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
Aging → Delay upstream effects of aging

Processes of aging:
- Inflammation
- Oxidative stress
- Mitochondrial dysfunction
- Cellular senescence
- Stem cell exhaustion
- Epigenetic alterations
- Genomic instability

Processes of prevention:
- Specific disease prevention

Age-related disorders:
- Alzheimer’s Disease
- Diabetes
- Cancer
- Disability
- CVD
- Parkinson’s Disease
- Osteoporosis

Processes of treatment:
- Specific disease treatment

Mortality

NUTRACEUTICALS

PHARMACEUTICALS
Oxidation and Inflammation
The link with age related chronic diseases

- Cancer
- Cardiovascular
- Neurological Diseases
- Diabetes
- Autoimmune Diseases
- Alzheimer’s Disease
- Pulmonary Diseases
- Arthritis

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

Antero Salminen\textsuperscript{a,b,*}, Kai Kaarniranta\textsuperscript{c,d}

Decline in AMPK activation with aging:
- Decreases autophagy
- Increases oxidative stress
- Increases endoplasmic stress
- Increases apoptotic resistance
- Increases inflammation
- Increases fat deposition
- Induces hyperglycemia
- 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?

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

Nutrients (dietary signals)
  Signalling through sensor mechanisms
  ↓
Genes (normal genotype)
  ↓
Normal phenotype
  ↓
Homeostasis
Nutrgerontology: a key for achieving successful ageing and longevity

Anna Aiello¹, Giulia Accardi¹, Giuseppina Candore¹, Giuseppe Carruba², Sergio Davinelli³, Giuseppe Passarino⁴, Giovanni Scapagnini³, Sonya Vasto⁵ and Calogero Caruso¹*

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, nutrgerontology 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, Nutrgerontology, Phytochemicals
‘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


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

Donald Craig Willcox, Giovanni Scapagnini, Bradley J. Willcox

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

Sonya Vasto, Giovanni Scapagnini, Claudia Rizzo, Roberto Monastero, Antonio Marchese, and Calogero Caruso
Almost 1000 Okinawan centenarians and numerous other elderly in their seventies, eighties, and nineties, have been studied from 1975.

In Okinawa, centenarian ratios may be the world's highest at approximately 50 per 100,000 population.
Gene Variant in Insulin Signaling Pathway Strongly Associated with Healthy Aging and Longevity (Willcox et al. Proc Nat Acad Sci 2008)

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.
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).

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>No. of deaths</th>
<th>HR* (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer</td>
<td>546</td>
<td>1.01 (0.85–1.19)</td>
<td>0.93</td>
</tr>
<tr>
<td>CHD (coronary heart disease)</td>
<td>524</td>
<td>0.75 (0.63–0.90)</td>
<td>0.001</td>
</tr>
<tr>
<td>Stroke</td>
<td>315</td>
<td>0.97 (0.77–1.21)</td>
<td>0.76</td>
</tr>
<tr>
<td>Dementia</td>
<td>221</td>
<td>1.01 (0.78–1.32)</td>
<td>0.93</td>
</tr>
<tr>
<td>Other cardiovascular disease (CVD)</td>
<td>213</td>
<td>0.85 (0.65–1.11)</td>
<td>0.23</td>
</tr>
<tr>
<td>Infectious disease</td>
<td>188</td>
<td>0.91 (0.68–1.21)</td>
<td>0.52</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease (COPD)</td>
<td>117</td>
<td>0.83 (0.57–1.19)</td>
<td>0.31</td>
</tr>
<tr>
<td>Renal failure</td>
<td>45</td>
<td>0.86 (0.48–1.55)</td>
<td>0.61</td>
</tr>
<tr>
<td>GI (gastrointestinal disease)</td>
<td>39</td>
<td>1.22 (0.65–2.30)</td>
<td>0.54</td>
</tr>
<tr>
<td>Other deaths</td>
<td>480</td>
<td>0.86 (0.72–1.03)</td>
<td>0.09</td>
</tr>
</tbody>
</table>
Long live FOXO: unraveling the role of FOXO proteins in aging and longevity
Conserved Nutrient Signaling Pathways Regulating Longevity

**Yeast**
- Dietary restriction
- Glucose, amino acids
- TOR is a protein kinase that is part of the TOR signaling pathway.

**Worms**
- Dietary restriction
- Ins/IGF-1–like
- DAF-2
- TOR
- AGE-1 (PI3K)
- S6K
- AKT
- RSK-1 (S6K)
- In yeast and mice, mutations that cause AC or PKA deficiency extend longevity.
  - In mice, such deficiencies also reduce age-related pathologies.

**Flies**
- Dietary restriction
- Ins/IGF-1–like
- INR
- CHICO
- (PI3K)

**Mammals**
- Dietary restriction
- IGF-1
- GH
- GHR
- GH signaling
- RAS
- PKA
- AC

Inhibition of nutrient-sensing pathways (colored dashed lines):
- TOR signaling pathway (green)
- RAS-AC-PKA (purple)
- Insulin/Igf-like signaling (blue)

In the presence of nutrients, these conserved biochemical signaling pathways are activated.

GIS1, MSN2/4, HIF-1, DAF-18, and FOXO are anti-aging transcription factors that are activated by dietary restriction and regulate the expression of enzymes and proteins involved in protective and metabolic activities that increase life span (solid red arrows).

In the presence of nutrients, anti-aging transcription factors are kept in the cytoplasm in an inactive form.

**Anti-aging**
- Glycogen accumulation (except flies and mammals), glyceral accumulation (only yeast), fat accumulation (except yeast), antioxidant enzyme SOD, catalase (except flies), HSPs (except mammals), autophagy, translation, ER stress, other?

Yeast is a simple and unicellular organism with a short life span, facilitating the study of aging mechanisms. Several pro-aging genes identified in yeast promote aging in mammals (S6K, AC, PKA).

In worms, the role of genes in different cell types in aging and age-dependent loss of function can be investigated. The pro-aging insulin/IGF-1–like genes were first identified in worms.

Studies of flies have begun to reveal how different genes, cell types, and factors affect life span. Mutants help to determine the tissue-specific effects of particular genes on aging.

Reduced activity of the pro-aging genes identified in yeast, worms, and flies seems to mediate some of the anti-aging effects of dietary restriction in mammals. Incidence of chronic diseases is lowered.
Caloric Restriction: Most Powerful Anti-Aging Intervention


Ad libitum       CR

P = 0.03
HR = 3.0
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.
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)
Extending healthy ageing: nutrient sensitive pathway and centenarian population

Sergio Davinelli¹, D Craig Willcox², Giovanni Scapagnini¹*
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.

Curcuma longa

Ipomoera batatas cultivar Ayamurasaki

Wakame Undaria pinnatifida

Curcumin

Anthocyanin

Phlorotannin
Microbial proportion
Changes in adhesion/colonization

Production of active metabolites
Changes in bioavailability

Gut microbiota

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

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

Sergio Davinelli¹*, Michael Maes²,³, Graziamaria Corbi¹, Armando Zarrelli⁴, Donald Craig Willcox⁵,⁶ and Giovanni Scapagnini¹

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.

Institute of Neurological Sciences, National Research Council (CNR), Catania, Italy., Blanchette Rockefeller Neurosciences Institute, West Virginia University, Rockville, Maryland.
Curcumin activates Nrf2 expression and stimulates ARE-binding activity

**Phase 2 Response**

**ANTIOXIDANT RESPONSIVE ELEMENT (ARE)**

1. GSH transferases → multifunctional roles
2. GSH-reductase → regeneration of GSH and dehydroascorbate
3. Catalase → antioxidant
4. Thioredoxin → regeneration of oxidized thioredoxin and dehydroascorbate
5. \(\gamma\)-glutamylcysteine synthetase → GSH synthesis
6. Heme oxygenase 1 → biliverdin/bilirubin
7. Ferritin → CO/Fe
8. NAD(P)H:quinone oxidoreductase 1 → regeneration of ubiquinol and tocopherol
9. UDP-glucuronosyltransferases → regeneration of oxidized thioredoxin and dehydroascorbate

**ANTIOXIDANT AND CYTOPROTECTIVE ACTION**

**Nrf2/keap1/ARE** → Cytoprotection

**Keap1** → Nrf2
Multi-organ protection by the Nrf2 pathway

- Lung
  - Antioxidant Detoxification
  - Inflammation

- Skin
  - Antioxidant Detoxification
  - Inflammation

- Liver
  - Antioxidant Detoxification
  - Proteasome

- Brain
  - Antioxidant Detoxification
  - Inflammation
  - Calcium homeostasis
  - Signaling
  - Growth factor

- GI Tract
  - Antioxidant Detoxification
  - Drug metabolism
  - NADPH regeneration

- Kidney
  - Antioxidant Detoxification

- Spleen
  - Cytokine
  - T, B cell-specific

- Erythrocyte
  - Antioxidant

- Retinal Epithelia
  - Antioxidant Detoxification
Regulation of Nrf2 signaling and longevity in naturally long-lived rodents

Kaitlyn N. Lewis, Emily Wason, Yael H. Edrey, Deborah M. Kristan, Eviatar Nevo, and Rochelle Buffenstein

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

PNAS March 24, 2015 vol. 112 no. 12

A

Nrf2:ARE Binding Activity

\[ \text{Species} \]

\[ \text{Nrf2-ARE Binding Activity} \]

\[ \text{OD}_{450} \text{ nm} \]

\[ p = 0.0001 \]

B

Hmox1

Gsta1

Nqo1

\[ \text{Relative Fold Expression (AU)} \]

\[ \text{Mouse} \]

\[ \text{NMR} \]

\[ p = 0.0376 \]

\[ p = 0.0336 \]

\[ p = 0.0200 \]

C

Total GST Activity

\[ \text{Mouse} \]

\[ \text{NMR} \]

\[ p = 0.0001 \]

\[ p = 0.0002 \]

NQO1 Activity

\[ \text{Mouse} \]

\[ \text{NMR} \]
Naked mole-rat constitutive Nrf2 upregulation

- **Graph A**: Total Keap1 protein levels with a p-value of 0.0013.
- **Graph B**: Total βTrCP protein levels with a p-value of 0.0037.

**Table**

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

- **Graph C**: Nrf2-signaling activity vs. bodyweight with a p-value of 0.6082.
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.

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 of Nrf2 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.

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

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

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

Susannah Havermann¹,²,³, Yvonni Chovolou¹, Hans-Ulrich Humpf², Wim Wätjen¹,³*  
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
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)

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

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

SCREENING
Baseline Symptom Assessment
Blood Chemistries
Hematology
Urine Analysis

Behavioral Outcome Measures

Behavioral Outcome Measures
Blood Chemistries
Hematology
Urine Analysis

0
4 weeks
10 weeks
18 weeks
22 weeks

ENROLLMENT RANDOMIZATION & FIRST TREATMENT
Baseline Symptom Assessment

Behavioral Outcome Measures
Blood Chemistries
Hematology
Urine Analysis

Behavioral Outcome Measures
Blood Chemistries
Hematology
Urine Analysis

DAILY TREATMENT
Broccoli Sprout Extract or Placebo

IRRITABILITY

LETHARGY

STEREOTYPY

HYPERACTIVITY

Change in ABC Subscore
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

Acute cigarette smoke exposure leads to Nrf2 activation in human macrophages, and Nrf2 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.

Metabonomic analysis of EBC by NMR

Design of the study

EBC/saliva sample (2-4 ml)

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

Spectra (Qualitative) analysis

Magnet

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

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
Francesca Siani, PhD
Chiara Demartini
Annamaria Zanaboni
Giuseppe Nanni, MD
Sergio Davinelli, PhD
Giovanni Scapagnini, MD
Cristina Tassorelli, MD, PhD

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

A

Phase I

Phase II

B

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

saline + NTG
AP (50mg/kg) + NTG
AP (25mg/kg) + NTG
Andrographis paniculata decreases fatigue in patients with relapsing-remitting multiple sclerosis: a 12-month double-blind placebo-controlled pilot study

J. C. Bertoglio¹, M. Baumgartner², R. Palma², E. Ciampi³, C. Carcamo³, D. D. Cáceres⁴, G. Acosta-Jamett⁵, J. L. Hancke⁶ and R. A. Burgos⁶*

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>A. paniculata n = 13</th>
<th>Placebo n = 11</th>
<th>Mean</th>
<th>SD</th>
<th>min</th>
<th>max</th>
<th>Mean</th>
<th>SD</th>
<th>min</th>
<th>max</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>35.09</td>
<td>38.70</td>
<td>11.79</td>
<td>10.65</td>
<td>15</td>
<td>47</td>
<td>22</td>
<td>51</td>
<td>0.3066</td>
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<td>Sex (m/f)</td>
<td>9/4</td>
<td>7/4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.5230</td>
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<tr>
<td>Disease duration prior to study (year)</td>
<td>3.62</td>
<td>6.00</td>
<td>4.56</td>
<td>8.20</td>
<td>0</td>
<td>16</td>
<td>22</td>
<td>24</td>
<td>0.8067</td>
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<tr>
<td>Relapse (2 years)</td>
<td>1.73</td>
<td>1.46</td>
<td>1.27</td>
<td>0.52</td>
<td>1</td>
<td>5</td>
<td>1.2</td>
<td>2</td>
<td>0.9236</td>
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<tr>
<td>EDSS</td>
<td>2.64</td>
<td>2.08</td>
<td>1.29</td>
<td>1.66</td>
<td>1</td>
<td>5</td>
<td>0</td>
<td>6</td>
<td>0.1663</td>
<td></td>
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<tr>
<td>FSS</td>
<td>4.15</td>
<td>3.76</td>
<td>1.88</td>
<td>1.68</td>
<td>1</td>
<td>6.4</td>
<td>1</td>
<td>5.5</td>
<td>0.3990</td>
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</tbody>
</table>

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.
Mitochondrial biogenesis induction by grape ex. or maqui ex.

(a) Western blot analysis showing (top to bottom) SIRT1, pAMPK, and Sp1 expression under different conditions: C (control), Rev, and Maq.

(b) RT-PCR gel showing mRNA expression levels of M, HPRT, PGC1α, Nrf-1, and Tfam for the same conditions: C, GE, and Maq.

(c) qRT-PCR graph illustrating fluorescence (F) over cycle number, with different amplification curves for various mRNA expression levels.

(d) Bar graph illustrating PGC1α mRNA expression levels in C, GE, and Maq.

(e) Bar graph illustrating Nrf-1 mRNA expression levels in C, GE, and Maq.

(f) Bar graph illustrating Tfam mRNA expression levels in C, GE, and Maq.
Berry polyphenols

- Sirtuin activation
  - Insulin down
  - PGC-1α up
  - Mitochondrial biogenesis up
  - Metabolic diseases down
  - CVD down
  - Neurodegenerative disorders down

- AMPK
  - FOXO up
  - Apoptosis down
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
Table 1. Omega-3 PUFA intake recommendations of expert international bodies for adults

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

DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; LC, long chain; PUFA, polyunsaturated fatty acid.
Dietary omega-3 fatty acids can affect synaptic plasticity and cognition.
Associations between serum omega-3 fatty acid levels and cognitive functions among community-dwelling octogenarians in Okinawa, Japan: The KOCOA study

Junko Nishihira, MD\textsuperscript{1}), Takashi Tokashiki, MD, PhD\textsuperscript{1}), Yasushi Higashiuesato, MD, PhD\textsuperscript{2}), Donald Craig Willcox, MHSc, PhD\textsuperscript{3),4}), Nora Mattek, MPH\textsuperscript{5}), Lynne Shinto, ND, MPH\textsuperscript{5}), Yusuke Ohya, MD, PhD\textsuperscript{1}), and Hiroko H. Dodge, PhD\textsuperscript{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.
Omega-3 Fatty Acids, Oxidative Stress, and Leukocyte Telomere Length: A Randomized Controlled Trial

Janice K. Kiecolt-Glaser, Elissa S. Epet, Martha A. Belury, Rebecca Andridge, Jue Lin, Ronald Glaser, William B. Malarkey, Beom Seuk Hwang, and Elizabeth Blackburn

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) 1.25 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.

<table>
<thead>
<tr>
<th>Effect</th>
<th>Estimate</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>1040</td>
<td>(296, 1785)</td>
<td>0.007</td>
</tr>
<tr>
<td>Telomere length, baseline</td>
<td>−0.15</td>
<td>(−0.27, −0.031)</td>
<td>0.01</td>
</tr>
<tr>
<td>n-6:n-3 fatty acids, baseline</td>
<td>−21</td>
<td>(−44, 20)</td>
<td>0.07</td>
</tr>
<tr>
<td>Decrease in n6:n3 fatty acids</td>
<td>20</td>
<td>(4, 36)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

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

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