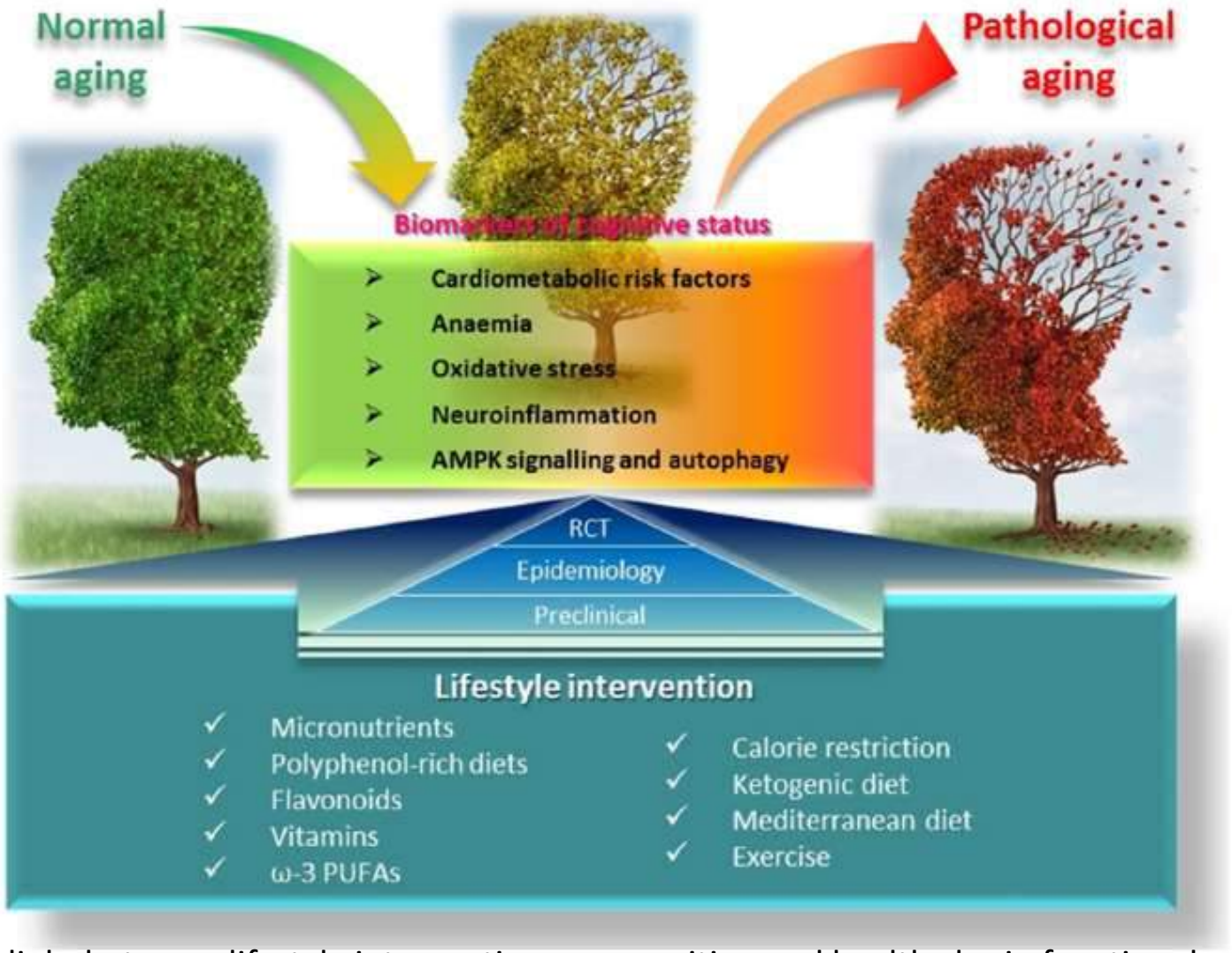
Ageing Research Reviews

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

Vauzour D, et al. 2016



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

Ageing Research Reviews 49 (2019) 1–10

Contents lists available at ScienceDirect

Ageing Research Reviews

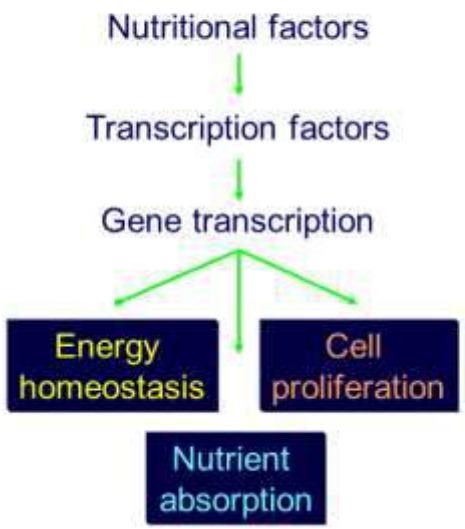
journal homepage: www.elsevier.com/locate/arr

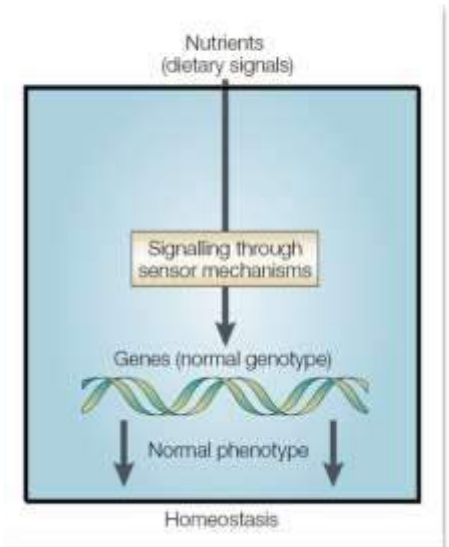
Review

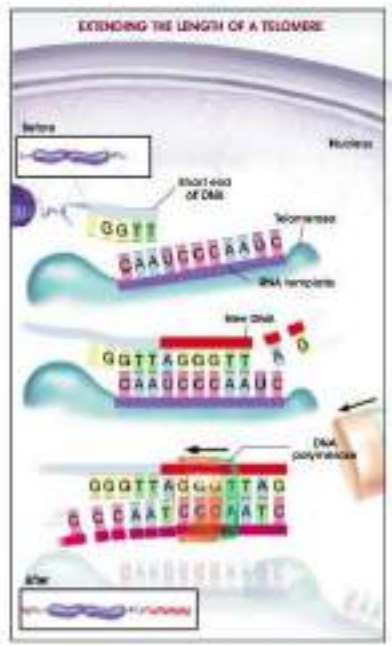
The potential nutrigeroprotective role of Mediterranean diet and its functional components on telomere length dynamics

Sergio Davinelli[a,b], Antonia Trichopoulou[c], Graziamaria Corbi[b], Immaculata De Vivo[a,d,e], Giovanni Scapagnini[b,*]

Nutrients acts as dietary signals







Professor Antonia Trichopoulou, MD, PhD is Director of the World Health Organization Collaborating Center for Nutrition at the Department of Hygiene and Epidemiology, School of Medicine, University of Athens, Greece. She has served as President of the Federation of the European Nutrition Societies and has received numerous honors and awards concerning the health effects of the Mediterranean diet. In 2003 she was decorated by the President of the Greek Republic with the Golden Cross of Honor.

Mol Nutr Food Res 2007

Olive oil and longevity

Antonia Trichopoulou and Vardis Dilis

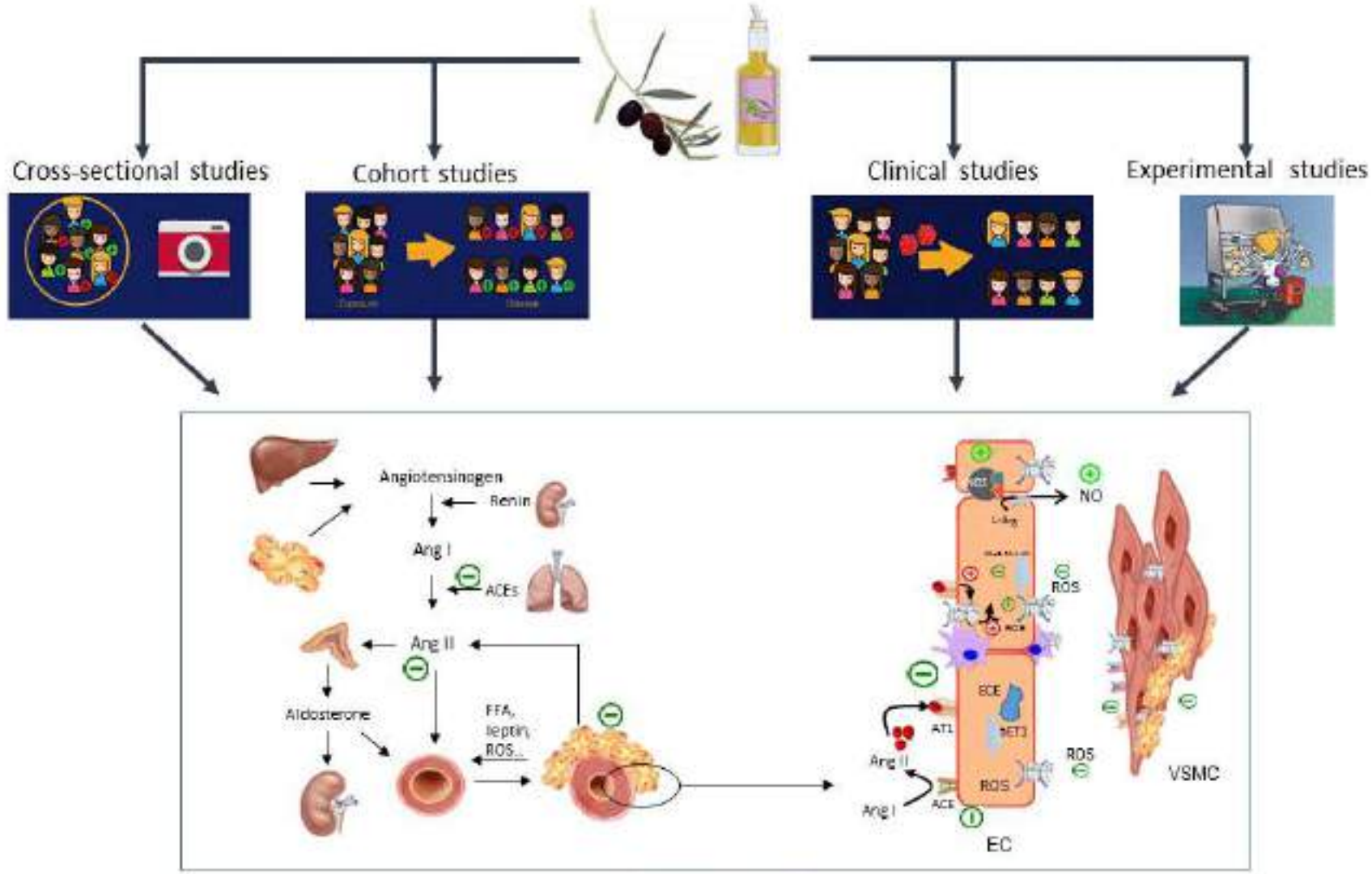
Department of Hygiene and Epidemiology, University of Athens Medical School, Athens, Greece

Several lines of evidence point to olive oil and the olive oil-centered Mediterranean diet as conducive to longevity. The evidence stems from ecological, as well as analytic epidemiological studies assessing olive oil, monounsaturated lipids or the Mediterranean dietary pattern in relation to the incidence of, or mortality from, major common diseases, or overall mortality. Mechanistic considerations are addressed by biochemical studies, whereas randomized clinical trials provide further support to the evidence generated from observational investigations. The content of olive oil in several microcomponents with antioxidant potential, as well as its high content in monounsaturated lipids appear to be essential for the beneficial effect of this food.

Nutrients **2020**, 12, 1548

nutrients

Effects of Olive Oil on Blood Pressure: Epidemiological, Clinical, and Mechanistic Evidence



VSMC relaxation

Inhibition of proliferation, blood pressure reduction

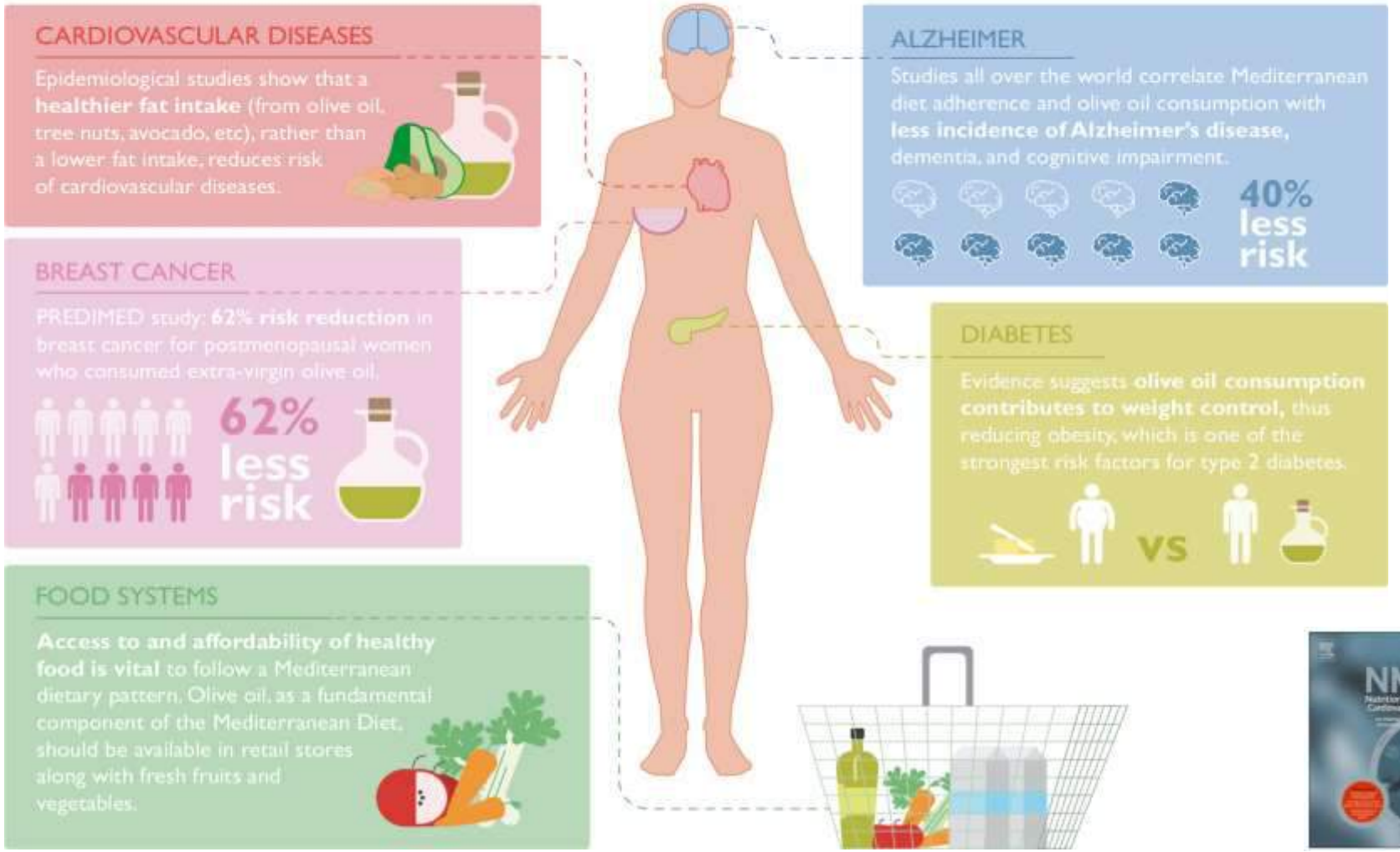
Nutrition, Metabolism and Cardiovascular Diseases, 2018

Olive oil and prevention of chronic diseases: Summary of an International conference

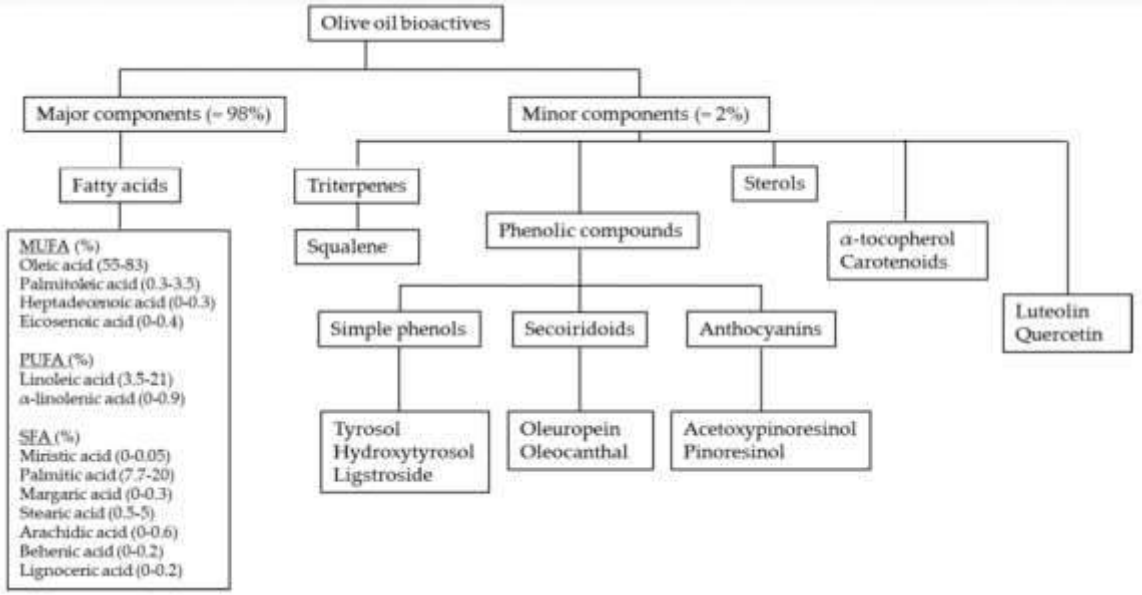
F. Visioli et al

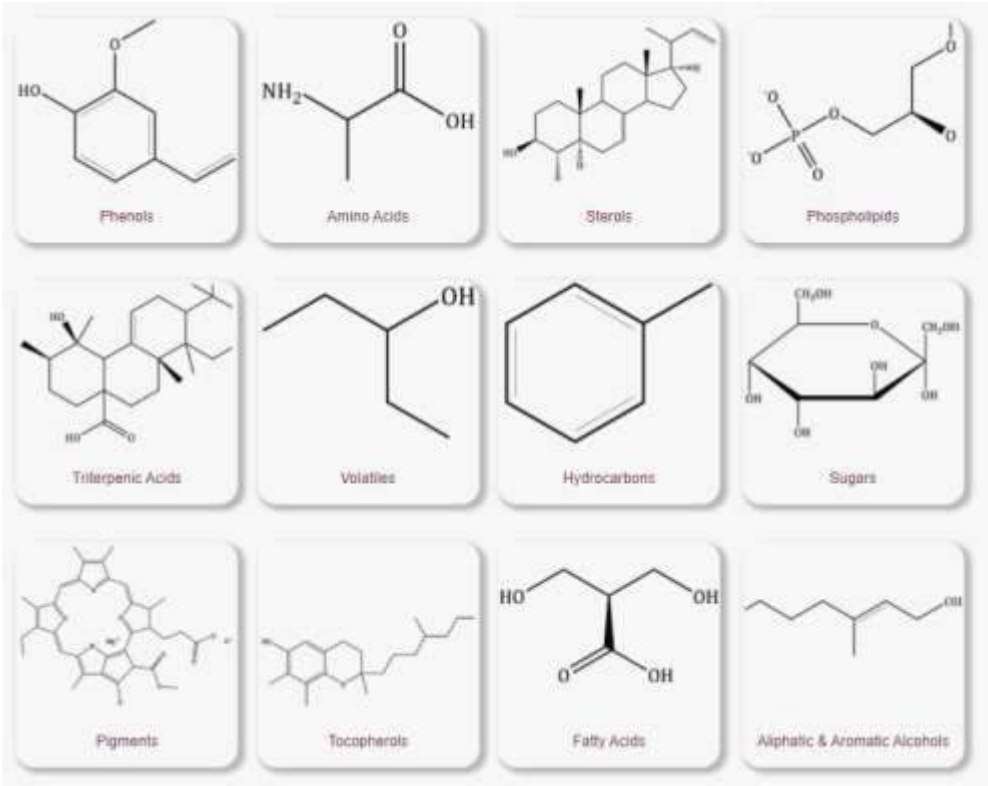
HEALTH BENEFITS OF OLIVE OIL

Olive oil is one of the most important features of the Mediterranean diet, replacing the saturated fats that are common in other diets by **healthier monounsaturated fat.**
Although more research is needed, evidence shows that **olive oil consumption improves risk factors** for a multitude of diseases.



Olive oil nutraceutical

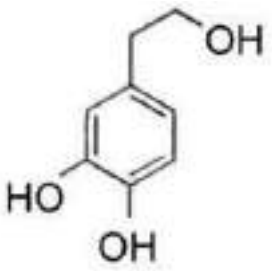




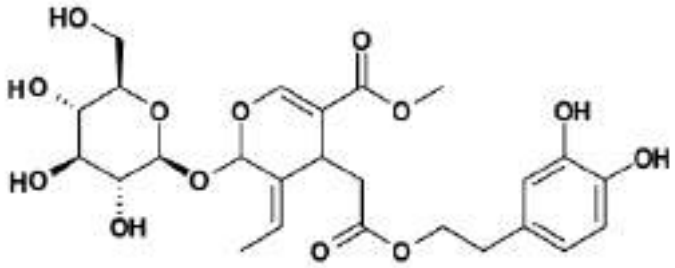
Consumption of olive oil polyphenols helps protect blood lipids against oxidative stress.

efsa
European Food Safety Authority

The European Food Safety Agency (ELSA) has issued a positive opinion on the use of a Health Claim for olive polyphenols: "Scientific Opinion on the substantiation of health claims related to polyphenols in olive and protection of LDL particles from oxidative damage." EFSA Journal 2011;9(4):2033, which indicates that the panel concludes that there is a relationship of cause and effect between the consumption of olive polyphenols (mainly hydroxytyrosol and its derivatives) and the protection of the cholesterol LDL particles from oxidative damage.

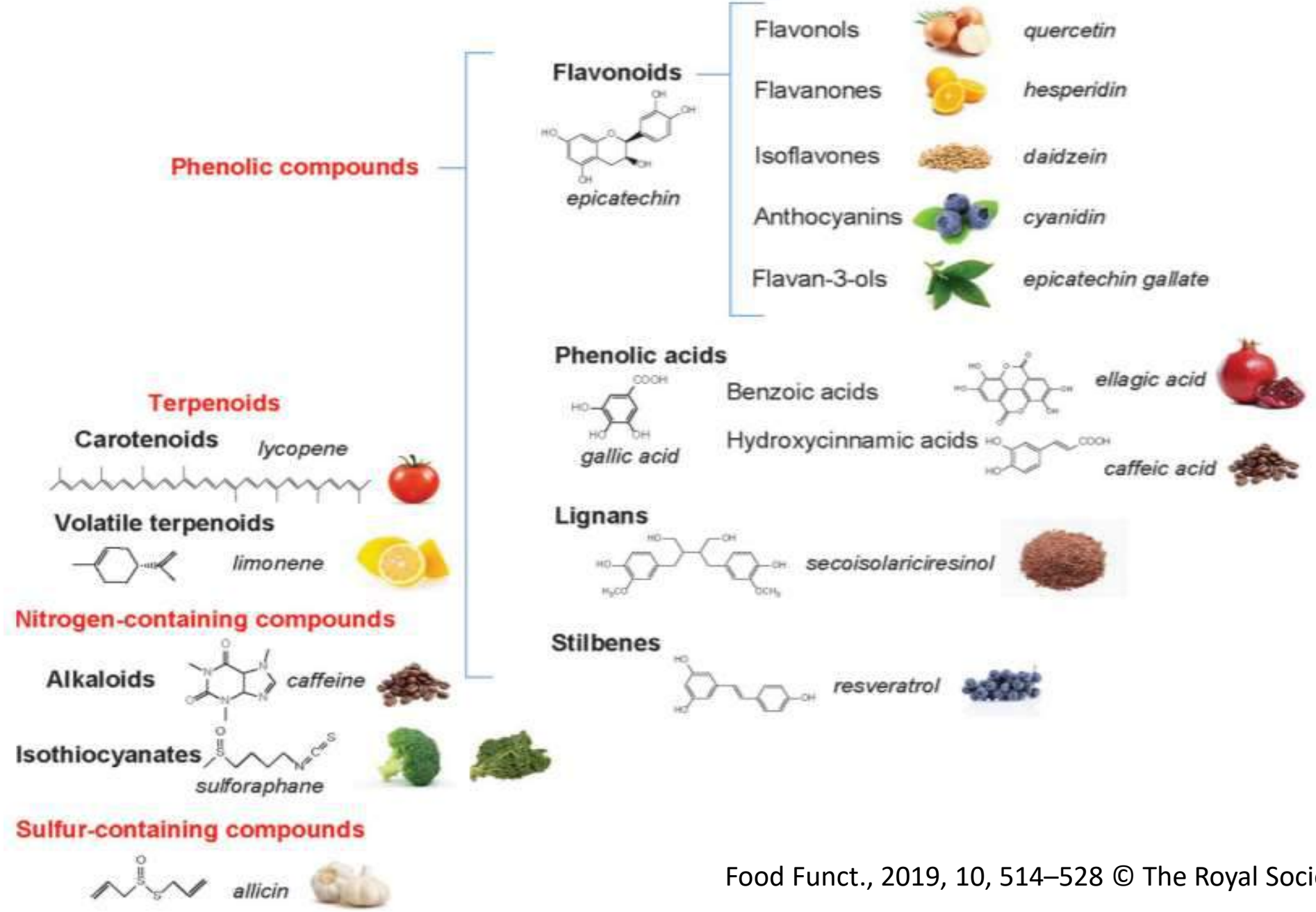


Hydroxytyrosol

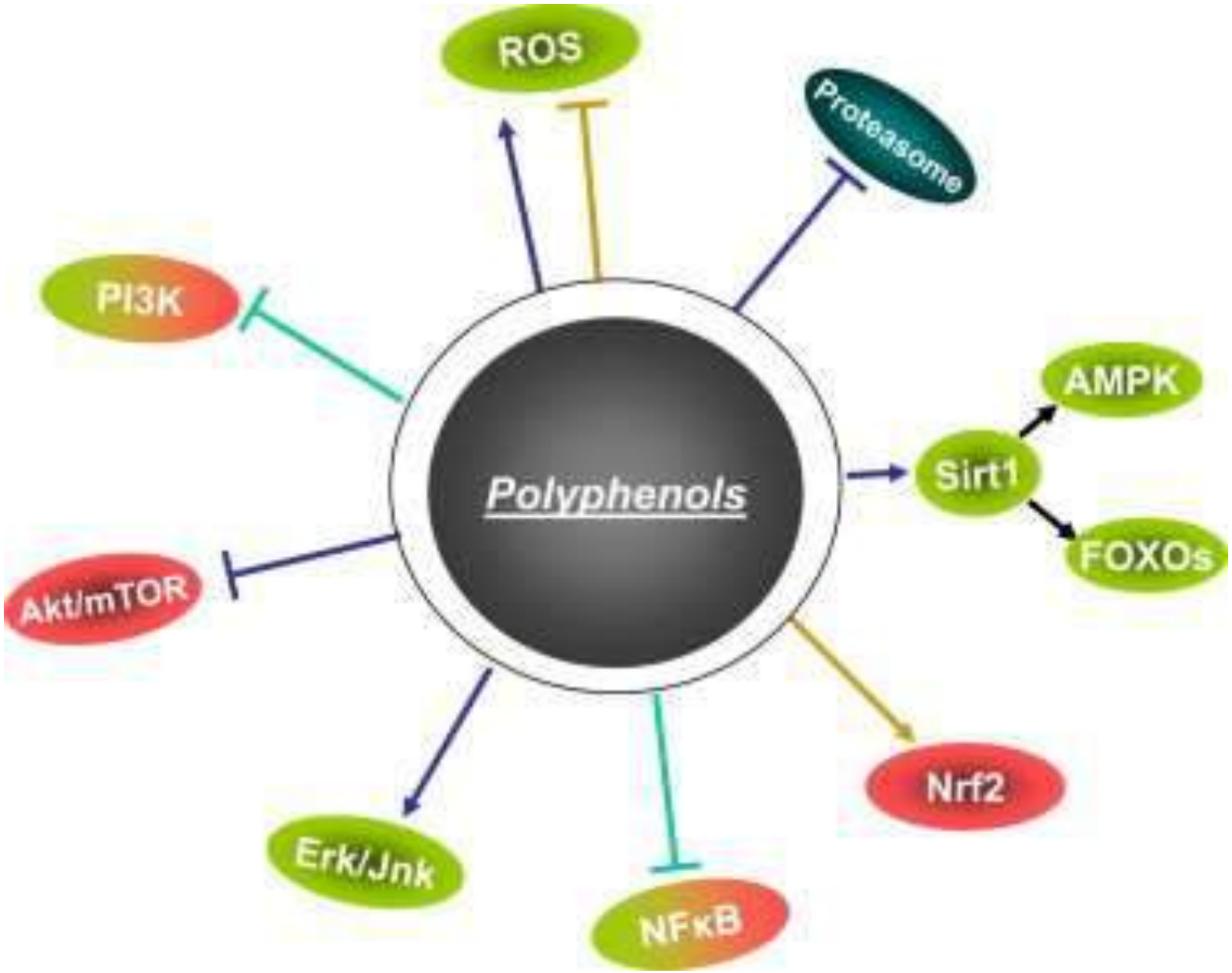


Oleuropein

Structure of common phytochemicals



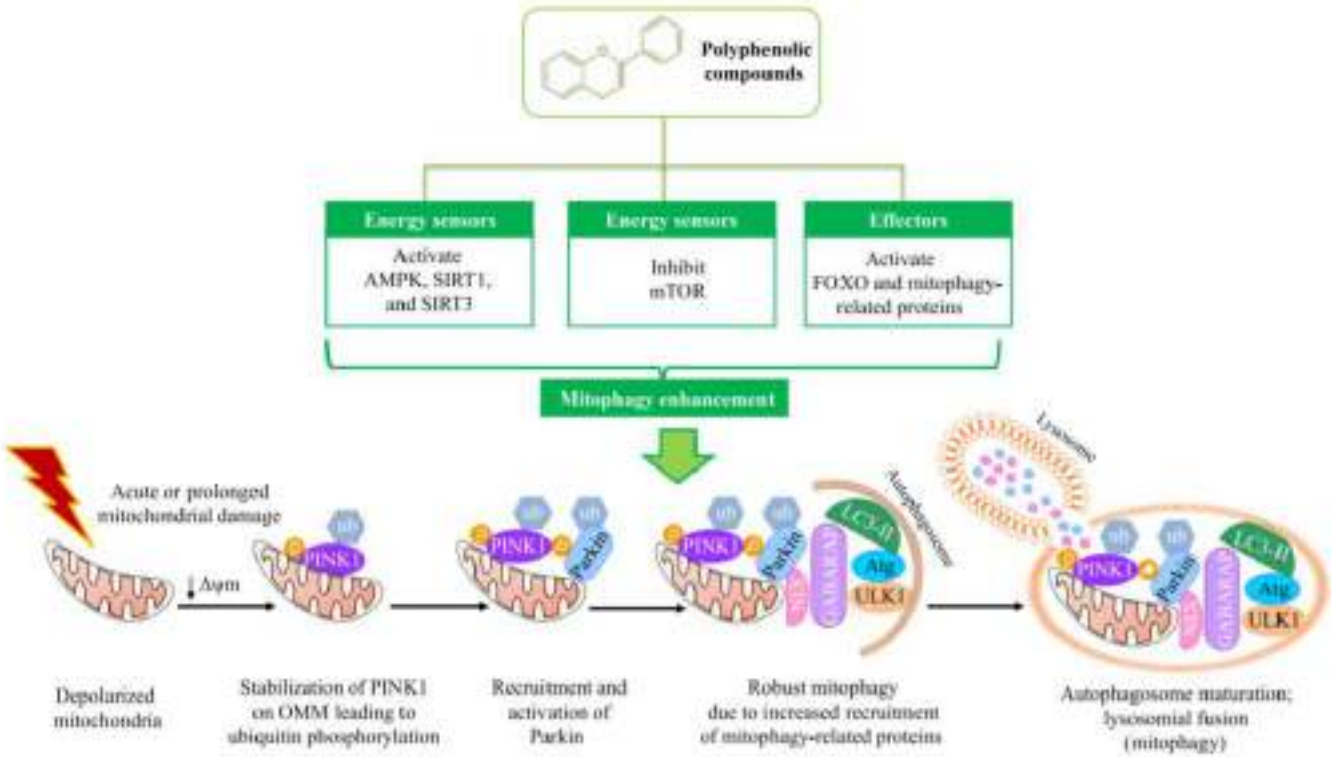
Major pathways activated by polyphenols



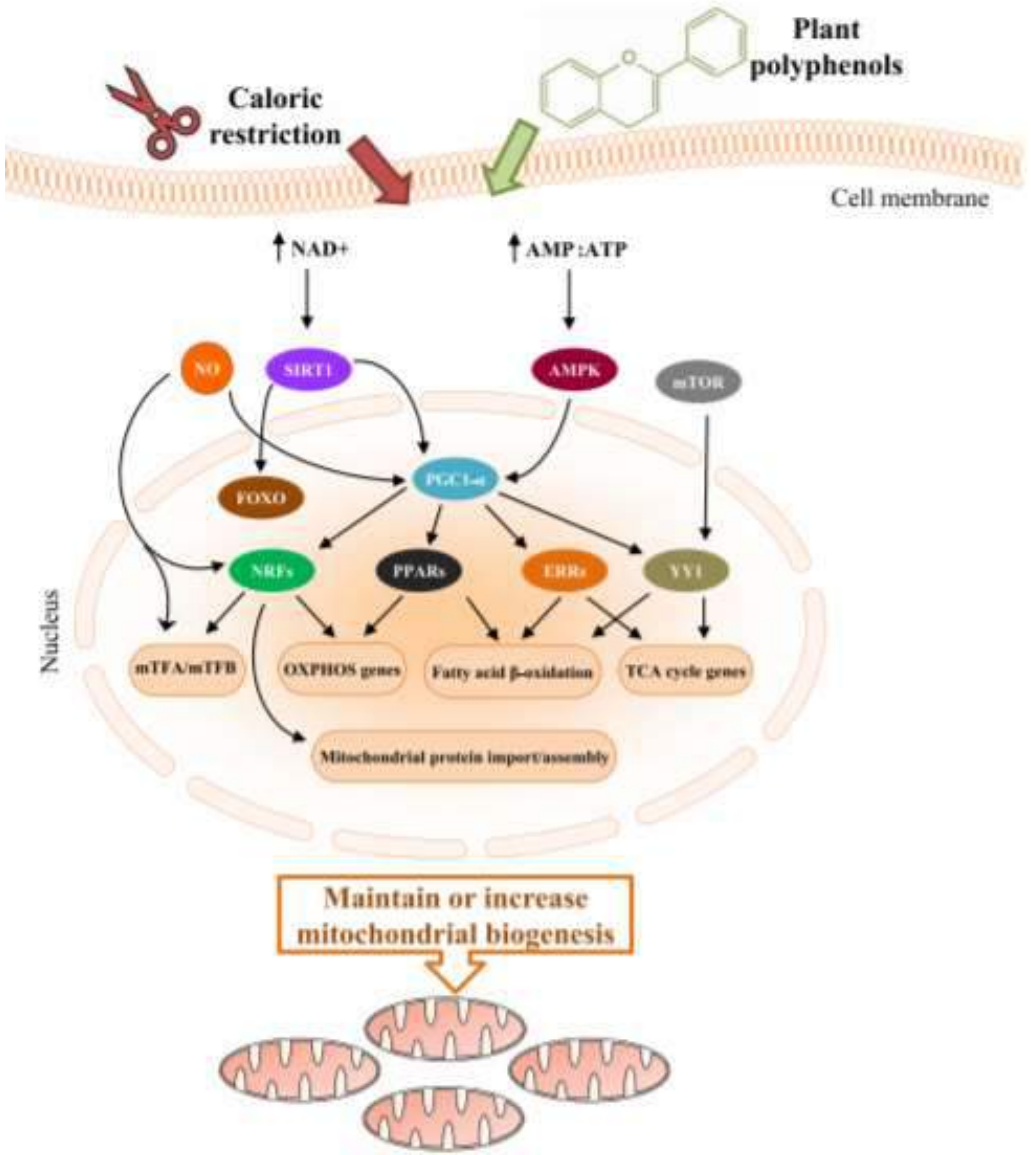
Trends in Endocrinology & Metabolism 2020

Polyphenols as Caloric Restriction Mimetics Regulating Mitochondrial Biogenesis and Mitophagy

Sergio Davinelli,[1,2,*] Diego De Stefani,[3] Immaculata De Vivo,[1] and Giovanni Scapagnini[2]



Mitophagy Regulation by Polyphenols.



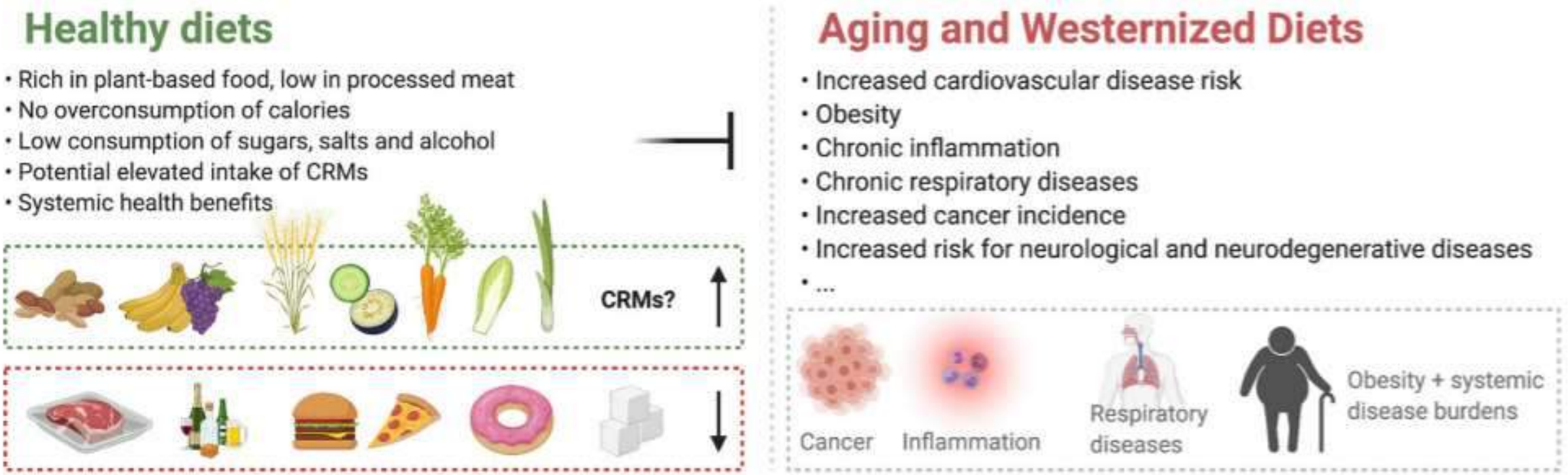
Key Players Involved in Mitochondrial Biogenesis.

frontiers in Nutrition

REVIEW
published: 06 September 2021
doi: 10.3389/fnut.2021.717343

Caloric Restriction Mimetics in Nutrition and Clinical Trials

Hofer SJ, Davinelli S, Bergmann M, Scapagnini G and Madeo F.



Healthy diet plans stand opposite to Westernized Diets and counteract age-associated deteriorations.

1998-2001

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

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

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

The Journal of Nutrition
Nutritional Epidemiology

J. Nutr. 143: 1445–1450, 2013

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

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

JAGS 63:938–946, 2015

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

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

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

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

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

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

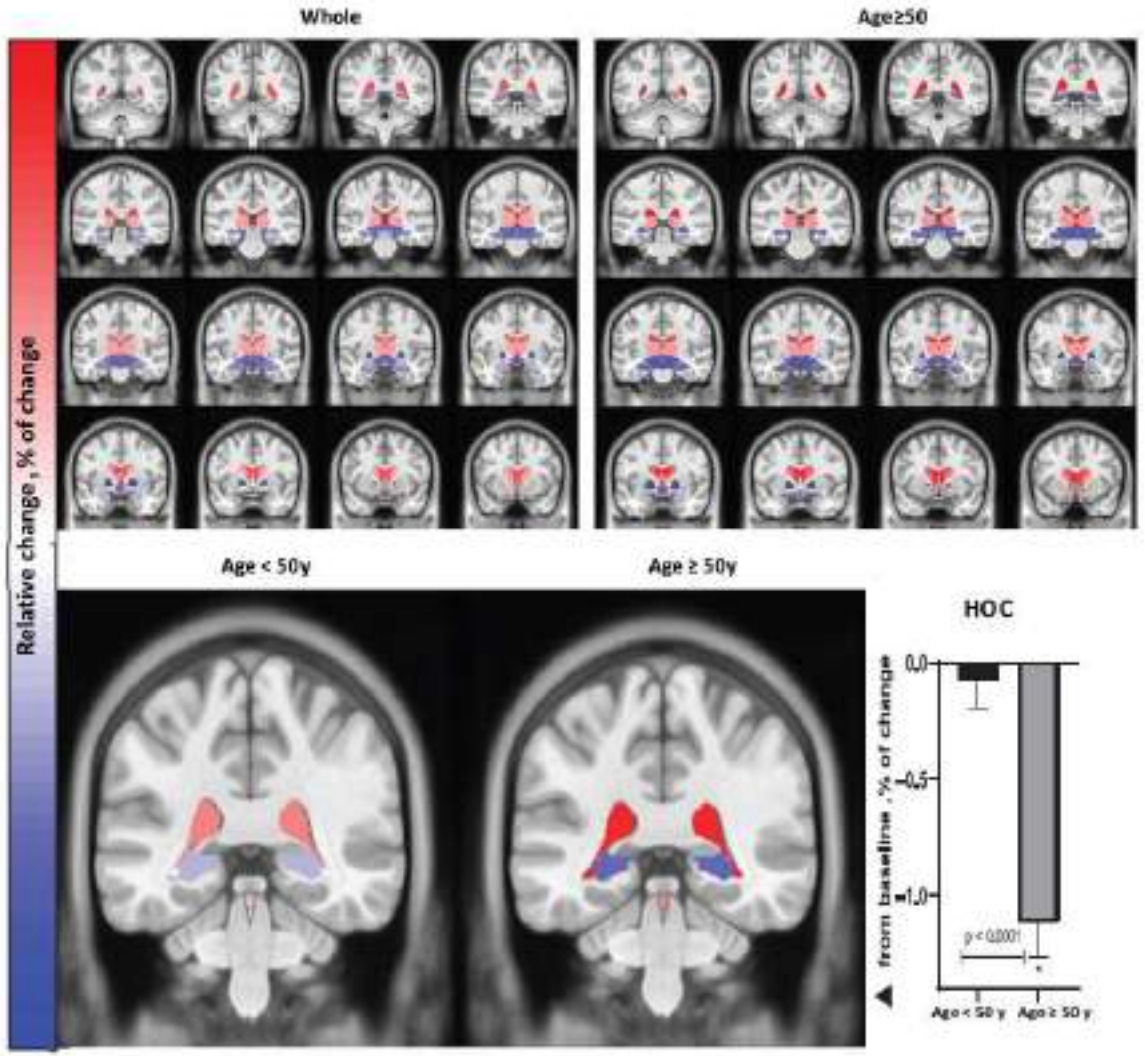
[a] Adjusted for baseline cognitive score only.

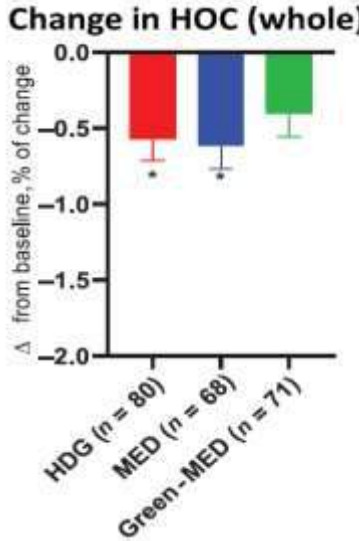
[b] Obtained by assigning the median of each tertile as scores.

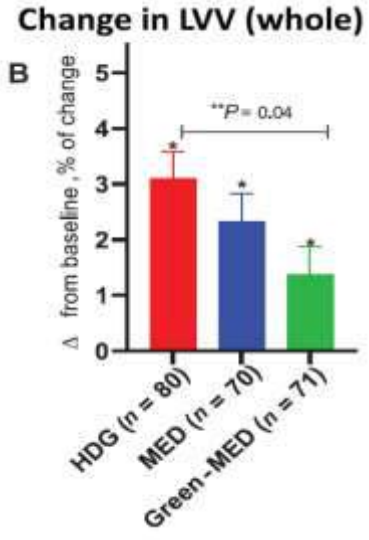
[c] Adjusted for baseline cognitive score, sex, age, education, body mass index, total energy intake, physical activity, total cholesterol, impaired renal function, smoking status, congestive heart failure, cancer, stroke, diabetes mellitus, and depressive symptoms.

Am J Clin Nutr 2022;115:1270–1281

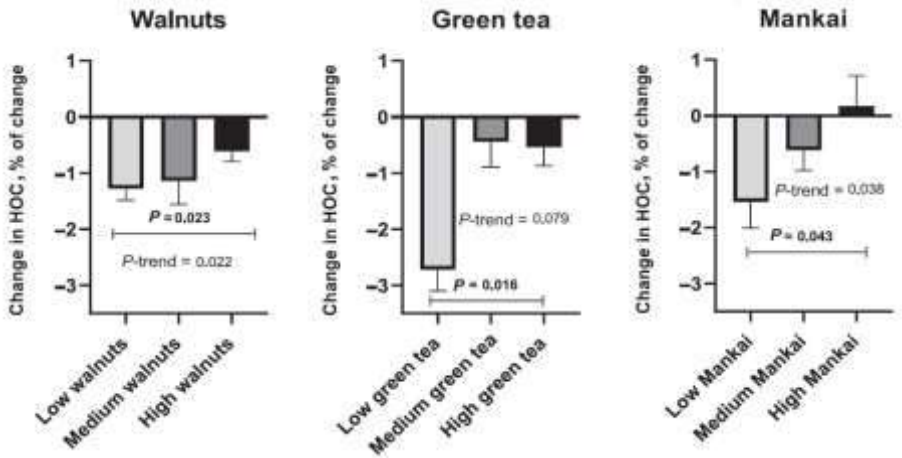
The effect of a high-polyphenol Mediterranean diet (Green-MED) combined with physical activity on age-related brain atrophy: the Dietary Intervention Randomized Controlled Trial Polyphenols Unprocessed Study (DIRECT PLUS)







***Wolffia globosa* (Mankai)**



jbc THE JOURNAL OF BIOLOGICAL CHEMISTRY

CURCUMIN: THE INDIAN SOLID GOLD

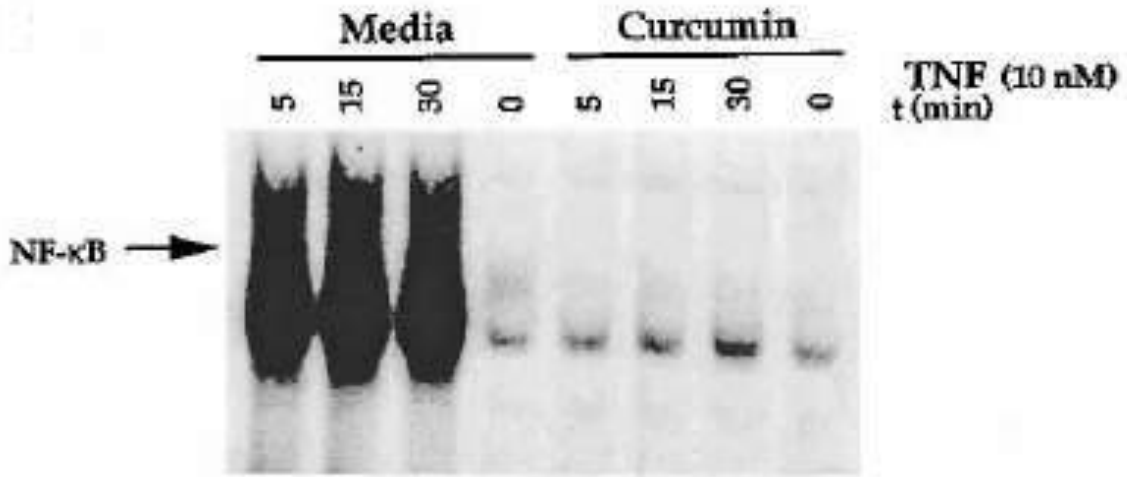
THE JOURNAL OF BIOLOGICAL CHEMISTRY
Vol. 270, No. 42, Issue of October 20, pp. 24995–25000, 1995
Printed in U.S.A.

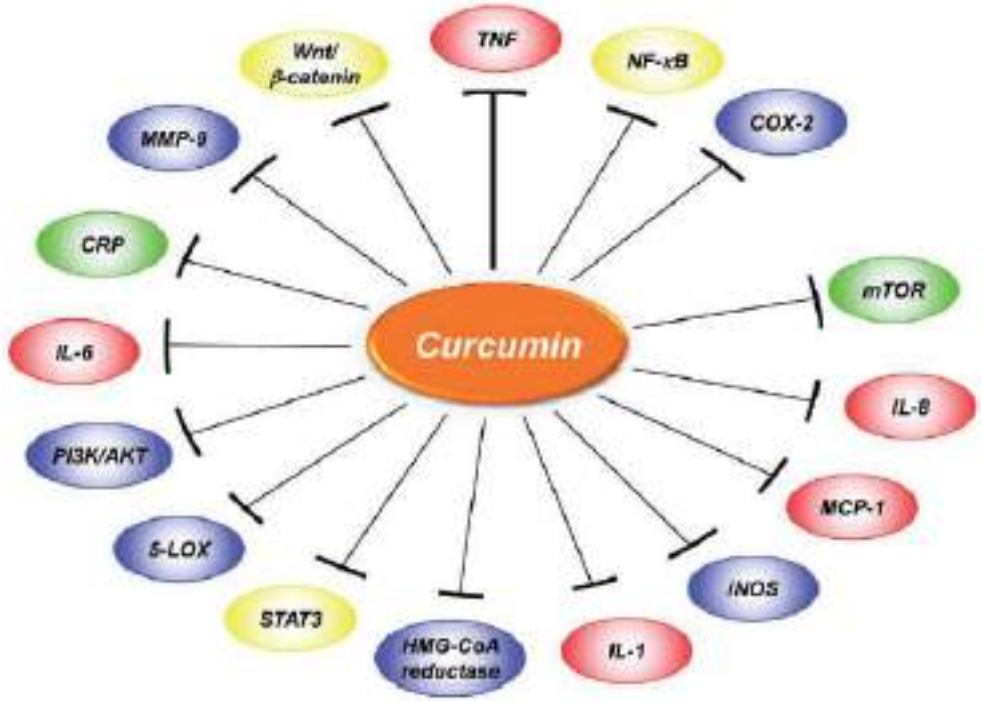
Activation of Transcription Factor NF-κB Is Suppressed by Curcumin (Diferulolylmethane)*

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

Sanjaya Singh and Bharat B. Aggarwal‡

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

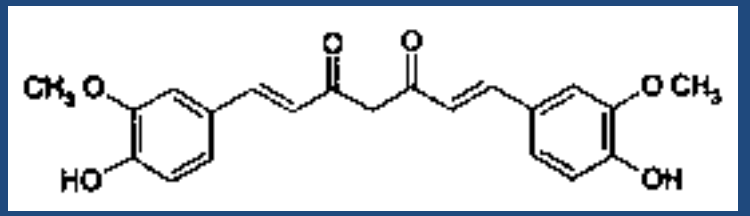




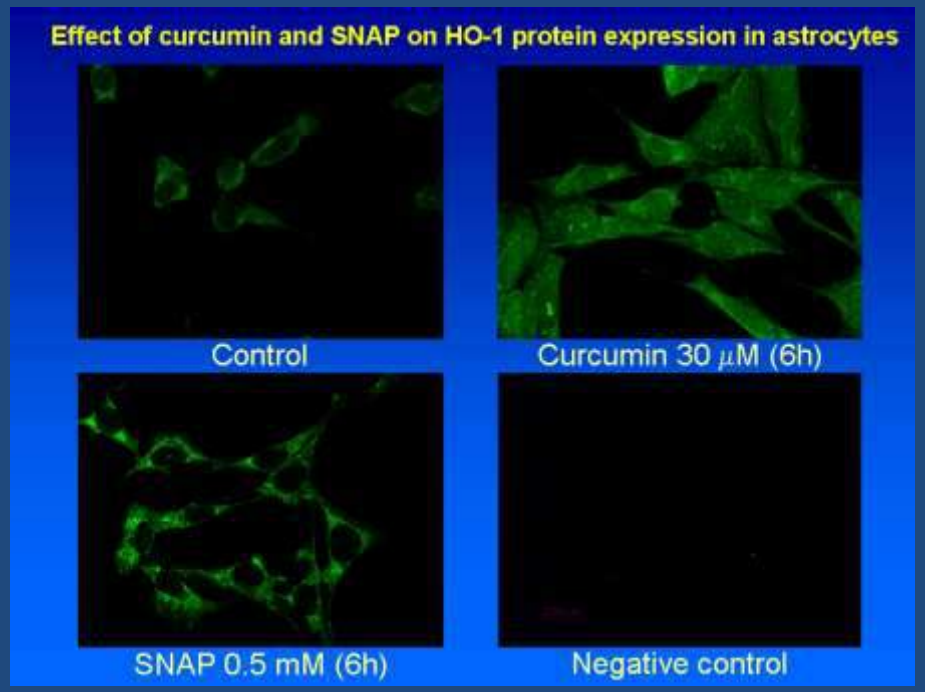
Antioxid Redox Signal. 2006 Mar-Apr;8(3-4):395-403

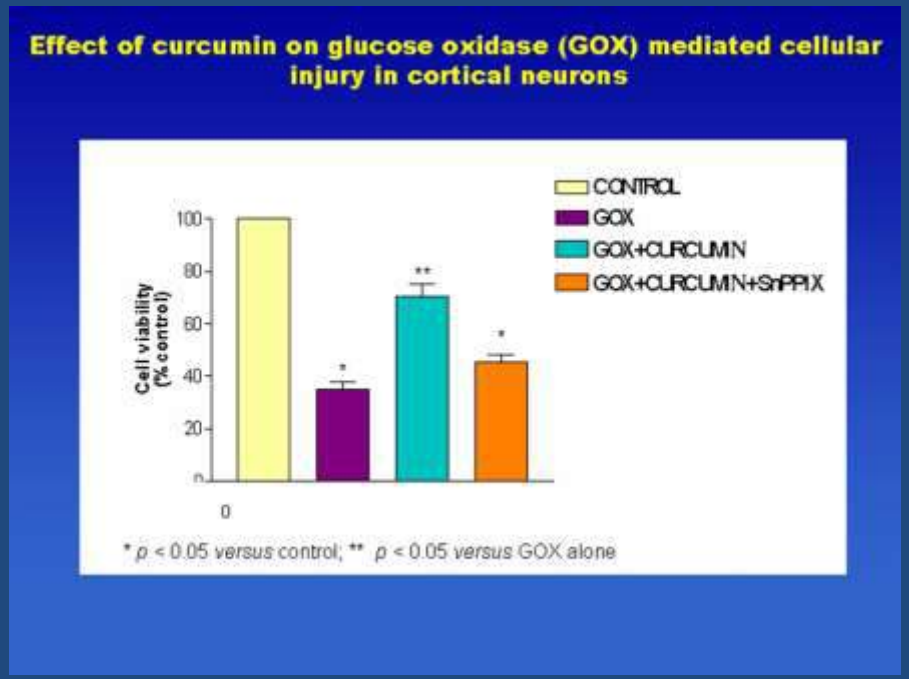
Curcumin activates defensive genes and protects neurons against oxidative stress.

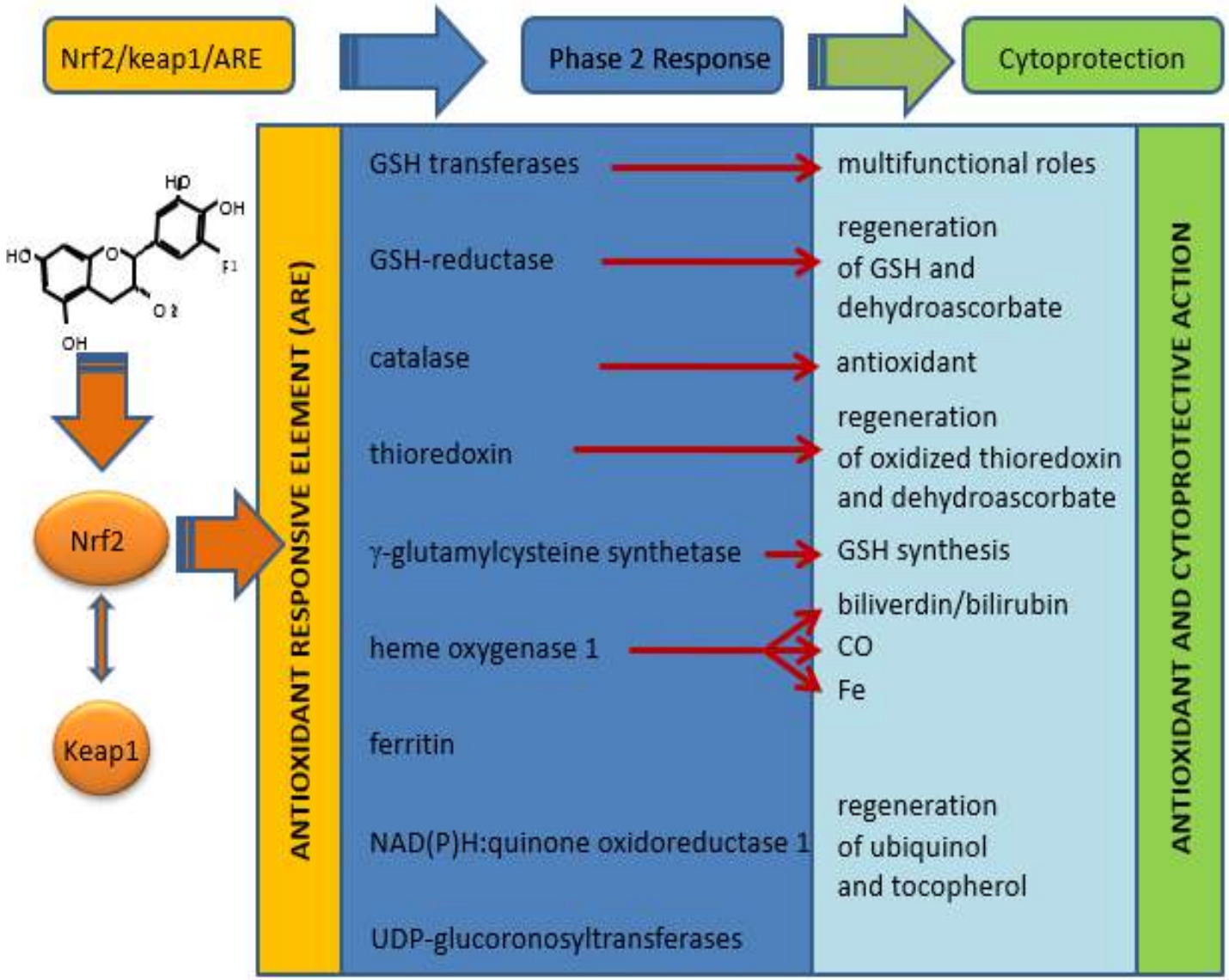
Scapagnini G, Colombrita C, Amadio M, D'Agata V, Arcelli E, Sapienza M, Quattrone A, Calabrese V.



CURCUMIN





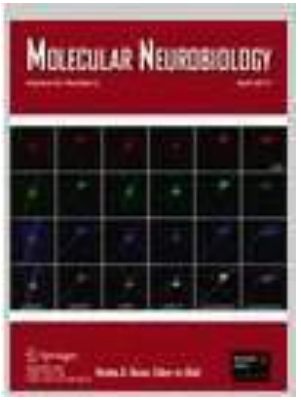

Nrf2/keap1/ARE
Phase 2 Response
Cytoprotection
HO
OH
HO
O
OH
OH
Nrf2
Keap1
ANTIOXIDANT RESPONSIVE ELEMENT (ARE)
GSH transferases
multifunctional roles
GSH-reductase
regeneration of GSH and dehydroascorbate
catalase
antioxidant
thioredoxin
regeneration of oxidized thioredoxin and dehydroascorbate
γ-glutamylcysteine 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


NRF2

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

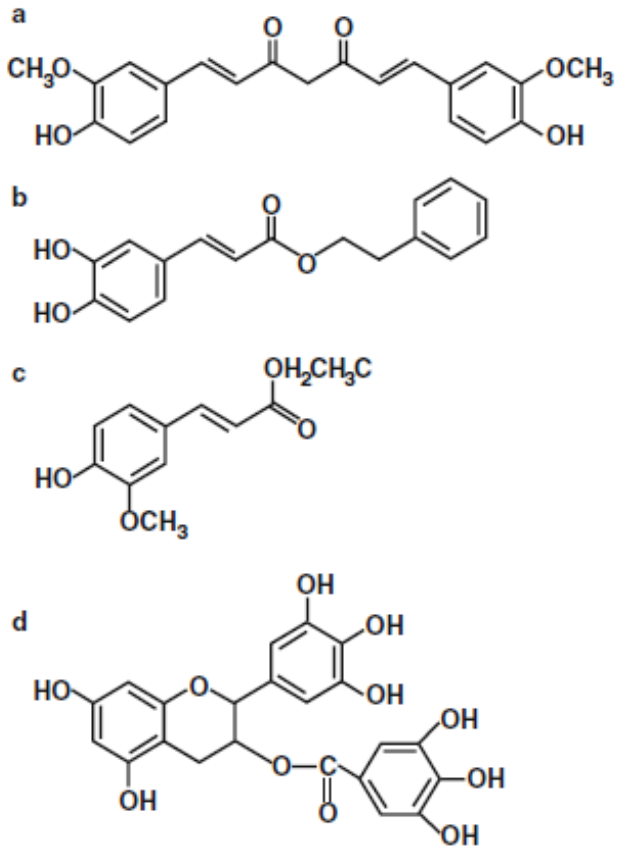
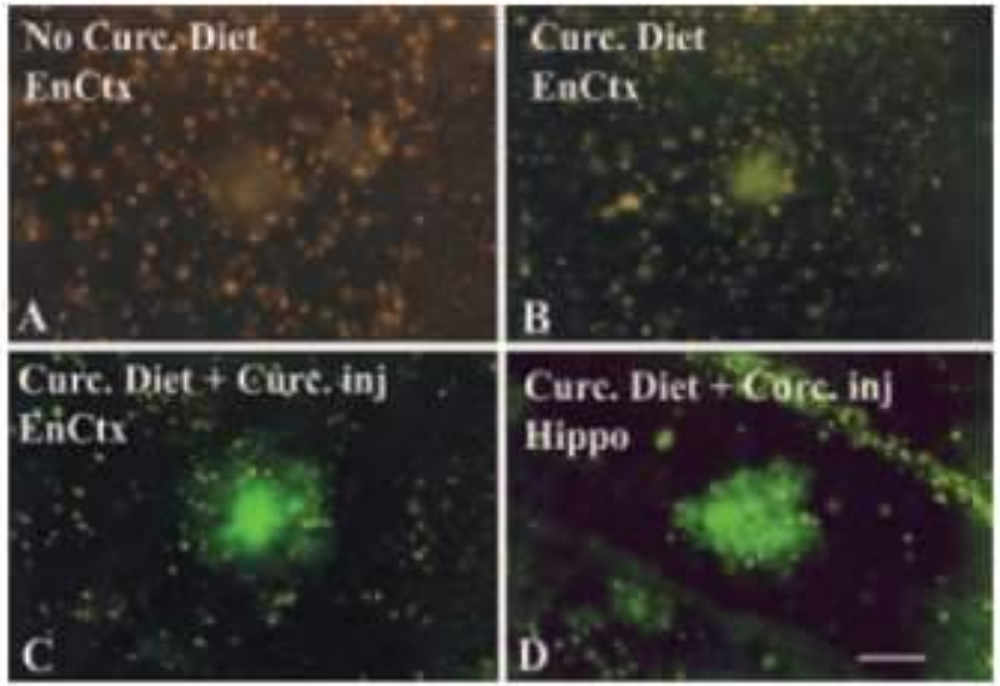


Fig. 1 The chemical structures of curcumin (**a**), CAPE (**b**), EFE (**c**), (−)-EGCG (**d**)

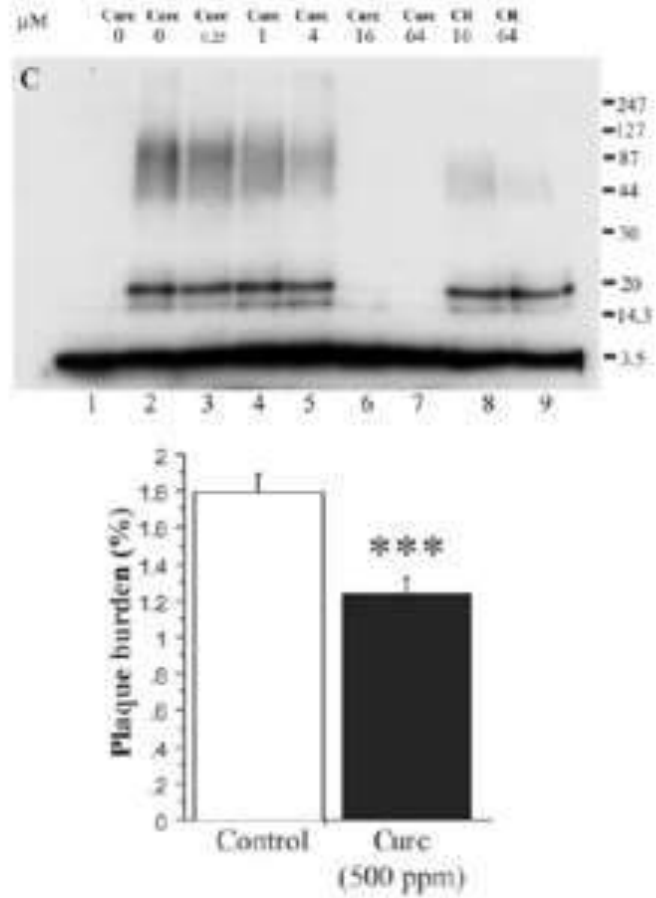
THE JOURNAL OF BIOLOGICAL CHEMISTRY Vol. 280, No. 7, Issue of February 18, pp. 5892–5901, 2005

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

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



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

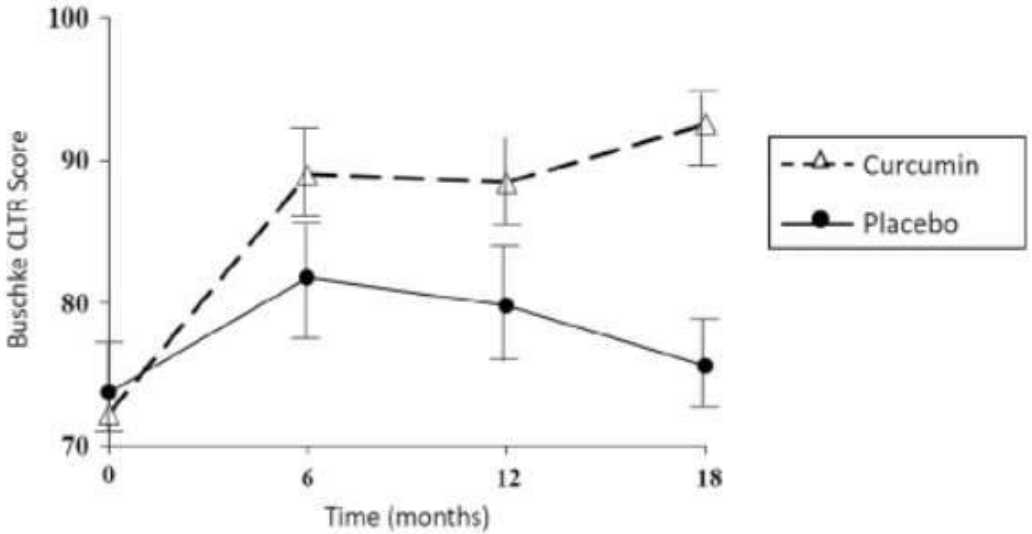


Curcumin inhibits formation of Aβ oligomers.

Am J Geriatr Psychiatry 26:3, March 2018

Memory and Brain Amyloid and Tau Effects of a Bioavailable Form of Curcumin in Non-Demented Adults: A Double-Blind, Placebo-Controlled 18-Month Trial

Gary W. Small, et al.



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

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

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

The major classes of flavonoids and their dietary sources.

Flavonoids as Prospective Neuroprotectants and Their Therapeutic Propensity in Aging Associated Neurological Disorders. Front. Aging Neurosci. 11:155.

Am J Clin Nutr 2020

Long-term dietary flavonoid intake and risk of Alzheimer disease and related dementias in the Framingham Offspring Cohort

Esra Shishtar,[1,2] Gail T Rogers,[1] Jeffrey B Blumberg,[2] Rhoda Au,[3,4,5,6,7] and Paul F Jacques[1,2]

HRs (95% CIs) of Alzheimer disease and related dementias (ADRD) events over 26 y of follow-up based on a 5-y cutoff between ADRD diagnosis and updated flavonoid intake data

	Flavonoid intake percentile category				
Flavonoid class	≤15th	>15th to 30th	>30th to 60th	>60th	*P*-trend[2]
Flavonols	(n[1] = 420/36)	(n = 420/36)	(n = 841/63)	(n = 1120/58)	
Model 1[4]	1.00 (ref.)	1.00 (0.62, 1.59)	0.89 (0.58, 1.36)	0.58 (0.37, 0.91)	0.004
Model 2[5]	1.00 (ref.)	0.96 (0.60, 1.56)	0.84 (0.54, 1.29)	0.51 (0.32, 0.82)	0.001
Model 3[6]	1.00 (ref.)	1.00 (0.61, 1.64)	0.85 (0.53, 1.35)	0.54 (0.32, 0.90)	0.003
Flavones	(n = 420/31)	(n = 420/21)	(n = 841/47)	(n = 1120/94)	
Model 1[4]	1.00 (ref.)	0.75 (0.43, 1.31)	0.60 (0.38, 0.95)	0.86 (0.55, 1.32)	0.92
Model 2[5]	1.00 (ref.)	0.76 (0.44, 1.33)	0.57 (0.35, 0.91)	0.83 (0.53, 1.30)	0.99
Model 3[6]	1.00 (ref.)	0.83 (0.47, 1.46)	0.61 (0.38, 0.99)	0.92 (0.57, 1.48)	0.72
Flavanones	(n = 418/26)	(n = 422/20)	(n = 840/38)	(n = 1121/109)	
Model 1[4]	1.00 (ref.)	0.62 (0.34, 1.11)	0.49 (0.30, 0.81)	0.88 (0.56, 1.37)	0.22
Model 2[5]	1.00 (ref.)	0.61 (0.34, 1.10)	0.48 (0.29, 0.80)	0.84 (0.53, 1.33)	0.32
Model 3[6]	1.00 (ref.)	0.66 (0.36, 1.20)	0.52 (0.31, 0.88)	0.92 (0.57, 1.49)	0.21
Flavan-3-ols	(n = 419/33)	(n = 422/36)	(n = 840/49)	(n = 1120/75)	
Model 1[4]	1.00 (ref.)	1.13 (0.7, 1.83)	0.74 (0.47, 1.16)	0.77 (0.50, 1.20)	0.19
Model 2[5]	1.00 (ref.)	1.08 (0.66, 1.75)	0.66 (0.41, 1.06)	0.68 (0.44, 1.07)	0.09
Model 3[6]	1.00 (ref.)	1.03 (0.63, 1.70)	0.65 (0.40, 1.05)	0.69 (0.43, 1.09)	0.13
Anthocyanins	(n = 420/49)	(n = 421/32)	(n = 840/65)	(n = 1120/47)	
Model 1[4]	1.00 (ref.)	0.52 (0.33, 0.82)	0.53 (0.36, 0.77)	0.29 (0.19, 0.45)	<0.001
Model 2[5]	1.00 (ref.)	0.50 (0.32, 0.79)	0.53 (0.36, 0.78)	0.26 (0.16, 0.40)	<0.001
Model 3[6]	1.00 (ref.)	0.48 (0.30, 0.77)	0.49 (0.32, 0.74)	0.24 (0.15, 0.39)	<0.001
Flavonoid polymers	(n = 420/33)	(n = 420/34)	(n = 840/57)	(n = 1121/69)	
Model 1[4]	1.00 (ref.)	0.90 (0.55, 1.47)	0.70 (0.45, 1.10)	0.60 (0.38, 0.95)	0.03
Model 2[5]	1.00 (ref.)	0.88 (0.54, 1.44)	0.63 (0.40, 1.00)	0.53 (0.33, 0.85)	0.008
Model 3[6]	1.00 (ref.)	0.88 (0.53, 1.46)	0.65 (0.40, 1.05)	0.58 (0.35, 0.94)	0.03
Total flavonoids	(n = 419/27)	(n = 421/30)	(n = 841/61)	(n = 1120/75)	
Model 1[4]	1.00 (ref.)	0.96 (0.56, 1.63)	0.94 (0.58, 1.50)	0.78 (0.48, 1.27)	0.22
Model 2[5]	1.00 (ref.)	0.91 (0.53, 1.56)	0.86 (0.53, 1.39)	0.68 (0.41, 1.12)	0.08
Model 3[6]	1.00 (ref.)	0.89 (0.51, 1.55)	0.90 (0.54, 1.48)	0.73 (0.43, 1.24)	0.18

Led by scientists at the Jean Mayer USDA Human Nutrition Research Center on Aging (USDA HNRCA) at Tufts University, this study followed 2,800 people aged 50 and older to examine the long-term relationship between eating foods containing flavonoids and risk of Alzheimer's disease (AD) and Alzheimer's disease and related dementias (ADRD).

While many studies have looked at associations between nutrition and dementias over short periods of time, this study published in the *American Journal of Clinical Nutrition* looked at exposure over 20 years.

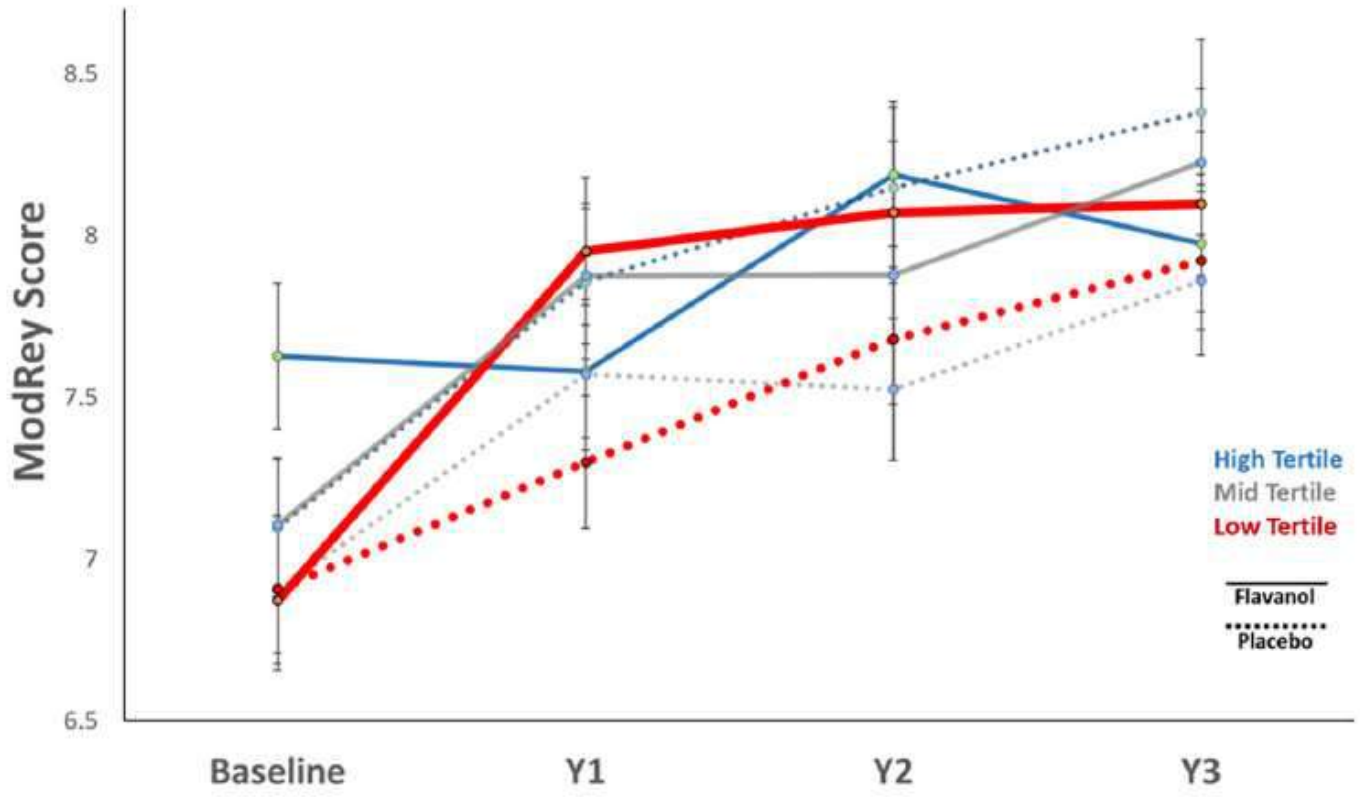
The research team determined that low intake of three flavonoid types was linked to higher risk of dementia when compared to the highest intake. Specifically: Low intake of flavonols (apples, pears and tea) was associated with twice the risk of developing ADRD; Low intake of anthocyanins (blueberries, strawberries, and red wine) was associated with a four-fold risk of developing ADRD; and low intake of flavonoid polymers (apples, pears, and tea) was associated with twice the risk of developing ADRD.

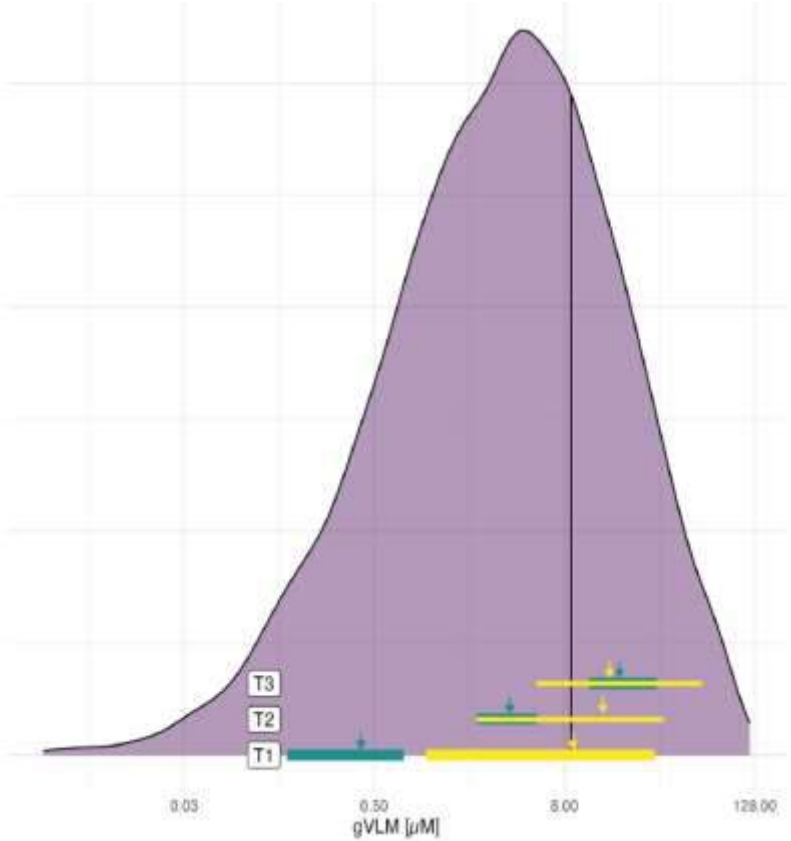
PNAS 2023 Vol. 120 No. 23 e2216932120

Dietary flavanols restore hippocampal-dependent memory in older adults with lower diet quality and lower habitual flavanol consumption

Adam M. Brickman[a,b,c,1], Lok-Kin Yeung[a,b,c], Daniel M. Alschuler[d], Javier I. Ottaviani[e], Gunter G. C. Kuhnle[f], Richard P. Sloan[g,s], Heike Luttmann-Gibson[h,i], Trisha Copeland[h], Hagen Schroeter[e], Howard D. Sesso[h,j], JoAnn E. Manson[h,j], Melanie Wall[d,s], and Scott A. Small[a,b,c,g,1]

This study, a culmination of 15 y of research from mice to humans, provides biomarkerbased evidence that dietary consumption of flavanols, a food constituent found in certain fruits and vegetables, can be etiologically linked to age-related memory decline.

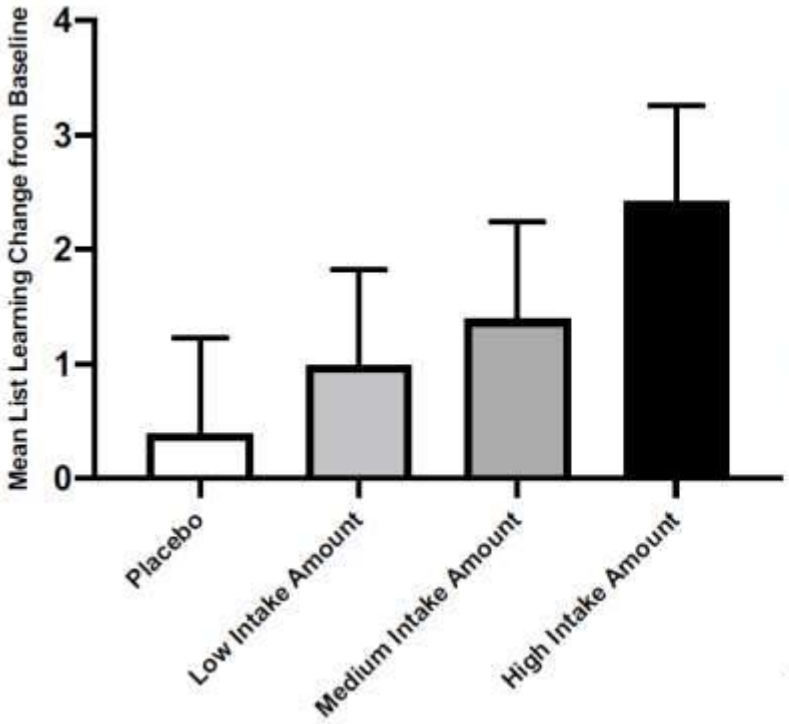


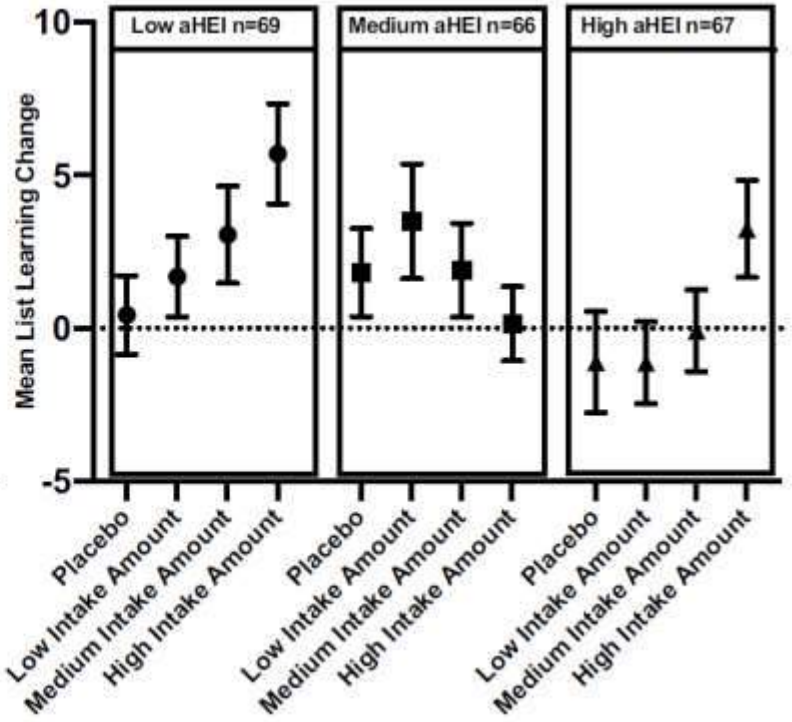


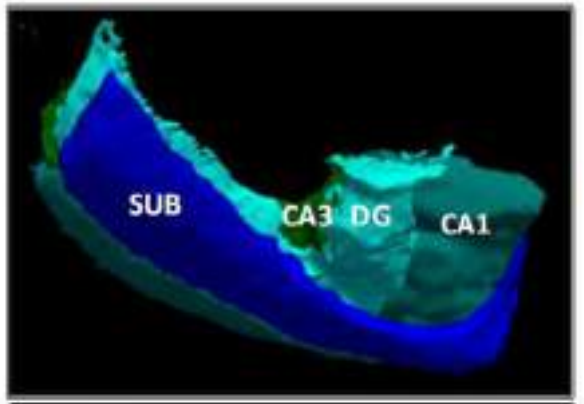
Scientific Reports | (2021) 11:3837

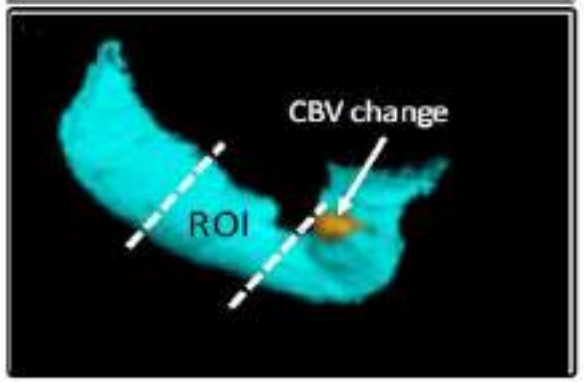
Insights into the role of diet and dietary flavanols in cognitive aging: results of a randomized controlled trial

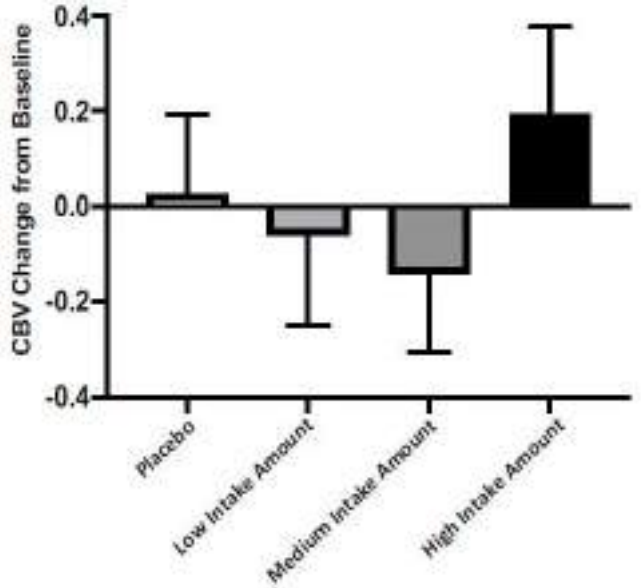
Richard P. Sloan[1,2]✉, Melanie Wall[2], Lok-Kin Yeung[3,4], Tianshu Feng[2], Xinyang Feng[3], Frank Provenzano[3,4], Hagen Schroeter[5], Vincenzo Lauriola[1], Adam M. Brickman[3,4] & Scott A. Small[3,4]✉











Dietary Flavonoids and Adult Neurogenesis: Potential Implications for Brain Aging

Current Neuropharmacology, 2023

Sergio Davinelli*, Alessandro Medoro, Sawan Ali, Daniela Passarella, Mariano Intrieri and Giovanni Scapagnini

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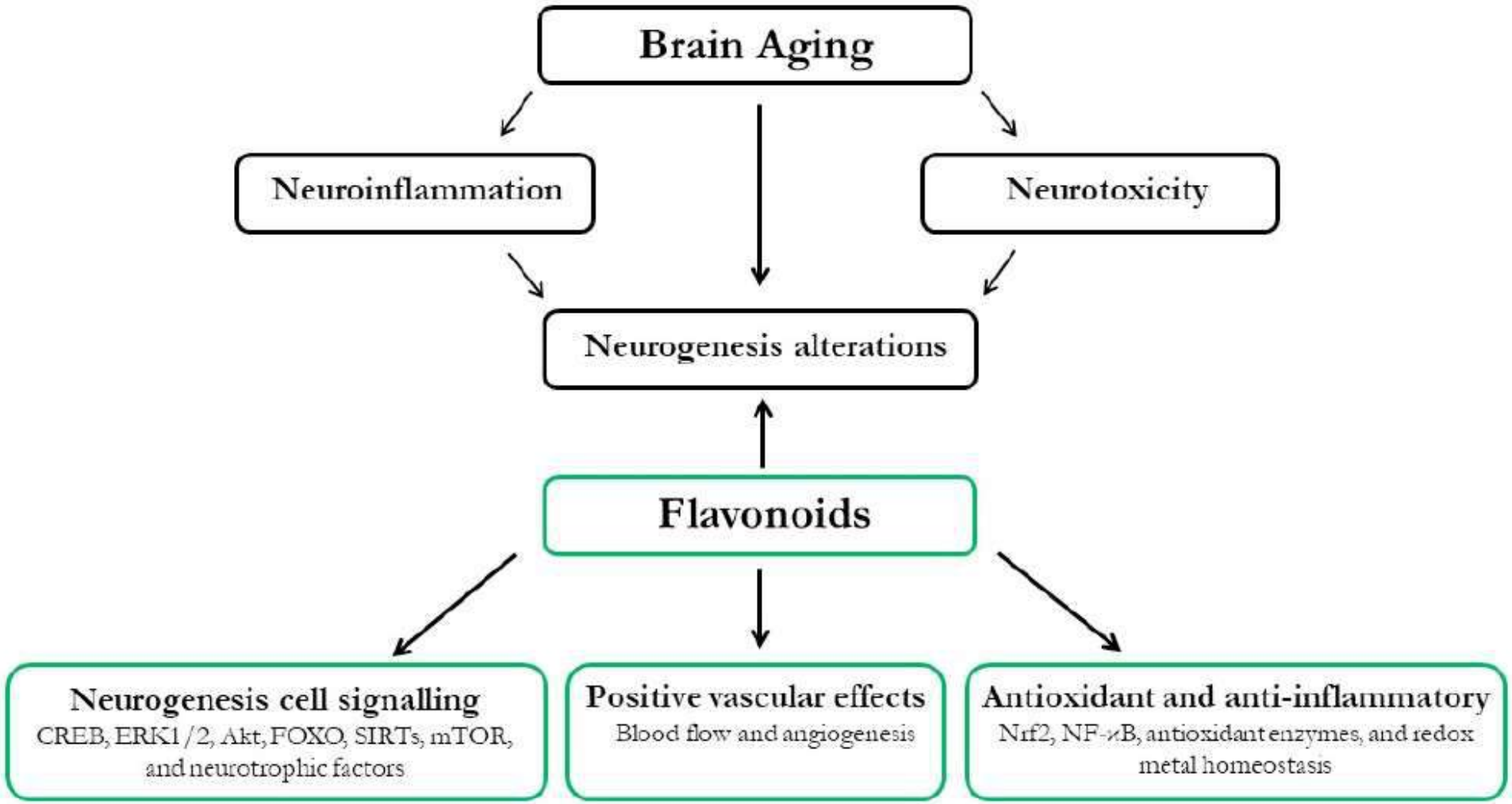


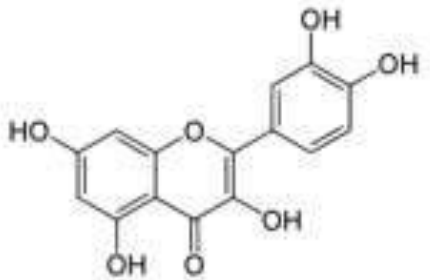
Am Geriatr Soc. 2017 October ; 65(10): 2297–2301.

The Clinical Potential of Senolytic Drugs

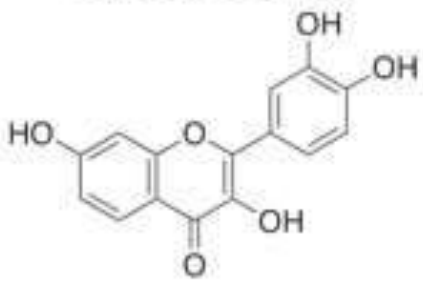
James L. Kirkland, MD, PhD*, Tamara Tchkonia, PhD*, Yi Zhu, PhD*, Laura J. Niedernhofer, MD, PhD‡, and Paul D. Robbins, PhD‡

Senescent Cell Anti-Apoptotic Pathways (SCAPs)

SCAP	Original Description	Agents Targeting SCAP	Effective *in vitro*	Effective *in vivo*
1. BCL-2 / BCL-X_L family	22	Navitoclax (ABT-263)[25, 27, 38]	√	√
		Fisetin[39, 40]	√	
		A1331852[40]	√	
		A1155463[40]	√	
2. PI3K6/ AKT/ ROS-protective/ metabolic *§	22	Quercetin[22]	√	√
		Fisetin[40, 41]	√	
		Piperlongumine[42, 43]	√	
3. MDM2/ p53/ p21/ serpine (PAI-1&2) *	22	Quercetin[22]	√	√
		Fisetin[40, 44]	√	
		FOXO4-related peptide	√	√
4. Ephrin/ dependence receptors/ tyrosine kinases	22	Dasatinib (ephrin receptor)[22]	√	√
		Piperlongumine (androgen receptor)[45]	√	
5. HIF-1α	22	Quercetin[46]	√	√
		Fisetin[40]	√	
6. HSP-90§	24	17-AAG (Tanespimycin)	√	
		Goldanamycin	√	
		17-DMAG (Alvespimycin)	√	√



Quercetin



Fisetin