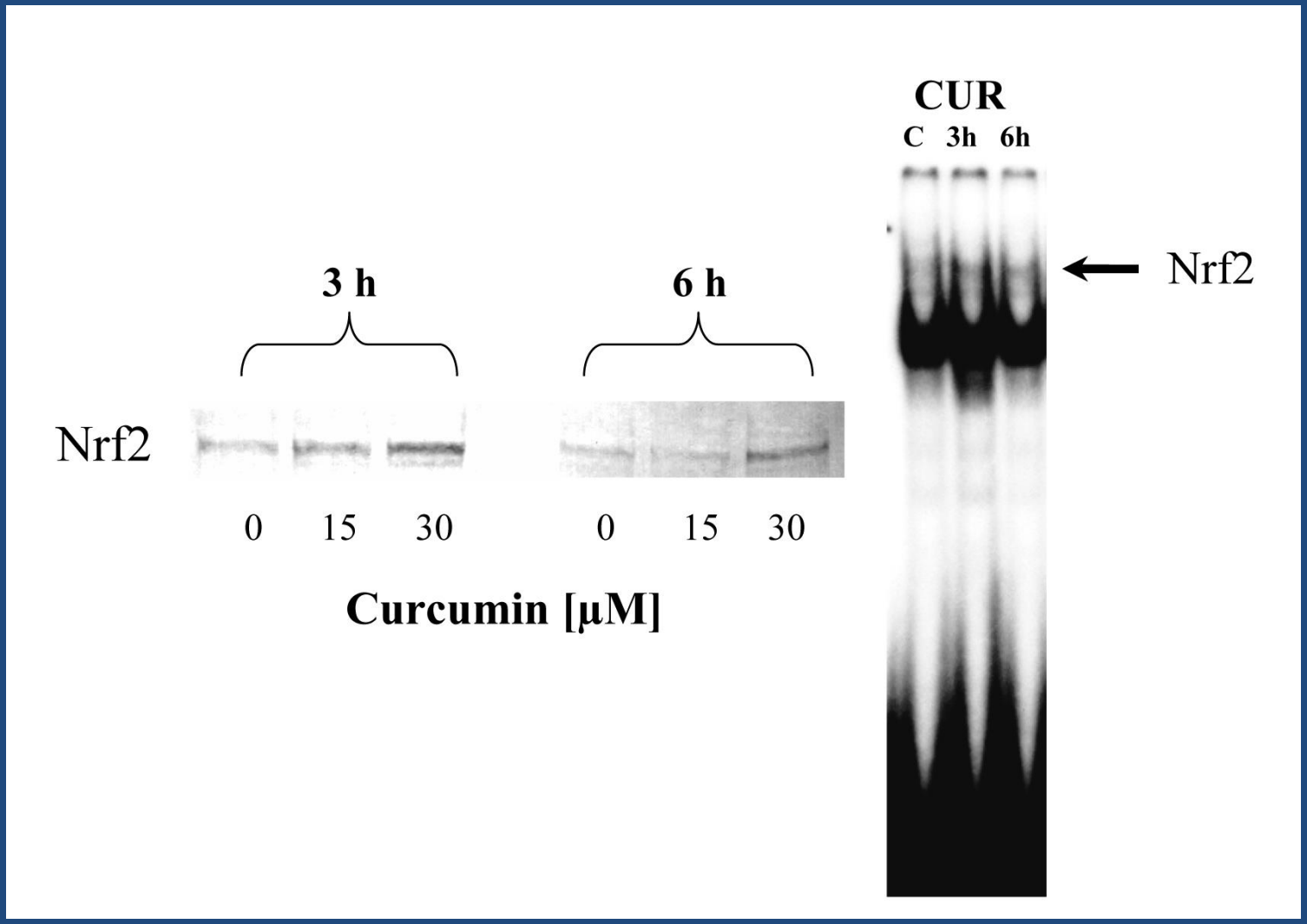
Effect of curcumin and SNAP on HO-1 protein expression in astrocytes



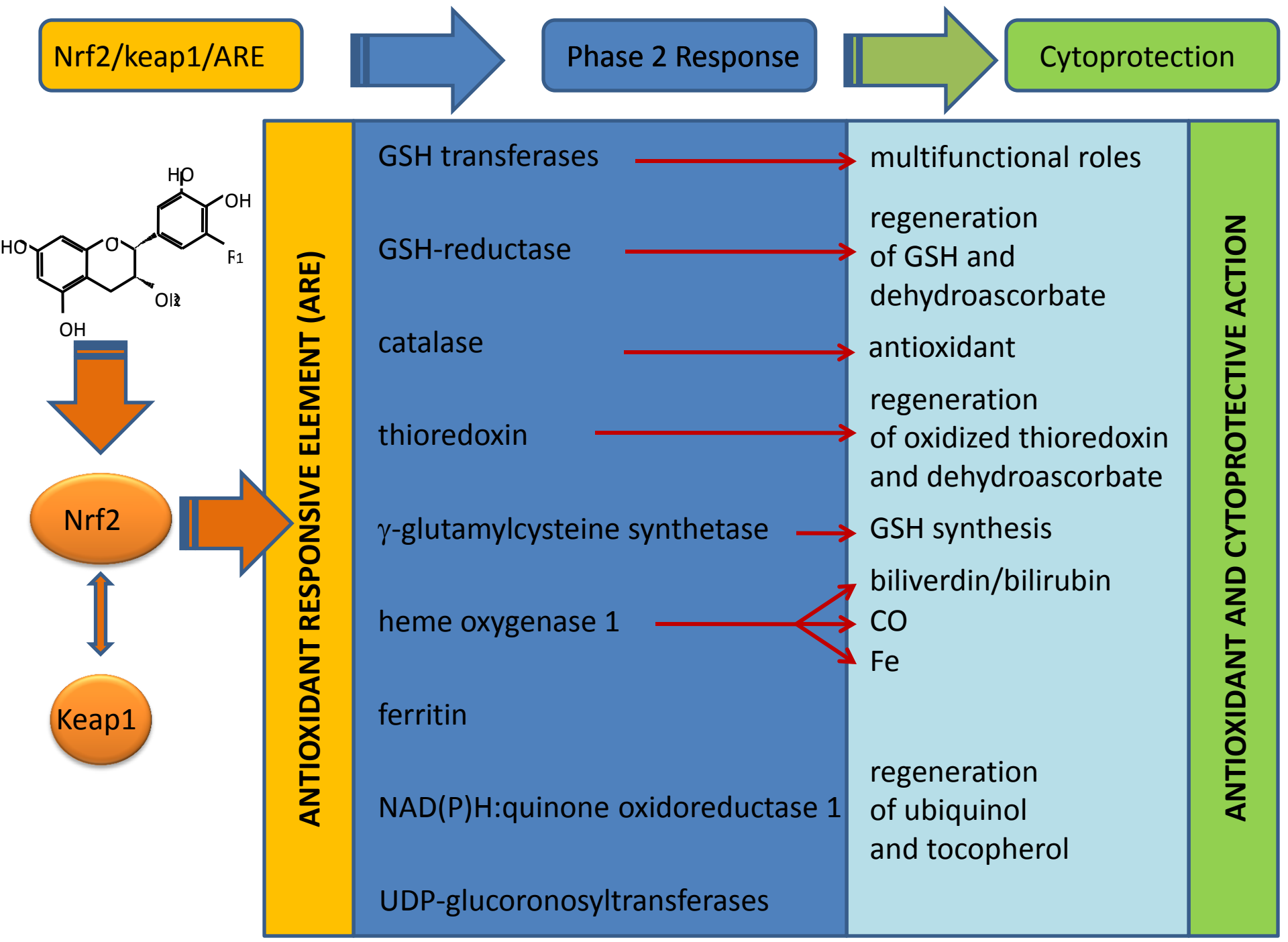
Effect of curcumin on glucose oxidase (GOX) mediated cellular injury in cortical neurons



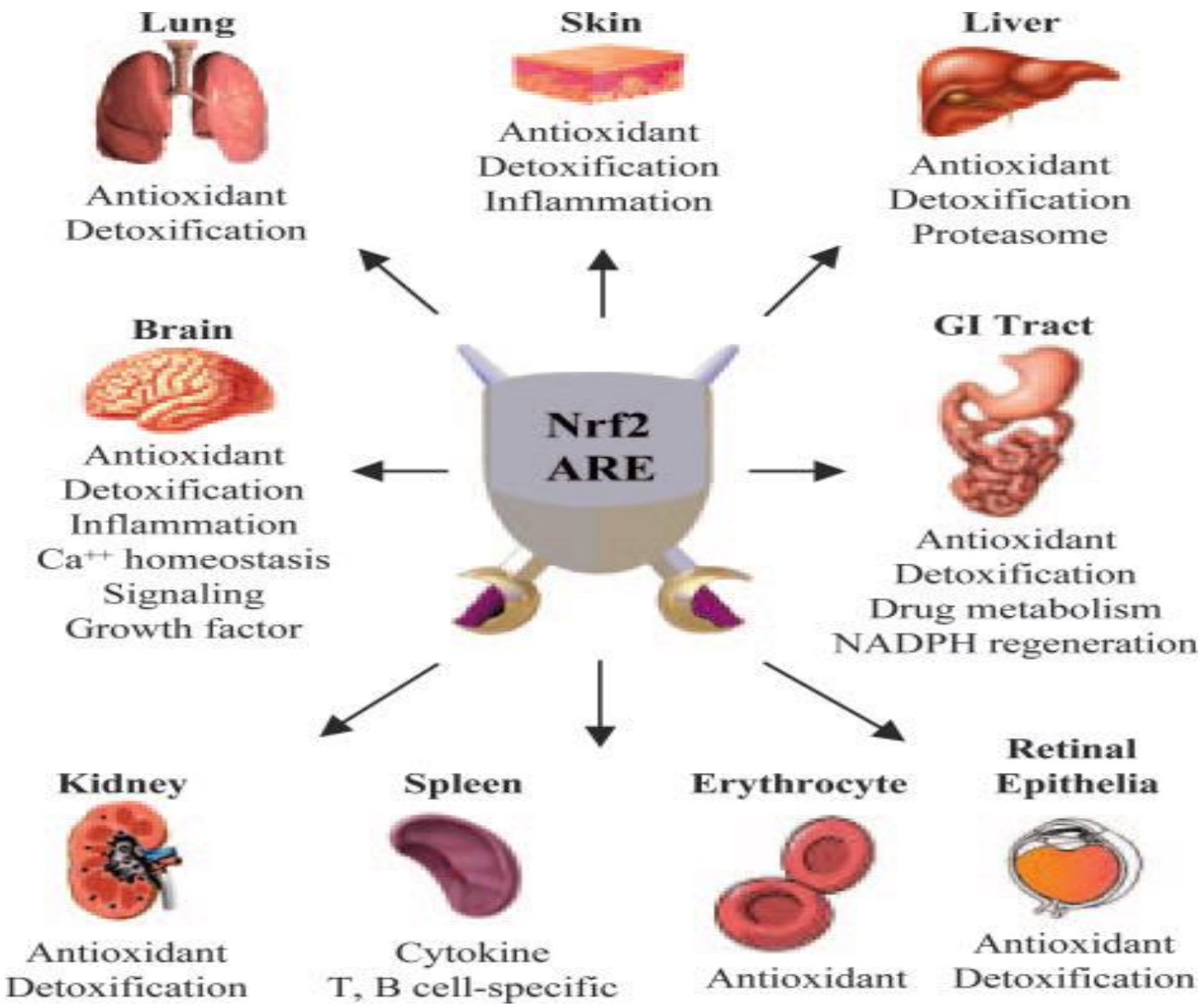
Curcumin activates Nrf2 expression and stimulates ARE-binding activity



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
multifunctional roles
GSH-reductase
regeneration of GSH and dehydroascorbate
catalase
antioxidant
thioredoxin
regeneration of oxidized thioredoxin and dehydroascorbate
γ-glutamylcysteine synthetase
GSH synthesis
heme oxygenase 1
biliverdin/bilirubin
CO
Fe
ferritin
NAD(P)H:quinone oxidoreductase 1
regeneration of ubiquinol and tocopherol
UDP-glucoronosyltransferases
ANTIOXIDANT AND CYTOPROTECTIVE ACTION

Multi-organ protection by the Nrf2 pathway

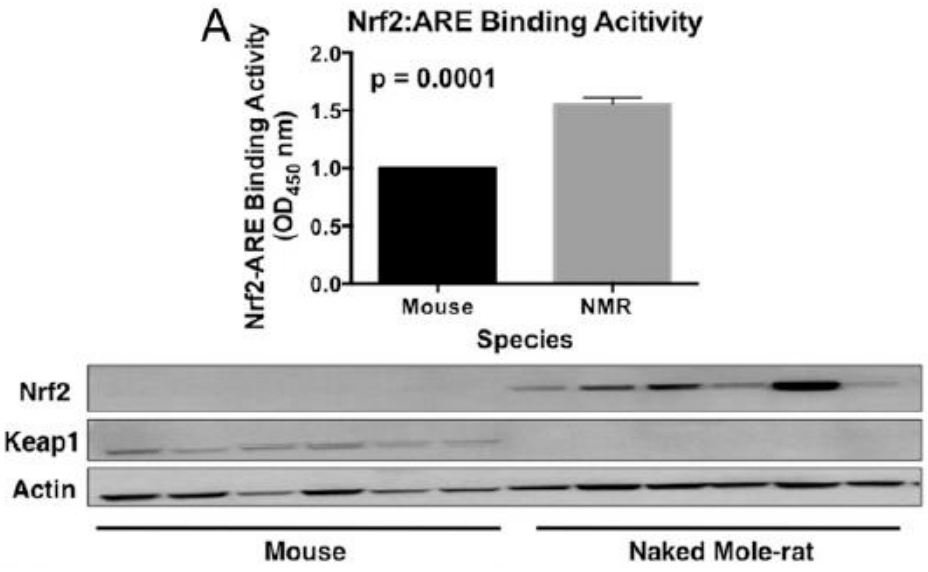


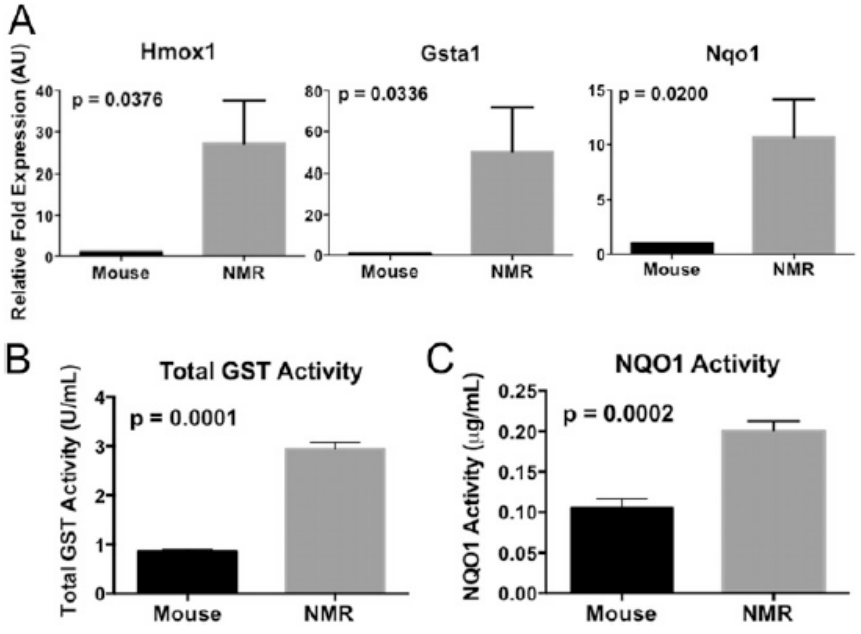
Regulation of Nrf2 signaling and longevity in naturally long-lived rodents

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

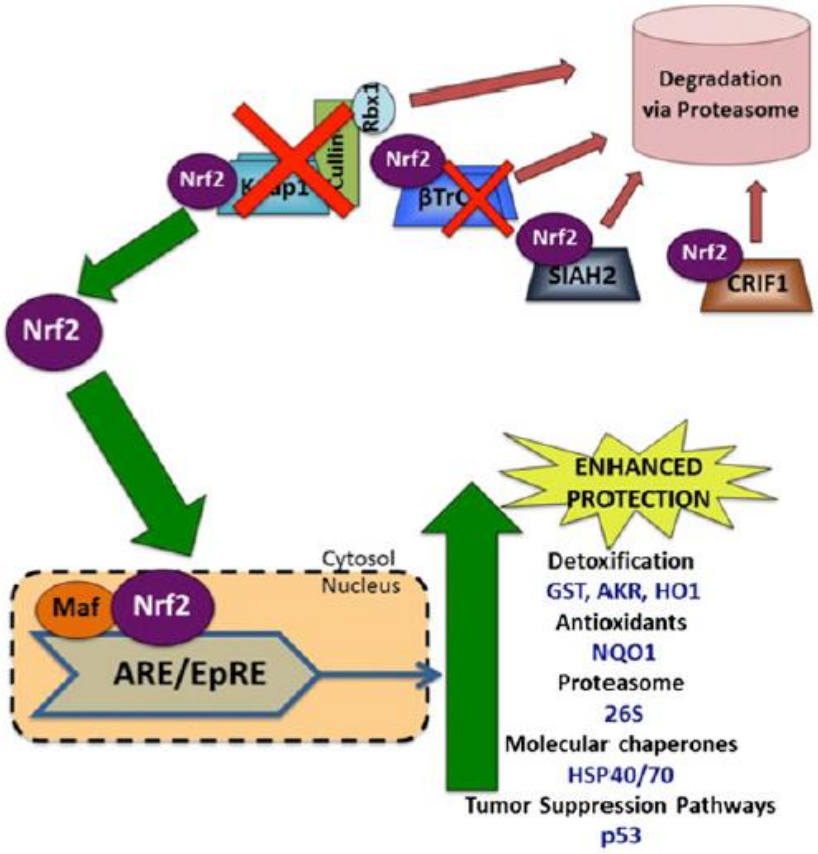
3722–3727 | PNAS | March 24, 2015 | vol. 112 | no. 12

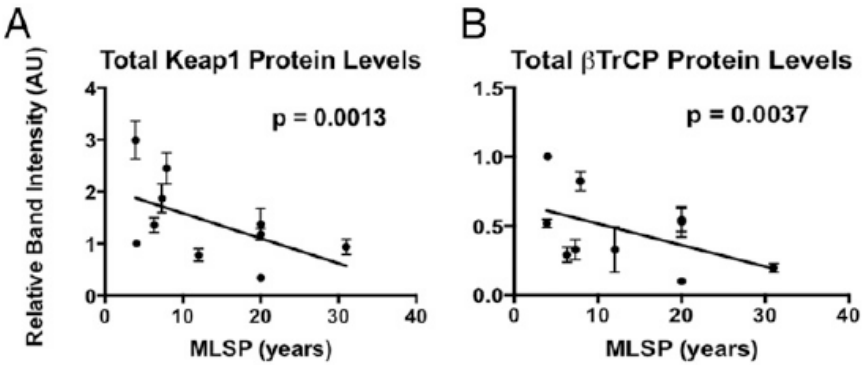




3722–3727 | PNAS | March 24, 2015 | vol. 112 | no. 12

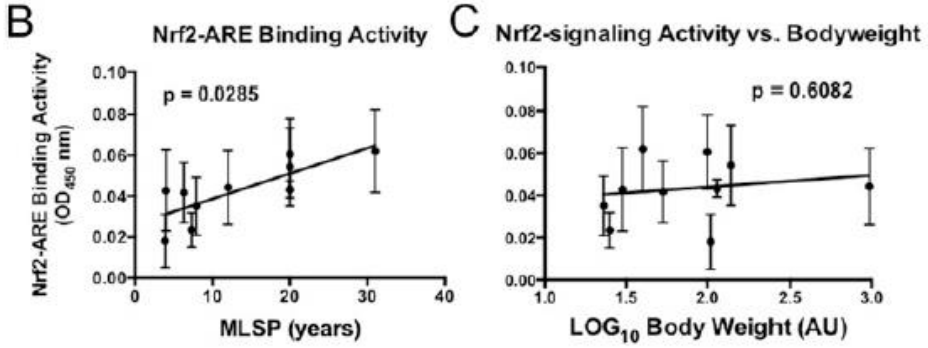
Naked mole-rat constitutive Nrf2 upregulation





A

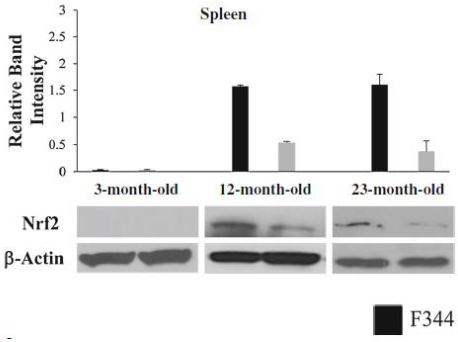
Common Name	Species Name	MLSP (years)	BW (g)
Laboratory Mouse	*Mus musculus*	4	30
Naked Mole-rat	*Heterocephalus glaber*	31	40
White-footed Mouse	*Peromyscus leucopus*	7.9	23
Damaraland Mole-rat	*Fukomys damarensis*	20	140
Guinea Pig	*Cavia porcellus*	12	970
Gerbil	*Meriones unguiculatus*	6.3	53
Blind Mole-rat	*Spalax judaei*	20	100
Blind Mole-rat	*Spalax carmeli*	20	115
Hamster	*Mesocricetus auratus*	3.9	105
Cactus Mouse	*Peromyscus eremicus*	7.3	25

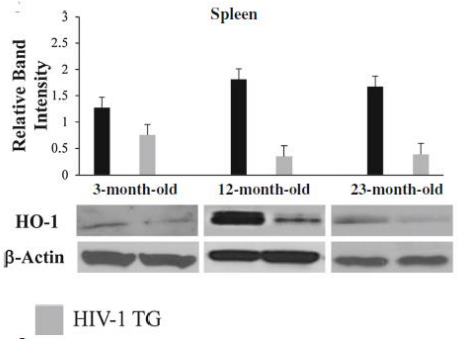


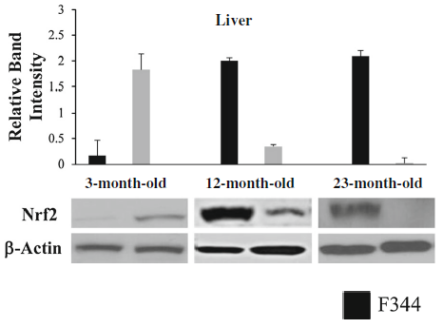
Altered expression pattern of Nrf2/HO-1 axis during accelerated-senescence in HIV-1 transgenic rat

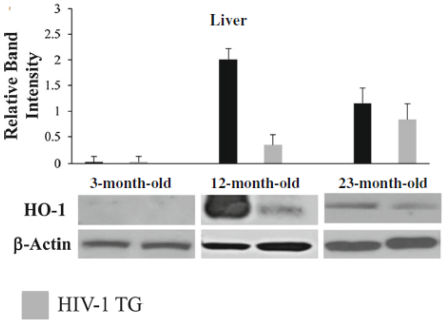
Biogerontology Received: 25 January 2014 / Accepted: 23 June 2014

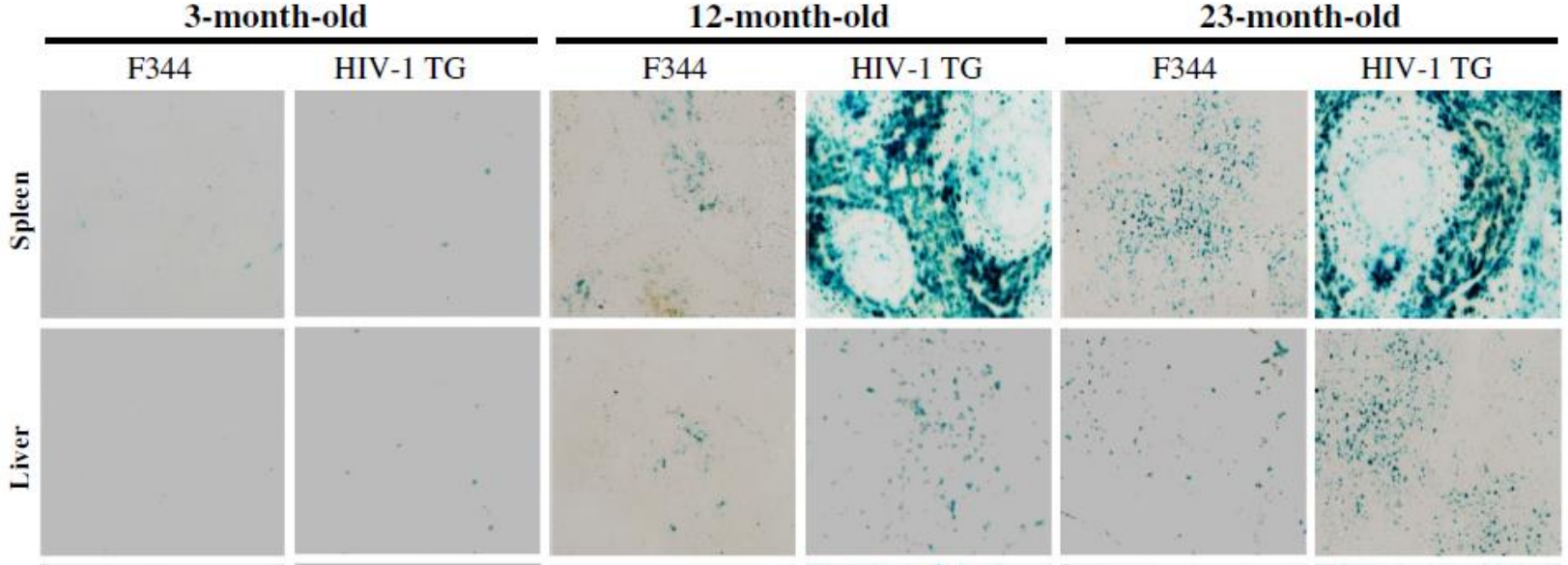
Sergio Davinelli · Giovanni Scapagnini · Frank Denaro · Vittorio Calabrese · Francesca Benedetti · Selvi Krishnan · Sabrina Curreli · Joseph Bryant · Davide Zella







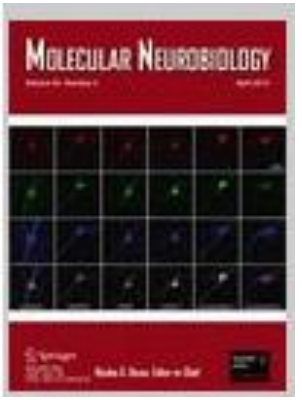




Modulation of Nrf2/ARE pathway by food polyphenols: a nutritional neuroprotective strategy for cognitive and neurodegenerative disorders.

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.

G. Scapagnini (✉)
Department of Health Sciences, University of Molise, Campobasso, Italy
e-mail: gscapag@gmail.com

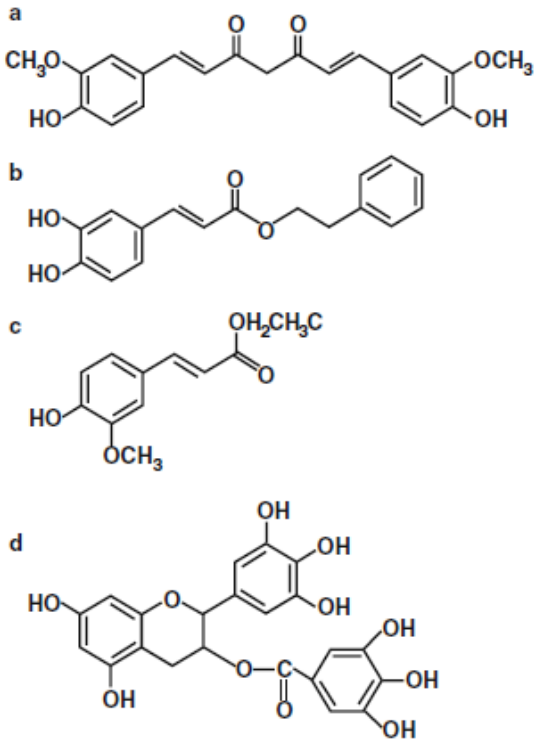
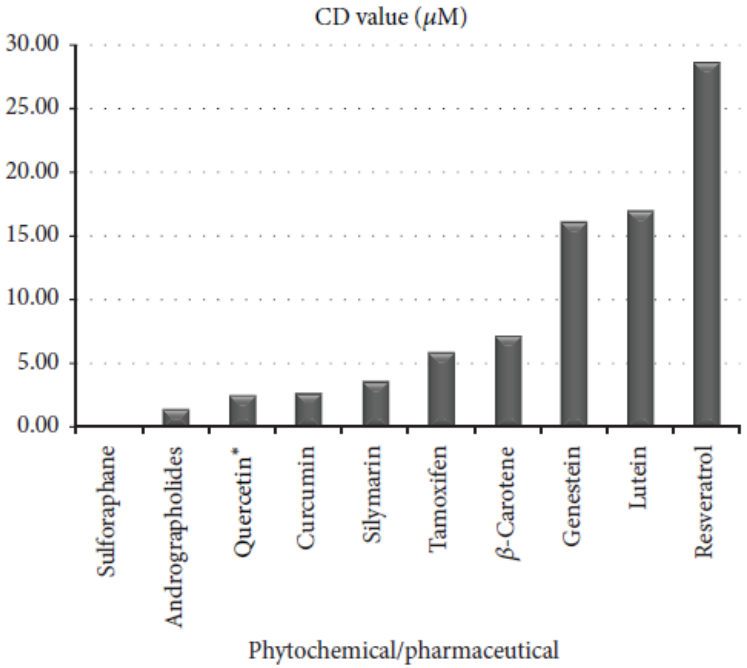


Fig. 1 The chemical structures of curcumin (**a**), CAPE (**b**), EFE (**c**), (−)-EGCG (**d**)

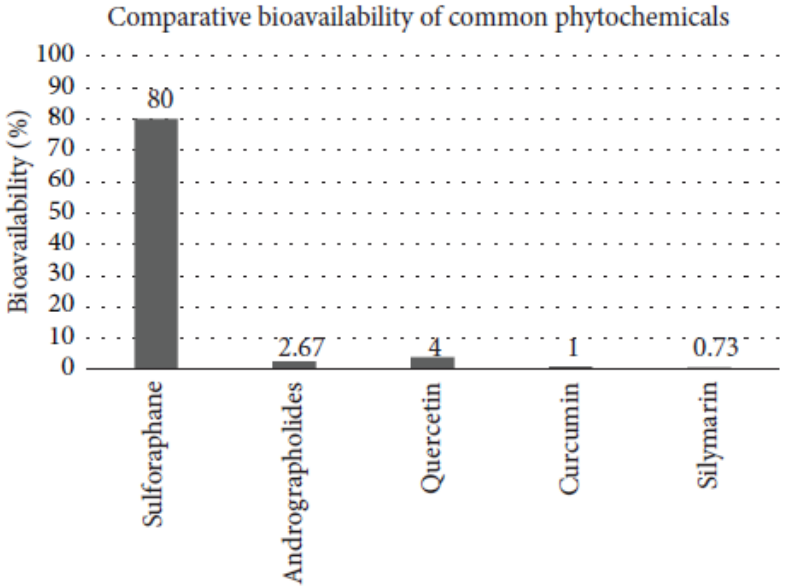
Sulforaphane and Other Nutrigenomic Nrf2 Activators: Can the Clinician's Expectation Be Matched by the Reality?

Oxidative Medicine and Cellular Longevity Volume 2016

Christine A. Houghton, Robert G. Fassett, and Jeff S. Coombes



CDvalues of popular phytochemicals used as supplements and a commonly prescribed pharmaceutical. CD values refer to the concentration of a compound required to double the activity of the Phase II detoxification enzyme, quinone reductase



Comparative bioavailability of phytochemicals commonly used in supplements

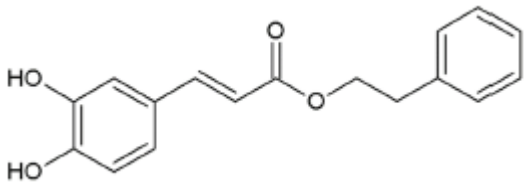
OPEN ACCESS Freely available online

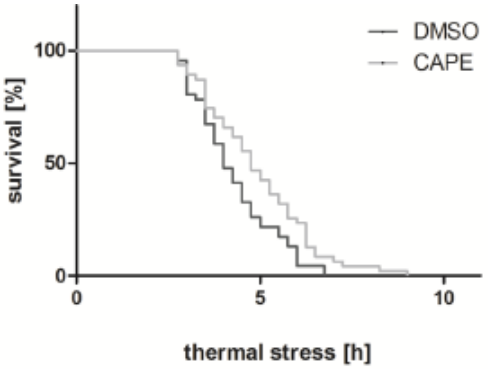
PLOS ONE

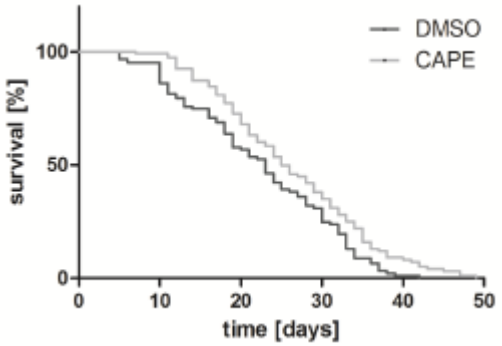
Caffeic Acid Phenethylester Increases Stress Resistance and Enhances Lifespan in *Caenorhabditis elegans* by Modulation of the Insulin-Like DAF-16 Signalling Pathway

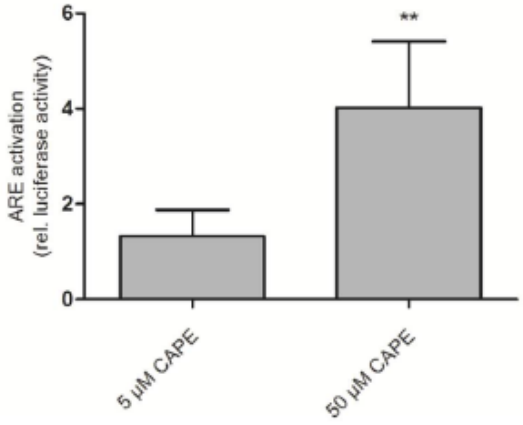
Susannah Havermann[1,2,3], Yvonni Chovolou[1], Hans-Ulrich Humpf[2], Wim Wätjen[1,3]*

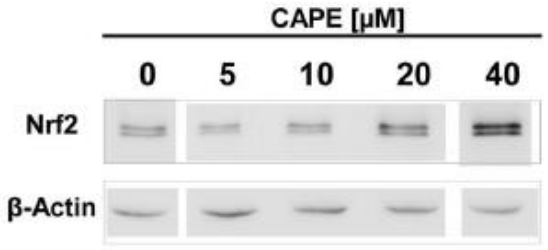
1 Institute of Toxicology, Heinrich-Heine-Universität, Düsseldorf, Germany, **2** Institute of Food Chemistry, Westfälische Wilhelms-Universität, Münster, Germany, **3** Institute of Agricultural and Nutritional Sciences, Martin-Luther-Universität Halle-Wittenberg, Halle/Saale, Germany

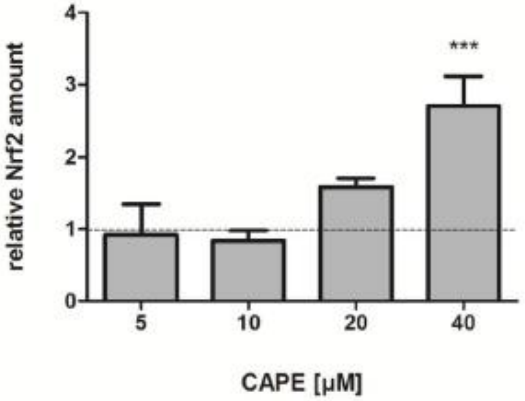












Contents lists available at ScienceDirect

Journal of Affective Disorders

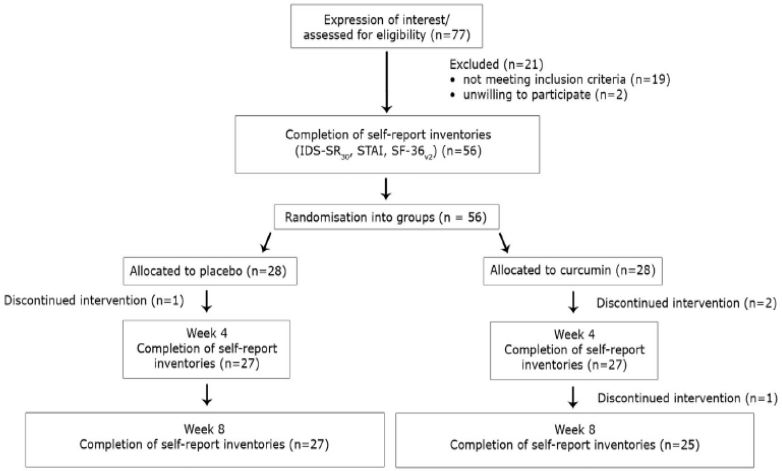
journal homepage: www.elsevier.com/locate/jad

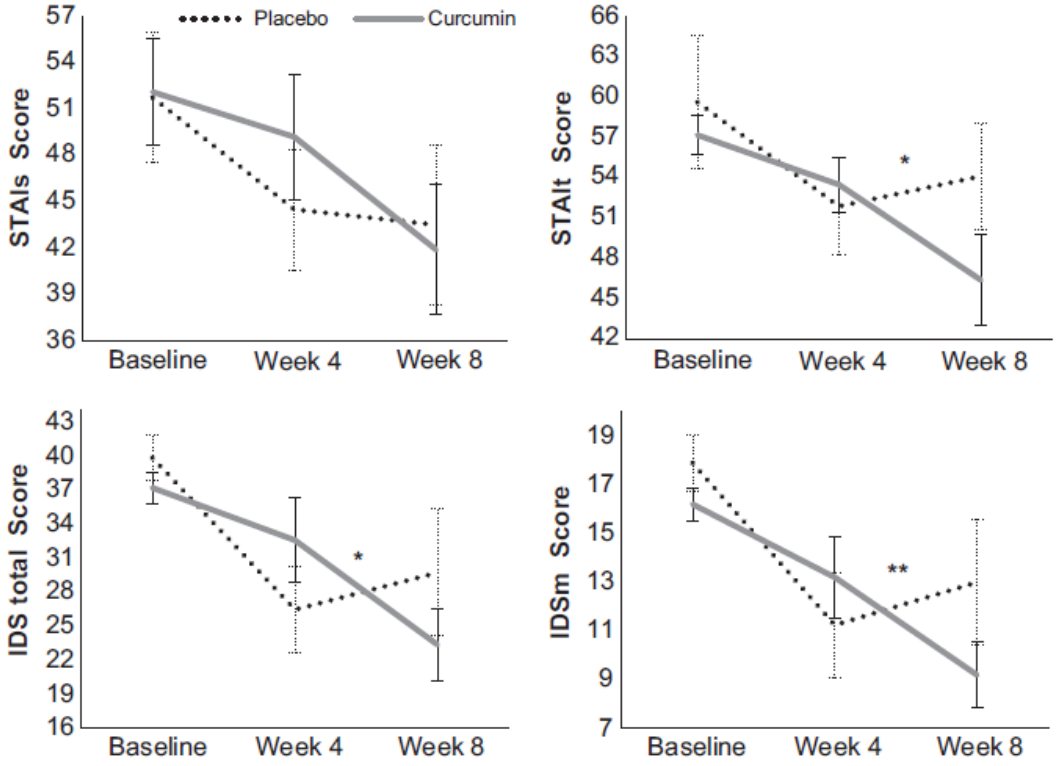
Research report

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]

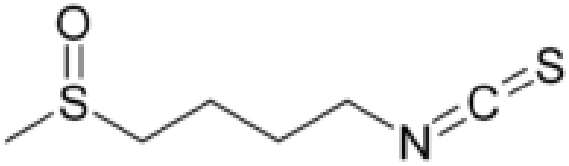


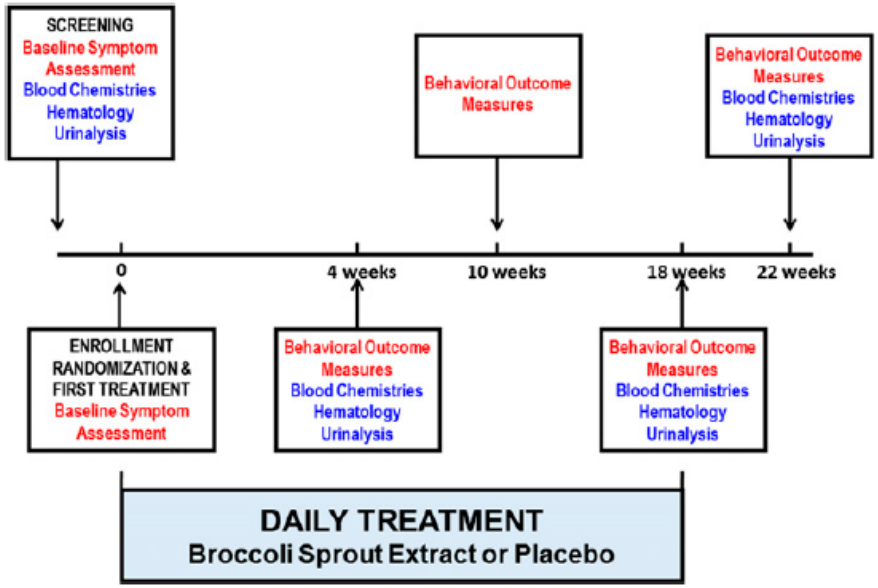


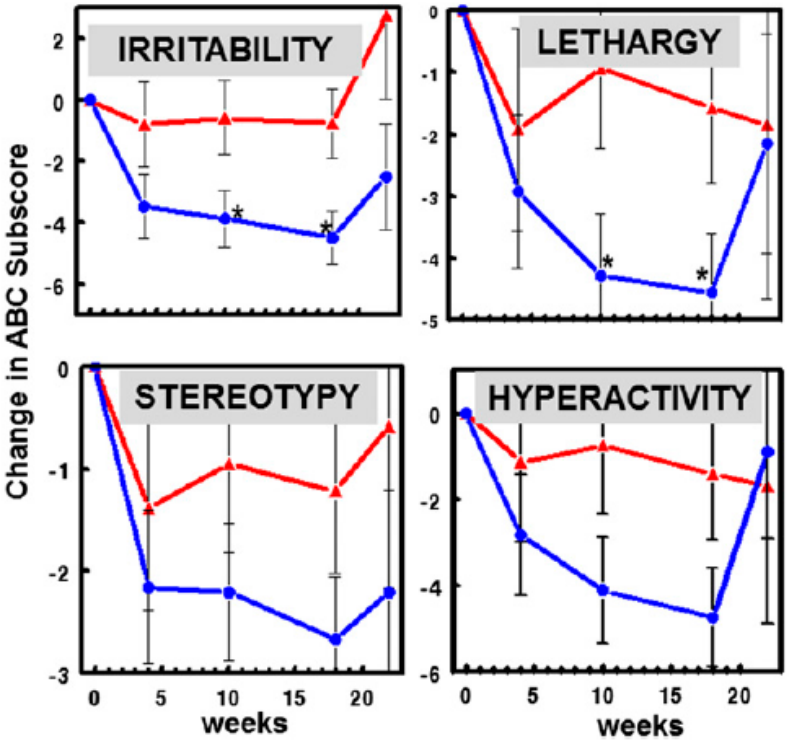
Sulforaphane treatment of autism spectrum disorder (ASD)

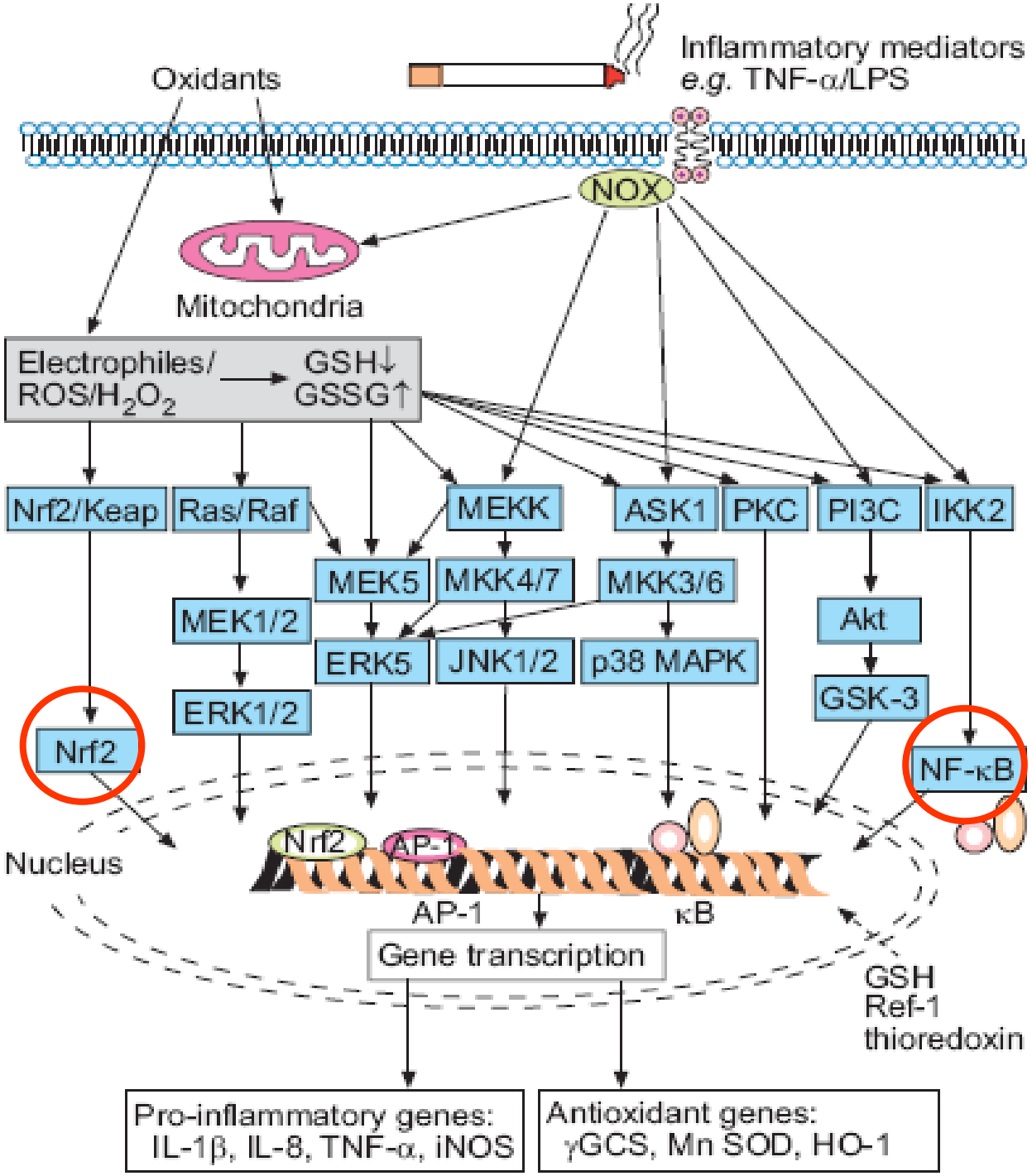
PNAS | October 28, 2014 | vol. 111 | no. 43

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]





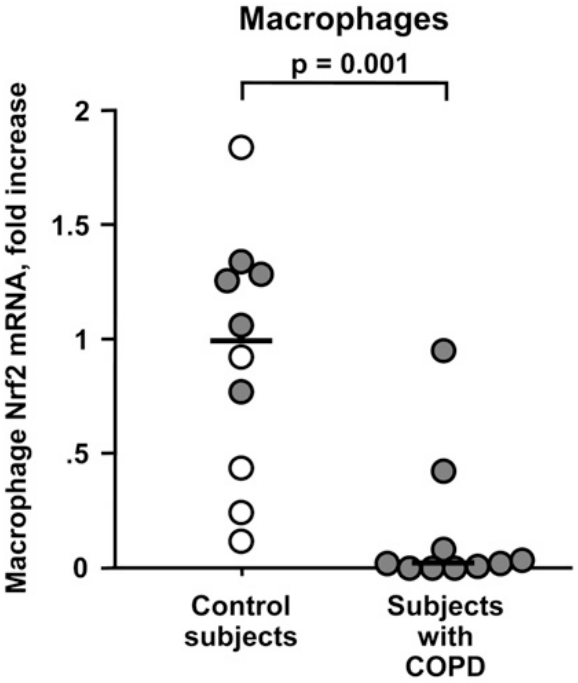



Inflammatory mediators
e.g. TNF-α/LPS
Oxidants
NOX
Mitochondria
Electrophiles/
ROS/H2O2
GSH↓
GSSG↑
Nrf2/Keap
Ras/Raf
MEKK
ASK1
PKC
PI3C
IKK2
MEK5
MKK4/7
MKK3/6
MEK1/2
ERK5
JNK1/2
p38 MAPK
Akt
GSK-3
ERK1/2
Nrf2
NF-κB
Nucleus
Nrf2
AP-1
AP-1
κB
Gene transcription
GSH
Ref-1
thioredoxin
Pro-inflammatory genes:
IL-1β, IL-8, TNF-α, iNOS
Antioxidant genes:
γGCS, Mn SOD, HO-1

Down-Regulated NF-E2–Related Factor 2 in Pulmonary Macrophages of Aged Smokers and Patients with Chronic Obstructive Pulmonary Disease

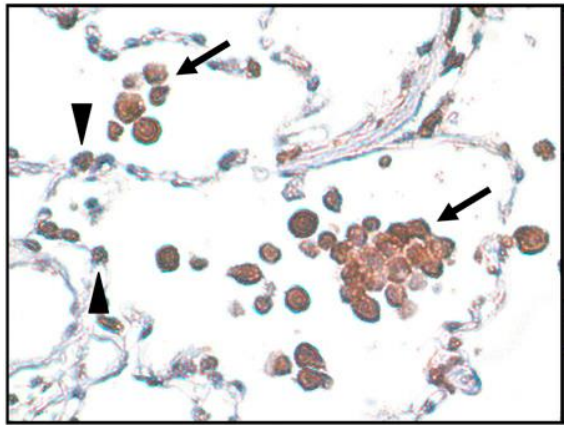
Masaru Suzuki1, Tomoko Betsuyaku1, Yoko Ito1, Katsura Nagai1, Yasuyuki Nasuhara1, Kichizo Kaga2, Satoshi Kondo2, and Masaharu Nishimura1

Am J Respir Cell Mol Biol Vol 39. pp 673–682, 2008

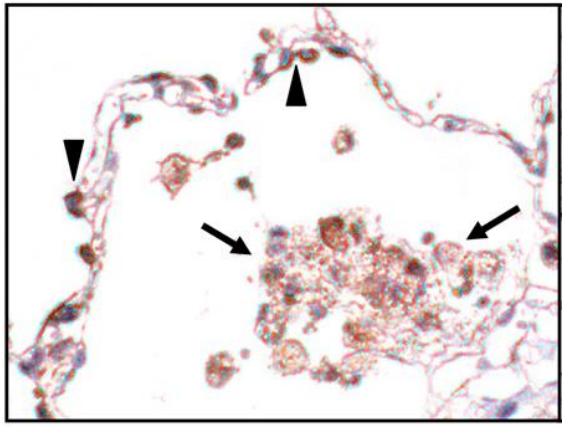


Acute cigarette smoke exposure leads to Nrf2 activation in human macrophages, andNrf2 expression is decreased in pulmonary macrophages in current smokers and patients with COPD.

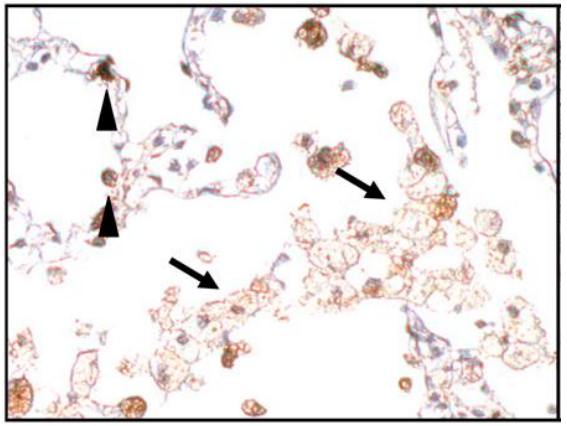
Nrf2 immunohistochemistry in human alveolar macrophages



Lifelong nonsmokers



GOLD stage I COPD



GOLD stage IV COPD

Pilot study on 30 COPD patients (age 63.3 ± 7.9)

- *Patients were evaluated at baseline (time 0, T0) and after 12 weeks (time 1, T1) of oral administration of a mix of* ***curcumin/carnosol/piperine*** *once a day.*

- *At each visit were collected EBC samples, clinical (breath, cough, sputum and night awakening, BSCN score, CAT score and MMSE) data and spirometry. In 14 patients bronchoalveolar lavage fluid (BALF) was also collected.*

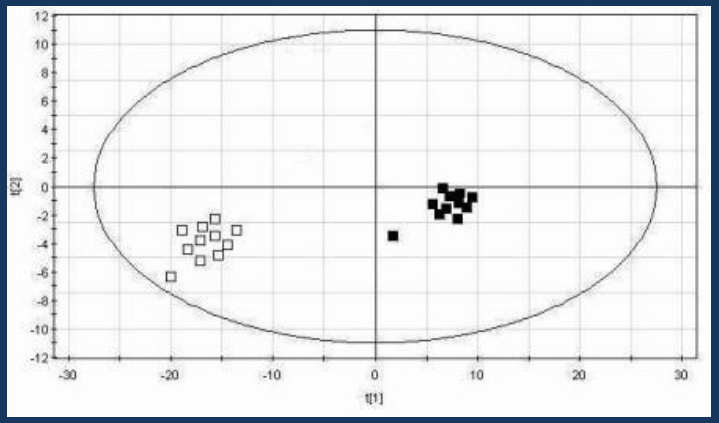
- *EBC samples were obtained using EcoScreen condenser (Jaeger, Wyrzburg, Germany)*

- *Reusable EBC parts were cleaned and treated using a sodium-ipochlorite solution rised with water.*

NMR EBC metabonomic to assess the nutricecutic effect in COPD. A pilot study of oral administration of a curcumin based herbal preparation
G Scapagnini, N Abraham, S Davinelli, et al. The FASEB Journal 26, 239. 2013

Metabonomic analysis of EBC by NMR

Design of the study



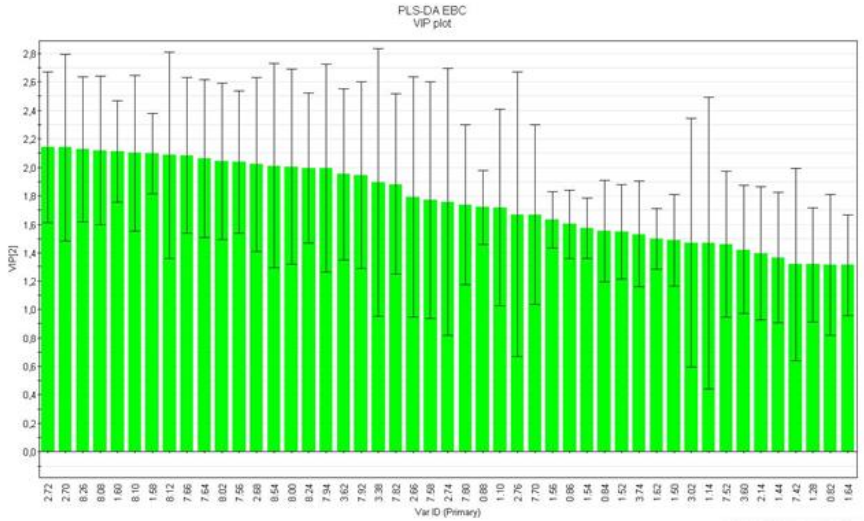
Statistic (Quantitative) analysis
(PCA, PLS-DA)

EBC/saliva
sample (2-4 ml)

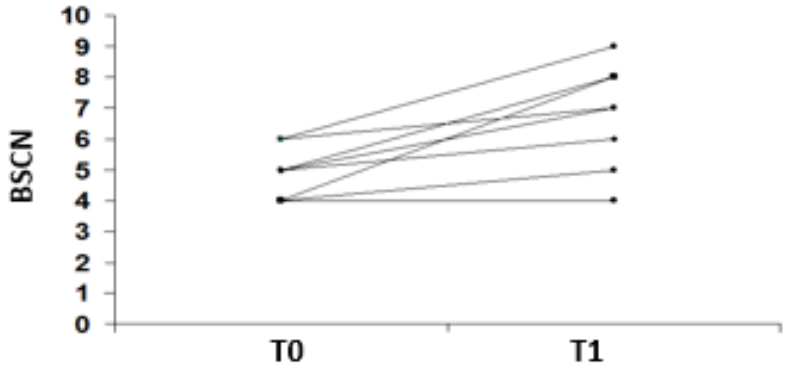
Magnet

Computer

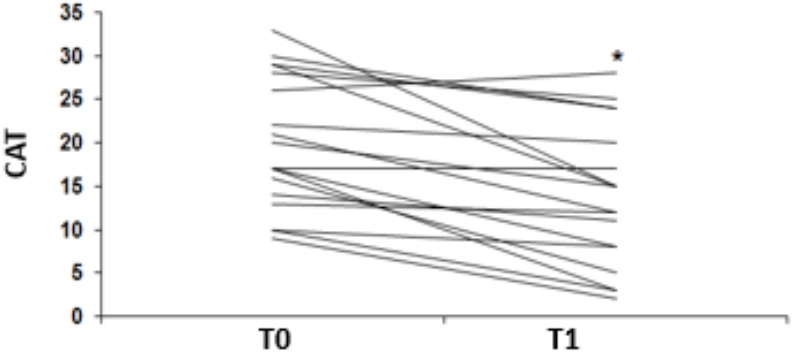
Spectra (Qualitative) analysis



Buckets	Metabolites
2.72; 2.70; 2.68; 2.74	Citrate, aspartate
8.26; 8.10;8.12; 8.54;	ADP
8.08; 8.10; 8.02; 8.00; 7.94; 7.92;	NAD; methyl paraben
8.24;	Hypoxanthine
1.60; 0.88; 1.56, 0.96, 1.54; 0.84; 1.52; 1.62; 1.50;	Saturated fatty acids, leucine
7.66; 7.64; 7.56; 7.82; 7.58; 7.80	Hippurate



BSCN score was 4.9 ± 0.9 at baseline and 7.5 ± 1.0 at T1



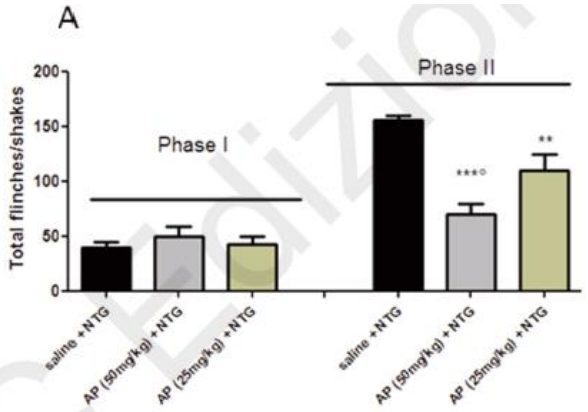
CAT score was 20.35 ± 6.32 at baseline and 12.72 ± 7.12 at T1

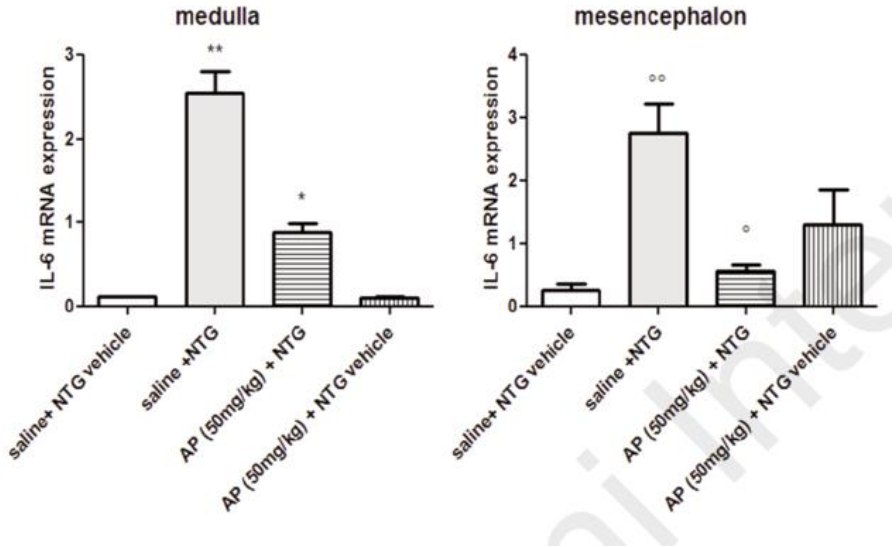
Andrographis Paniculata shows anti-nociceptive effects in an animal model of sensory hypersensitivity associated with migraine

Rosaria Greco, PhD [a]
Francesca Siani, PhD [b1]
Chiara Demartini [a1]
Annamaria Zanaboni [a,d]
Giuseppe Nappi, MD [a]
Sergio Davinelli, PhD [c]
Giovanni Scapagnini, MD [c]
Cristina Tassorelli, MD, PhD [a,d]

[a] Laboratory of Neurophysiology of Integrative Autonomic Systems, Headache Science Center, C. Mondino National Neurological Institute, Pavia, Italy

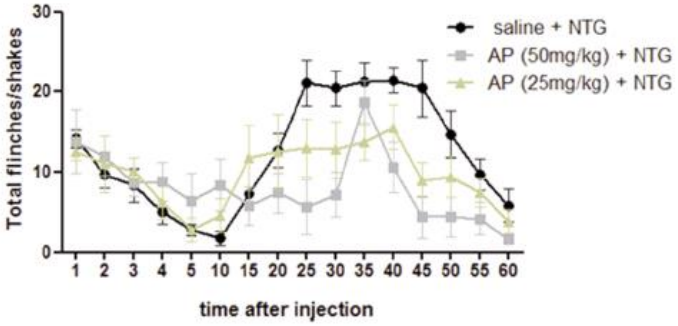
Functional Neurology 2016; 31(1): 53-60





B

Time course of the total flinches/shakes observed after s.c. injection of 1% formalin



Bertoglio et al. BMC Neurology (2016) 16:77
DOI 10.1186/s12883-016-0595-2

BMC Neurology

RESEARCH ARTICLE Open Access

Andrographis paniculata decreases fatigue in patients with relapsing-remitting multiple sclerosis: a 12-month double-blind placebo-controlled pilot study

J. C. Bertoglio[1], M. Baumgartner[2], R. Palma[2], E. Ciampi[3], C. Carcamo[3], D. D. Cáceres[4], G. Acosta-Jamett[5], J. L. Hancke[6] and R. A. Burgos[6*]

Table 1 Baseline clinical and radiological characteristics of patients after randomisation in *A. paniculata* and placebo treatment groups

Parameter	*A. paniculata* $n = 13$				Placebo $n = 11$				
	Mean	SD	min	max	Mean	SD	min	max	*p-value*
Age	35.09	11.79	15	47	38.70	10.65	22	51	*0.3066*
Sex (w/m)	9/4				7/4				*0.5250*
Disease duration prior to study (year)	3.62	4.56	0	16	6.00	8.20	0	24	0.8067
Relapse (2 years)	1.73	1.27	1	5	1.46	0.52	1	2	0.9236
EDSS	2.64	1.29	1	5	2.08	1.66	0	6	0.1663
FSS	4,15	1,88	1	6.4	3.76	1.68	1	5.5	0.3990
Gd lesion number	0				0				
Interferon-beta 1a im.(Avonex® 30 mcg)	7				5				
Interferon-beta 1a sc.(Rebif® 44 mcg)	6				6				

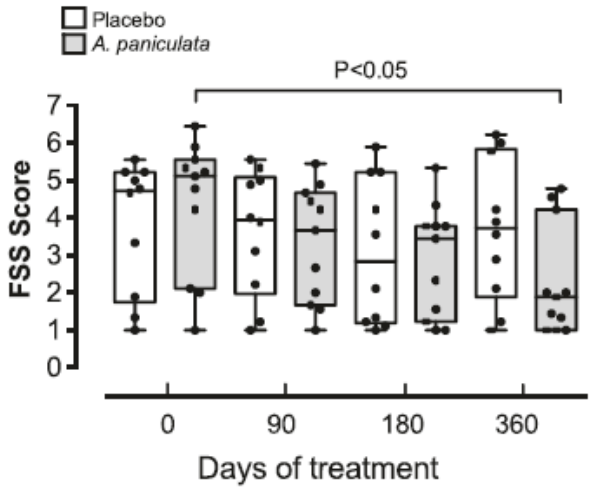


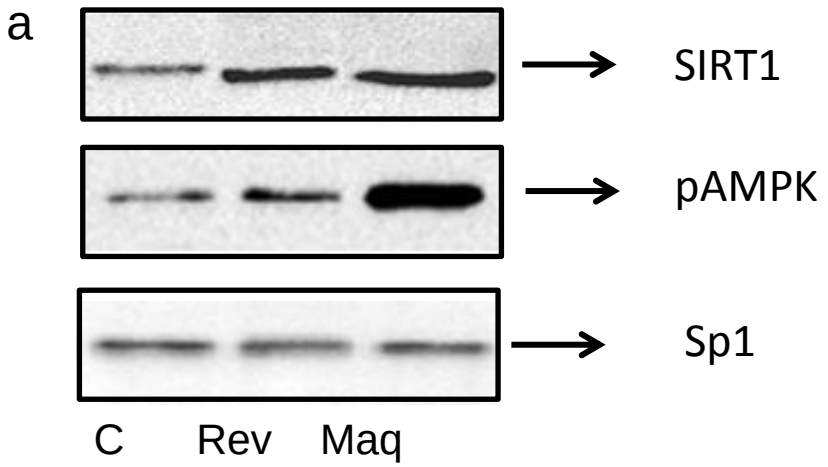
Fig. 2 FSS score is reduced in RRMS patients treated with *A. paniculata* compared to placebo during one year. Each point represents an individual score of patients measured at 0, 90, 180 and 360 days. A box-and-whisker plot with the minimum, 25th percentile, median, 75th percentile, and maximum values are depicted

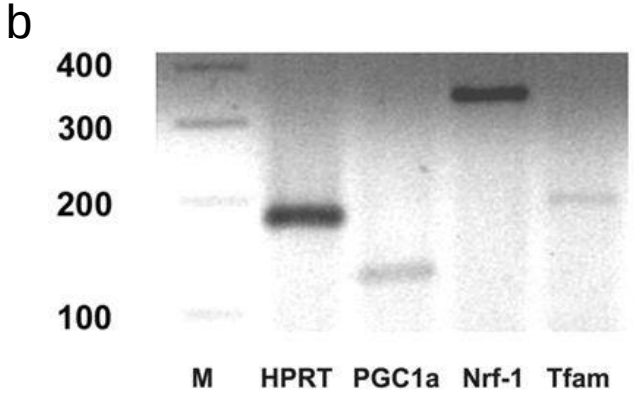

A
Isla Alejandro
Selkirk

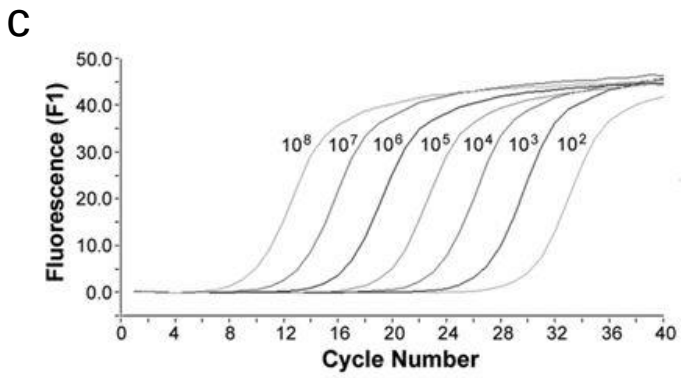

A
Santiago

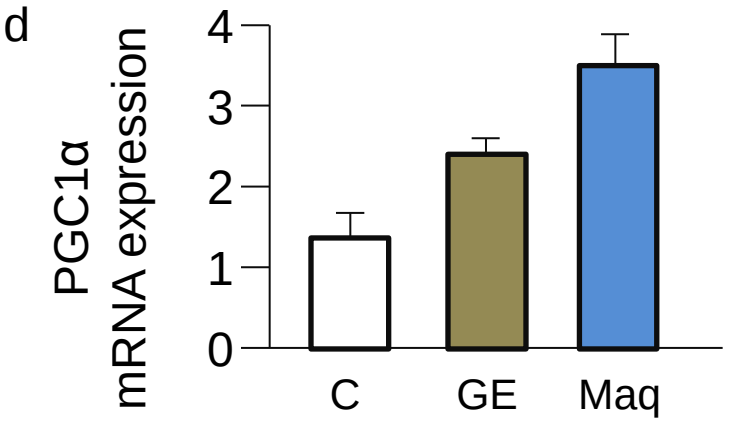

BIENVENIDO
AERODROMO
ROBINSON-CRUSOE-
V.REGION.
Dirección de Aeropuertos

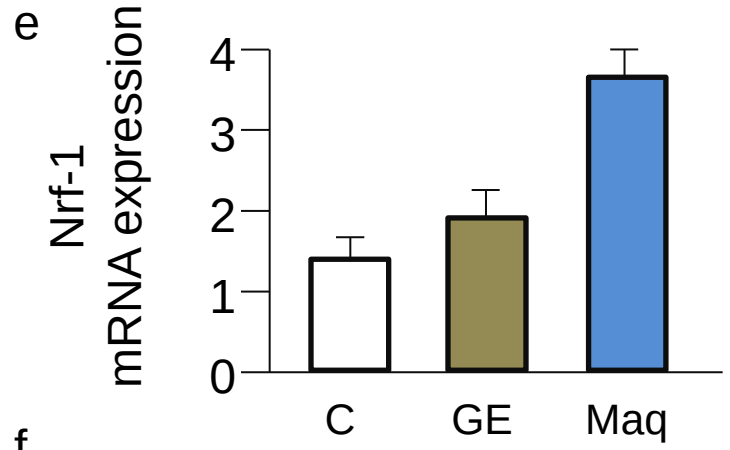
Mitochondrial biogenesis induction by grape ex. or maqui ex.

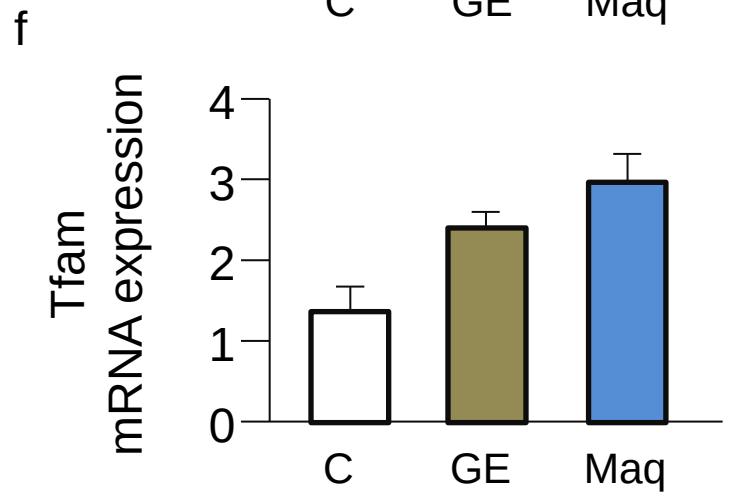


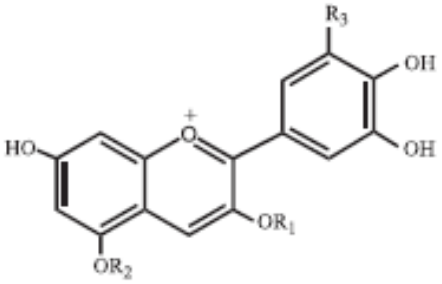












Berry polyphenols

Insulin

Sirtuin activation

AMPK

FOXO

Apoptosis

PGC-1α

mitochondrial biogenesis

Metabolic diseases

CVD

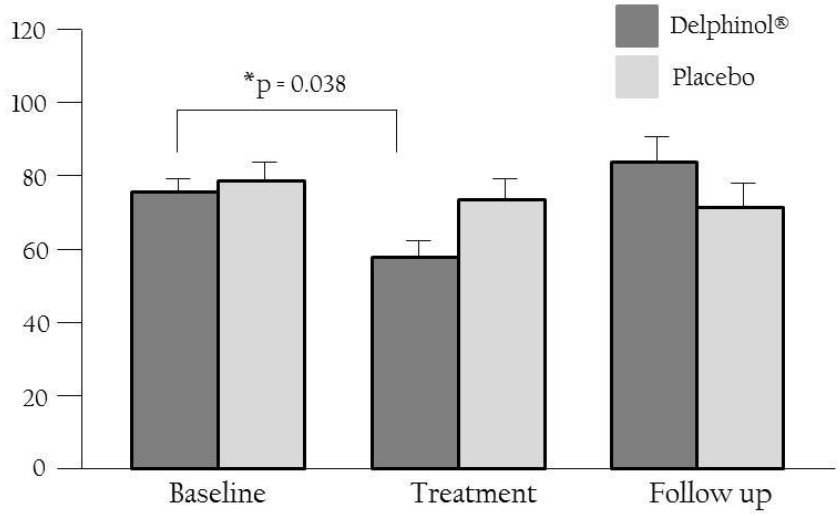
Neurodegenerative disorders

J Am Coll Nutr. 2015 Sep 15;34(sup1):28-33.

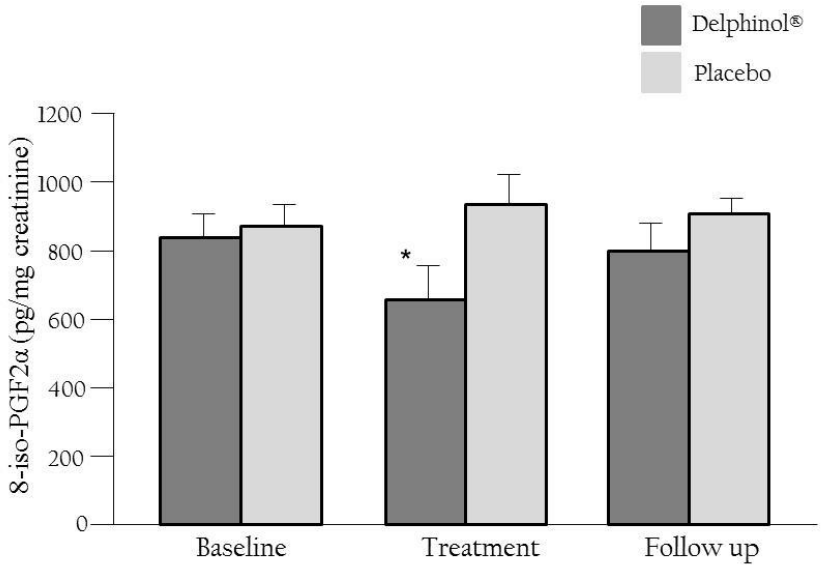
The American Journal of Clinical Nutrition

A Randomized Clinical Trial Evaluating the Efficacy of an Anthocyanin-Maqui Berry Extract (Delphinol®) on Oxidative Stress Biomarkers.

Davinelli S[1], Bertoglio JC[2], Zarrelli A[3], Pina R[4], Scapagnini G[1,5].



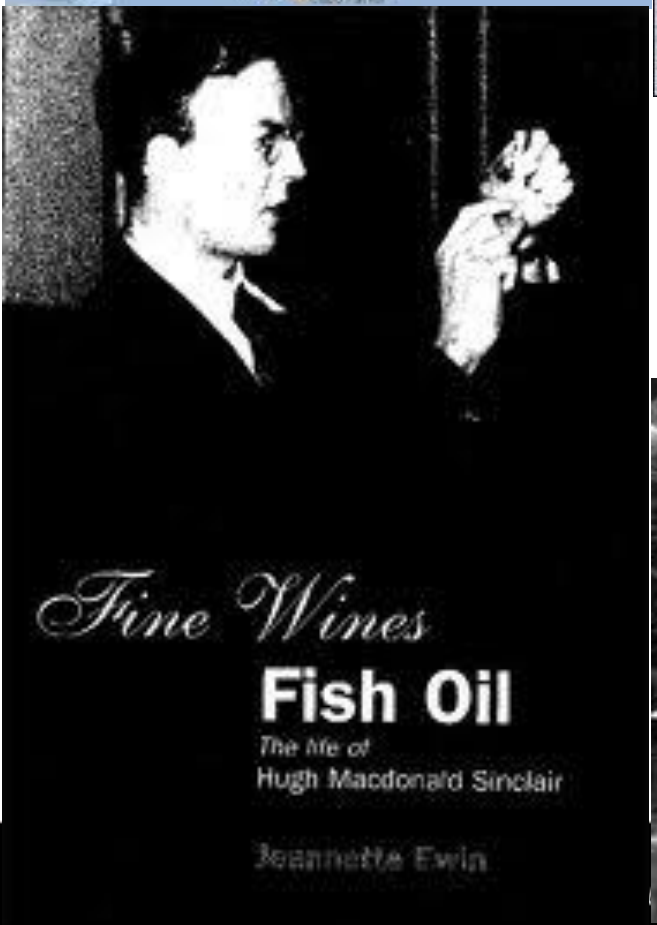
Change of oxidized LDL (Ox-LDL) values within each group after 4 wk of intervention and 40 days of follow up.
Data are expressed as mean ± SD.
* Significant p < 0.05 from baseline.



Effects of Delphinidin supplementation on urinary excretion of 8-iso-PGF2α in overweight smoker subjects.
Data are expressed as mean ± SD.
* Significant p < 0.05 from baseline.

The Connection Between Fats and Heart Diseases

1969, Bang & Dyerberg: investigation in Greenland near absence of thrombotic heart diseases in Greenlanders



efsa
European Food Safety Authority

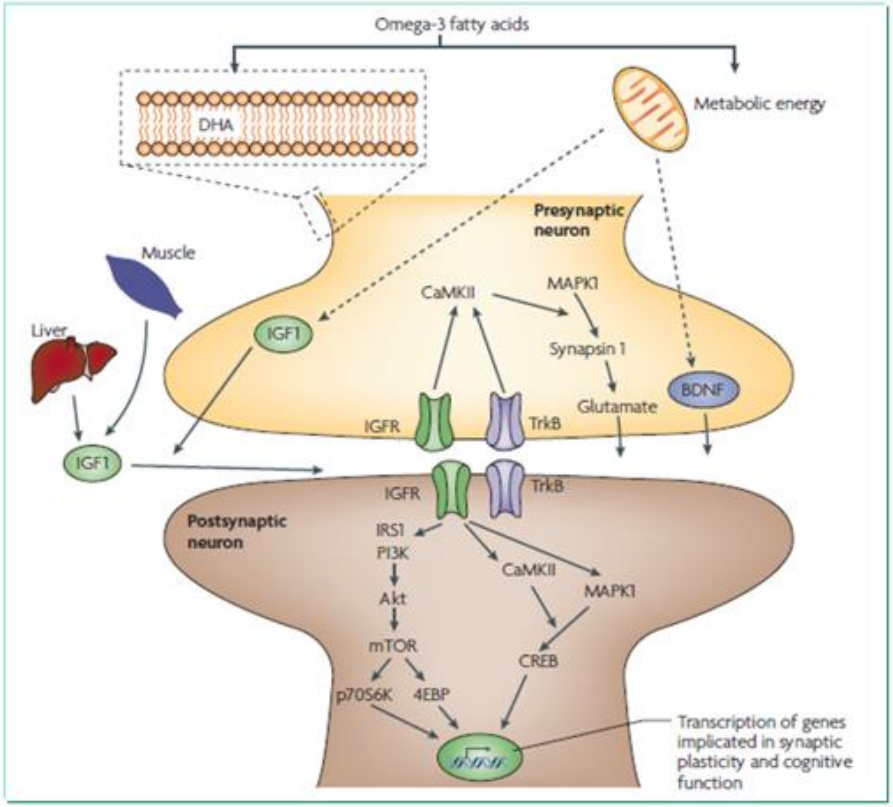
Table 1. Omega-3 PUFA intake recommendations of expert international bodies for adults

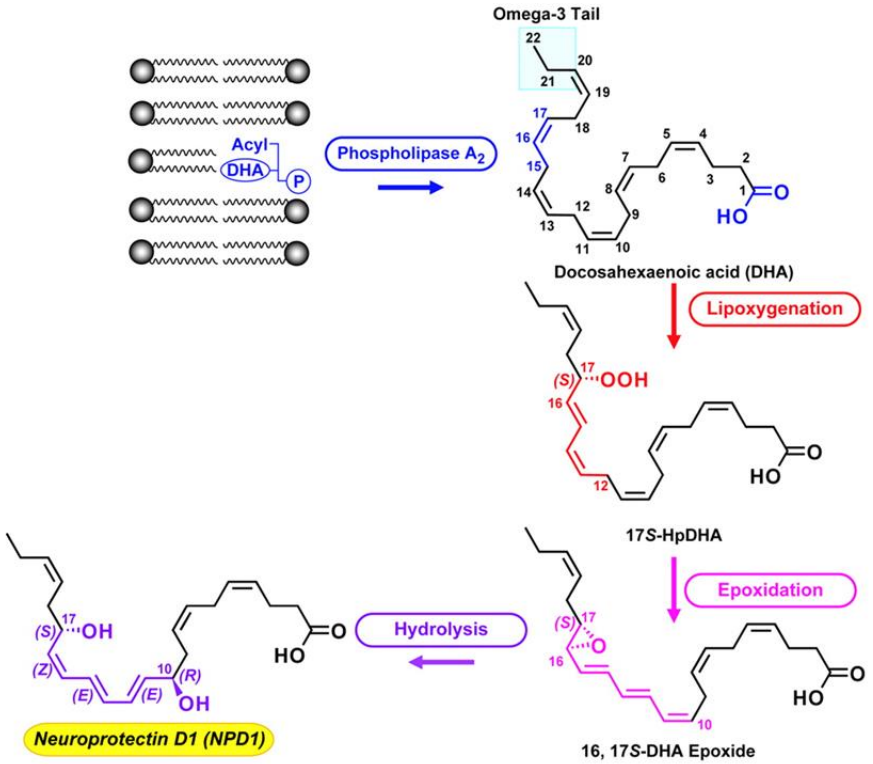
Expert body	Year	Target population	Daily recommendation
American Heart Association	2011	Heart health	Two fish meals for primary protection
Heart Foundation Australia	2008	Heart health	500 mg EPA/DHA for primary prevention
FAO/WHO Expert Consultation	2010	General health	250 mg EPA/DHA
European Food Safety Authority	2010	General health	250 mg EPA/DHA
Japanese Ministry of Health	2009	General health	>1 g EPA/DHA
Health Council Netherlands	2006	General health	450 mg EPA/DHA from fish
Australia New Zealand National Health and Medical Research Council	2006	Chronic disease	n-3 LC-PUFAs: 610 mg for men 430 mg for women
Belgian Superior Health Council	2009	Heart health	Daily fatty fish or 1 g capsule
Agence Francais de Securite Sanitaire des Aliments	2014	General health	500 mg EPA/DHA

DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; LC, long chain; PUFA, polyunsaturated fatty acid.

Salem N and Eggersdorfer M. Is the world supply of omega-3 fatty acids adequate for optimal human nutrition? Clinical nutrition 2015

Dietary omega-3 fatty acids can affect synaptic plasticity and cognition.





J Alzheimers Dis. 2016 February 16; 51(3): 857–866.

Associations between serum omega-3 fatty acid levels and cognitive functions among community-dwelling octogenarians in Okinawa, Japan: The KOCOA study

Junko Nishihira, MD[1)], **Takashi Tokashiki, MD, PhD**[1)], **Yasushi Higashiuesato, MD, PhD**[2)], **Donald Craig Willcox, MHSc, PhD**[3),4)], **Nora Mattek, MPH**[5)], **Lynne Shinto, ND, MPH**[5)], **Yusuke Ohya, MD, PhD**[1)], and **Hiroko H. Dodge, PhD**[5),6)]

Objective—To examine the association between serum PUFA levels and cognitive function among community-dwelling, non-demented elderly aged over 80 years old.

Results—Serum DHA levels decreased with increasing age ($p = 0.04$). Higher global cognitive function was associated with higher levels of serum EPA ($p = 0.03$) and DHA + EPA ($p = 0.03$) after controlling for confounders.

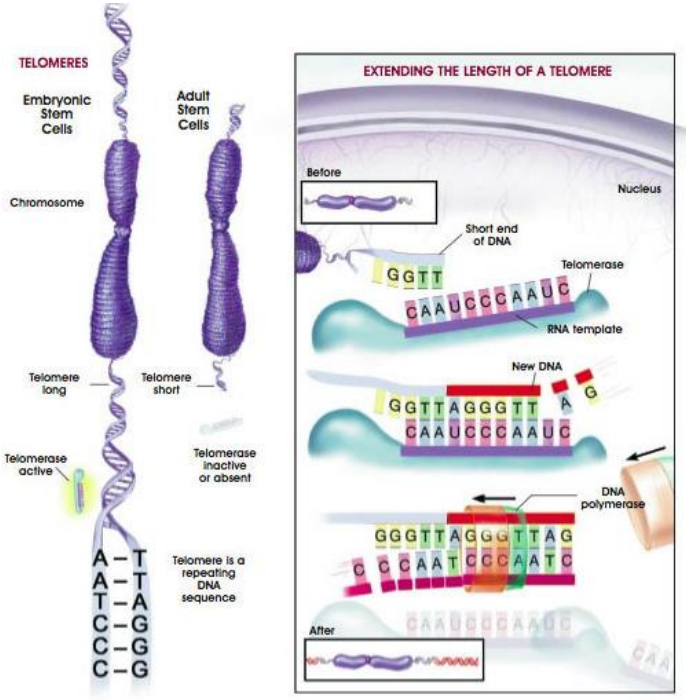
Conclusions—Higher serum EPA and DHA + EPA levels were independently associated with better scores on global cognitive function among the oldest old, free from dementia. Longitudinal follow-up studies are warranted.

Brain Behav Immun. 2013 February ; 28: 16–24. doi:10.1016/j.bbi.2012.09.004.

Omega-3 Fatty Acids, Oxidative Stress, and Leukocyte Telomere Length: A Randomized Controlled Trial

Janice K. Kiecolt-Glaser[a,1], **Elissa S. Epel**[b], **Martha A. Belury**[c], **Rebecca Andridge**[d], **Jue Lin**[e], **Ronald Glaser**[a], **William B. Malarkey**[a], **Beom Seuk Hwang**[d], and **Elizabeth Blackburn**[e]

The double-blind 4-month trial included 106 healthy sedentary overweight middle-aged and older adults who received (1) 2.5 g/day n-3 PUFAs, (2) l.25 g/day n-3 PUFAs, or (3) placebo capsules that mirrored the proportions of fatty acids in the typical American diet. Supplementation significantly lowered oxidative stress as measured by F2-isoprostanes (p=0.02). The estimated geometric mean log-F2-isoprostanes values were 15% lower in the two supplemented groups compared to placebo. Telomere length increased with decreasing n-6:n-3 ratios, p=0.02. The data suggest that lower n-6:n-3 PUFA ratios can impact cell aging.



Linear regression analysis for change in telomere length with change in n-6:n-3 fatty acid plasma ratio, controlling for baseline telomere length.

Effect	Estimate	95% CI	P-value
Intercept	1040	(296, 1785)	0.007
Telomere length, baseline	−0.15	(−0.27, −0.031)	0.01
n-6:n3 fatty acids, baseline	−21	(−44, 2.0)	0.07
Decrease in n6:n3 fatty acids[a]	20	(4, 36)	0.02

Units: telomere length = base pairs.

Regression model with change in telomere length (4 months minus baseline) as the outcome

[a]Decrease in *n*-6:n-3 PUFA ratio is calculated as baseline minus 4 months so that a positive value is a decrease in *n*-6:*n*-3 PUFA ratio.

Journal of Nutrigenetics and Nutrigenomics

J Nutrigenet Nutrigenomics 2014;7:191–211
DOI: 10.1159/000375495
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Published online: March 4, 2015

1661–6499/15/0076–0191$39.50/0
www.karger.com/jnn

Original Paper

The Impact of the Bellagio Report on Healthy Agriculture, Healthy Nutrition, Healthy People: Scientific and Policy Aspects and the International Network of Centers for Genetics, Nutrition and Fitness for Health

Artemis P. Simopoulos

The Center for Genetics, Nutrition and Health, Washington, D.C., USA

Table 5. International Network of Centers for Genetics, Nutrition and Fitness for Health (directors)

Last name	First name	Title/affiliation	City/country
Allayee	Hooman	Associate Professor, Department of Preventive Medicine, University of Southern California Keck School of Medicine, Los Angeles, Calif., USA	Los Angeles, Calif., USA
Cesuroglu	Tomris	Researcher, Department of Social Medicine, Maastricht University, Maastricht, The Netherlands	Maastricht, The Netherlands
Chrousos	George	Professor and Chairman, Department of Pediatrics, University of Athens, Athens, Greece	Athens, Greece
Gopalan	Sarath	Executive Director, Centre for Research on Nutrition Support Systems (CRNSS), New Delhi, India	New Delhi, India
Johnson	Richard	Professor of Medicine, Chief, Division of Renal Diseases and Hypertension, University of Colorado, Denver, Colo., USA	Denver, Colo., USA
Kang	Jing	Associate Professor of Medicine, Director, Laboratory for Lipid Medicine and Technology, Massachusetts General Hospital and Harvard Medical School, Boston, Mass., USA	Boston, Mass., USA
Kohlmeier	Martin	Professor, University of North Carolina School of Public Health, Chapel Hill, N.C., USA	Raleigh, N.C., USA
Li	Duo	Professor, Department of Food Science and Nutrition, Zhejiang University, Hangzhou, China	Shanghai Pudong, China
Marcos	Ascensión	Research Professor, Spanish National Research Council, Madrid, Spain	Madrid, Spain
Savas	Serdar	President, Turkish Society of Public Health Genomics and Personalized Medicine, Istanbul, Turkey	Istanbul, Turkey
Scapagnini	Giovanni	Associate Professor, Department of Medicine and Heath Science, University of Molise, Campobasso, Italy	Campobasso, Italy
Schmidt	Laura	Professor, Philip R. Lee Institute for Health Policy Studies and Department of Anthropology, History and Social Medicine, School of Medicine, University of California at San Francisco, San Francisco, Calif., USA	San Francisco, Calif., USA
Simopoulos	Artemis	President, The Center for Genetics, Nutrition and Health, Washington, D.C., USA	Washington, D.C., USA
Waitzberg	Dan	Associate Professor, Department of Gastroenterology, University of São Paulo Medical School, São Paulo, Brazil	São Paulo, Brazil

Physical Activity and psychological and social aspects, all play an important role in Okinawan longevity.