CONFLICT OF INTEREST DISCLOSURE

I have no potential conflict of interest to report
Use of antioxidants in preventive cognitive decline (pros vs cons)

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oxidative stress is defined as an imbalance between excess production of oxidants (reactive oxygen species or ROS) and antioxidants (reducing agents). In favour of ROS, leading to a disruption of redox signalling (indicating a positive effect of ROS in physiological or in moderate amount) and/or molecular damages to lipids, proteins and DNA.

Jones DP. Redefining oxidative stress. Antioxid Redox Signal 2006;8:1865–79.
Redox Based-Peripheral Biomarkers in Alzheimer’s Disease: Challenges, Limits and Prospects


Oxidative stress and cognitive longevity.

(Glade MJ, Nutrition, 2010)

maintenance of redox balance within the central nervous system can forestall cognitive decline and promote cognitive longevity.
Question:

which place for antioxidant therapy in preventing human cerebral disorders?
Alimentation et prévention du déclin cognitif et de la démence (Gillette-Guyonnet S et Vellas B, Revue Canadienne de la maladie d’Alzheimer)

review of 15 prospective studies (n = 42423) performed between 2000 and 2007 on the prevention of cognitif decline by synthetic antioxidants (vitamins C and E, β-carotene, selenium)

Conclusion:

Studies results evidence similitudes with respect to the positive impact of antioxidants intake by diet or supplements on cognitive decline and dementia, although great discrepancies are clearly existing.
Interest for the dietary “antioxidant” polyphenols (several thousand compounds)

Study in 1952 of the Cretan diet (few meat, fishes, fruits and vegetables, red wine, olive oil) which leads to a spectacular reduction of the incidence of the cardiovascular diseases and the cancers and a longer longevity

Classified in 2012 by the UNESCO as immaterial heritage of the humanity
Flavonoids, the major subclass of polyphenols

**Flavonol**

- **Flavanone**
  - $R = H$ kaempferol (broccoli)
  - $R = OH$ quercetin (apples)

- **Flavan-3-ol**
  - $R = OH$ catechin (dark chocolate)
  - $R = OH$ epicatechin gallate (green tea)

- **Flavanone**
  - $R1 = OCH_3$, $R2 = OH$ hesperitin (citrus fruit)
  - $R1 = R2 = H$ naringenin (grapefruit)

- **Flavone**
  - $R = H$ daidzein (soy)
  - $R = OH$ genistein (soy)

- **Anthocyanidin**
  - $R = H$ malvidin (red wine)
  - $R = OH$ delphinidin (bilberries)

- **Isoflavone**
  - $R = H$ daidzein (soy)
  - $R = OH$ genistein (soy)

- **Flavonoids** have antioxidant activity.
human epidemiological studies on dietary polyphenols and preventive cognitive decline

- fresh vegetables
- dry vegetables
- other
- fruit juices, red wine, coffee, tea, cocoa

- fruits: 41%
- dry vegetables: 8%
- other: 7%
- fresh vegetables: 11%
- fruit juices, red wine, coffee, tea, cocoa: 33%
animal studies: positive effect

Reversals of age-related declines in neuronal signal transduction, cognitive, and motor behavioral deficits with blueberry, spinach, or strawberry dietary supplementation (Joseph et al, J Neurosci, 1999)

The effects of grape juice on cognitive and motor deficits in aging (Shukitt et al, Exp Geront, 2006)

Effects of blackberries on motor and cognitive function in aged rats (Shukitt et al, Nutr Neuro, 2009)

Blueberry supplemented diet: effects on object recognition memory and nuclear factor – kB levels in aged rats (Nutr Neurosci, 2004)

Effect of a polyphenol-rich wild blueberry extract on cognitive performance of mice, brain antioxidant markers and acetylcholiesterase activity. (Papandreou et al, Beh Brain Res, 2009)

Differential brain regional specificity to blueberry and strawberry polyphenols in improved motor and cognitive function in aged rats. (Shukitt et al, Soc Neurosci Abstract, 2006)
Study of fruit, vegetable and fish in dementia and cognitive function in the Cache County Study on memory, health and aging. (n = 3632)

*Wengreen et al, J Nutr Health Aging, 2006*

Consommation d’aliments riches en antioxydants ou en acides gras et risque de démence chez la cohorte des 3 cités (n=8085)

*Raffaitin et al. Nutr Clin and Metab, 2006*

Associations of vegetable and fruit consumption with age-related cognitive change (n = 3718, CHAP study)

*Morris et al. Neurology, 2006*

Fruit and vegetable juices and Alzheimer’s disease:
the Kame projet (n = 1836)


Mediterranean diet and risk for Alzheimer’s disease (n = 2258)

*Scarmeas et al. Am Neurol, 2006*

**positive impact in all studies**
human epidemiological studies

Flavonoid Intake and Cognitive Decline over a 10-Year Period.

(Leuteneur et al. Am J Epidemiol, 2007)

n = 1640

quartile intake of flavonoids

MMSE : Mini Mental State Examination
human epidemiological studies

Polyphenol – rich foods in the Mediterranean diet are associated with better cognitive function in elderly subjects at high cardiovascular risk.

*(Valls-Pedret et al. *J Alzheimer’s Dis*, 2012)*

The Predimed Study *(n = 447)*

total olive oil with immediate verbal memory

virgin olive oil and coffee with delayed verbal memory

walnuts with working memory

red wine with Mini-Mental State Examination scores
Total and specific polyphenol intakes in midlife are associated with cognitive function measured 13 years later. (Kesse-Guyot et al. J Nutr, 2012) SUVIMAX study, n= 2574
What about intervention studies with dietary polyphenols for preventive cognitive decline?
Flavonoids and cognitive function: a review of human randomized controlled trial studies and recommendation for future studies.

(Macready et al. Genes Nutr, 2009)

15 studies

10 with soy isoflavones (post – menopausal women)

2 with Ginkgo biloba extracts (older adults with or without AD)

2 with Pine bark extract (healthy older adults)

1 with flavonol-rich extract (young healthy female adults)
Significant benefits to cognition have been reported in the majority of studies, mainly in executive function, working memory, other memory functions and more general measures such as processing speed.

However, there is little consistency across studies in terms of the cognitive domains measured, and the tasks used. While a wide range of tasks has been used, measures of important areas of everyday cognitive functioning are notable by their absence, for instance, prospective and implicit memory. Example: *Ginkgo biloba*

Moreover, although a wide range of tasks have been used within each cognitive domain, measurement of the full range of specific functions within these domains has by no means been covered.

Overall, the choice of individual outcome measures has been inconsistent, and there is general confusion as to what the various tasks actually measure.
High-flavonoid intake induces cognitive improvements linked to changes in serum brain-derived neurotrophic factor (BDNF): two randomised controlled trials. 

(Nesthatdoust et al. Nutrition and Healthy Aging, 2016)

BDNF has been identified as a significant plasma protein for optimal structure and function of hippocampal synapses, supporting the function of long-term memory in humans.
High-flavonoid intake induces cognitive improvements linked to changes in serum brain-derived neurotrophic factor (BDNF): two randomised controlled trials. 

*(Nesthatdoust et al. Nutrition and Healthy Aging, 2016)*

High flavonoid intake as fruit and vegetables (5 servings per day) intake but not low flavonoid intake (< 5 servings per day) increases plasma BDNF concentration concomittantly with a better cognitive function.
A berry thought-provoking idea: the potential role of plant polyphenols in the treatment of age-related cognitive disorders.


Berry supplementation and the aging brain.

More than 30 Memophenol™ phenolic metabolites have been identified and quantified in animal plasma. Some of them, including catechin and ferulic acid, were measured in mice brain, hence demonstrating a high bioavailability.

Memophenol™ is a unique combination of French grape and wild blueberry extracts (anthocyanins).

Neurophenols® Consortium includes 10 industrial and academic partenaires such as NutriNeuro (University of Bordeaux/INRA, France), Laval University (Canada), INRS (Canada) and Oniris (France).
Cognitive validated tests from Cambridge Cognition have been used to assess learning and memory performances at the beginning and at the end of the clinical study.

215 subjects aged 60 to 70, 300 mg twice daily during 6 months

verbal recall memory
conclusions

1° oxidative stress (alteration in redox balance) has been well identified in human cognitive decline

2° epidemiological studies suggest that food rich in antioxidants but not classical synthetic antioxidants (vitamins C and E, carotenoids) supplementation may prevent human cognitive decline

3° promising role of dietary polyphenols (as food or extracts) in preventive human cognitive decline