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NATURAL ANTIOXIDANTS AND NEURODEGENERATIVE DISEASES

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1. ABSTRACT

Neurodegenerative diseases such as Alzheimer's (AD) and Parkinson's (PD) diseases are defined by a progressive neuronal dysfunction and an ensuing behavioral dysfunction. Although protein aggregation (i.e beta-amyloid and alpha-synuclein) plays a pivotal role in both AD and PD, there is increasing evidence that excessive accumulation of reactive oxygen species (ROS) that occurs during normal and pathological brain aging contributes to neuronal losses and dysfunction. Based on these observations, it has been hypothesized that natural antioxidants derived from food, beverages and natural extracts may be beneficial to prevent or delay the occurrence of age-related cognitive deficits and neurodegenerative diseases. We will summarize in this review the role of oxidative stress in pathological brain aging, and provide evidence for a role for antioxidant molecules as therapeutic agents. We will also focus on the various mechanisms underlying their neuroprotective effects in *in vivo* and *in vitro* models of neurotoxicity.

2. EVIDENCE OF OXIDATIVE STRESS IN PATHOLOGICAL BRAIN AGING

Reactive oxygen species (ROS) are produced by different sources that include direct interactions between redox-active metals (i.e. copper, iron) and oxygen species, disruption of calcium homeostasis, and the release of hydrogen peroxide (H_2O_2) from mitochondria (for review, see 1). The excessive generation of ROS stimulates intracellular calcium signaling to elicit excitotoxicity, leading to further production of ROS and subsequent cell death (2). Age-related increase in transition metals (i.e. copper, iron, zinc) levels are also a major source of free-radical production in the brain and play a pivotal role in Parkinson's (PD) and Alzheimer's (AD) diseases (1). Disruption of the homeostasis of Zn, Cu and Fe occurs in AD brain and results in increased levels of beta-amyloid (Aß) fragments that in turn cause ROS production, through an interaction with Cu, Zn and Fe. Moreover, studies have also reported a direct interaction of Fe with α-synuclein that results in the aggregation and formation of protein deposits similar to those seen in PD (3).

Post-mortem analyses of AD and PD brains have demonstrated evidence of oxidative stress including elevated levels of products of lipid peroxidation (e.g. 4-hydroxy-2,3-nonenal, malondialdehyde and thiobarbituric acid-reactive substances) and DNA alterations. PD is associated with a significant increase in Fe contents in regions (e.g. substantia nigra) severely affected by oxidative damage-associated neurodegeneration (4). Increased activity or levels of endogenous antioxidant enzymes (i.e. catalase, superoxide dismutase, glutathione peroxidase and glutathione reductase) have also been observed along with β-amyloid deposits in temporal regions (e.g. hippocampus) of the AD brain, reflecting a compensatory mechanism to counter oxidative stress (1).

3. CLINICAL EFFICACY OF NATURAL ANTIOXIDANTS

3.1. Food and beverage

Accumulating evidence suggests that fruits and vegetables intake decreases the risk of age-related neurological disorders (for review, see 5). These effects are likely due to the presence of polyphenols in foods. In support of this hypothesis, an epidemiological study performed in 5000 elderly subjects reported that fruit and vegetable-derived flavonoid intake (mean consumption = 14.4 mg/day) was inversely correlated with the risk of dementia, with a relative risk (RR) of 0.45 (6) In this study, the most important source was fruits (35%), followed by vegetables, wine and tea (from 16 to 19%) (6). Moreover, another study suggested that dietary antioxidant flavonoids (more than 28.6 mg/day) protect against stroke (RR = 0.27) in a cohort of 500 men aged 50 to 69 years (7). These

results were confirmed by Johnsen et al (8) who demonstrated that persons in the top quintile of fruit and vegetable intake (median: 673 g/d) had a lower risk ratio of ischemic stroke (RR = 0.72) relative to persons in the bottom quintile (median: 147 g/d). The association appeared the most evident for fruit intake (RR = 0.60), particularly for citrus fruit (8). The beneficial effects of fruits were shown in another study reporting that the consumption of apples decreased the risk of thrombotic stroke both in men and women, with a relative risk of 0.60. This association seems not to be due only to the presence of the antioxidant flavonoid quercetin (9). Another 8 years follow-up study that enrolled persons aged 34 to 75 years reported that those in the highest quintile of fruit and vegetable intake (median of 5-6 servings per day) had a lower risk of stroke (RR = 0.69) compared with those in the lowest quintile, with cruciferous vegetables, green leafy vegetables and citrus fruit being the most effective (10). Finally, a prospective 8 years cohort study performed with 40000 Japanese demonstrated that daily consumption of green-yellow vegetables and fruits is associated with a lower risk of total stroke, intracerebral hemorrhage, and cerebral infarction mortality, with a significant 25-35% reduction compared with an intake of once or less per week (11).

Recent reports suggested that daily consumption of 3-4 glasses of red wine may be linked to lower risks of AD, cognitive impairment and macular degeneration (AMD) (12-17). Wine appeared to be more effective than liquors and beer, (13, 17; but see 16), in particular in elderly individuals without the APOE epsilon-4 allele (17). Other studies reported that a moderate consumption of alcohol ameliorated cognitive performance (18) and was associated with reduced white matter changes (15), relative to elderly that do not consume alcohol.

Clinical evidence supporting a beneficial role for various kinds of tea is still rather limited. In a study performed by Keli et al (7), black tea was the major source (about 70%) of flavonoid intake found to diminish the risk of stroke. Regarding tea consumption, the relative risk of stroke for a daily consumption of 4.7 cups or more of tea was 0.31 versus less than 2.6 cups of tea. Tea may also protect against PD and other neurodegenerative diseases (19) and this was confirmed by another study reporting that tea consumption (3 cups/day for 10 years) may reduce (about 28%) the risk of PD in an ethnic Chinese population (20).

It is likely that at least most of the purported beneficial effects of food (fruits, vegetables) and beverage (red wine, tea) relate to the presence of antioxidant polyphenols. Indeed, animal studies showed that polyphenols derived from fruits (e.g. blueberries) and vegetables (e.g. spinach) delayed and even reversed age-related cognitive behavioral impairments (21), whereas green tea (e.g. catechin derivatives) and red wine (e.g. catechin, resveratrol, quercetin) polyphenols have demonstrated neuroprotective activity in cell cultures and animal models (22-28).

3.2. Vitamins

The Rotterdam Study reported that dietary vitamins C and E lowered the risk of stroke in smokers (29). However, its was not confirmed by two cohort studies performed with male smokers, aged 50 to 69 years (30,31), whereas another report showed that α-tocopherol supplementation increased the risk of fatal hemorrhagic strokes but prevented cerebral infarction in hypertensive men (32,33). This discrepancy may be due to confounding factors and controlled clinical trials will be required to confirm the effectiveness of vitamins E and C supplementation in the prevention of stroke. Regarding other age-related neurological diseases, high dietary intake of vitamin E (10 mg per day) – but not vitamin C – dose-dependently decreased the risk of PD with an odd ratio of 0.5 (34). Moreover, daily intake of a combination of vitamins E and C supplements is associated with reduced prevalence and incidence of AD (35) while the consumption of vitamins E or C from supplements or diet failed to be protective (35,36). This discrepancy may be due to the type of individuals selected in a cohort. For example, another study performed by Morris et al (37) suggested that the protective effect of vitamin E intake from food against AD was observed only among individuals that did not carry the APOE e4 allele. Finally, two clinical trials suggested that a two-year treatment with α-tocopherol along with selegiline significantly reduced functional and cognitive deterioration in AD patients (38,39).

3.3. The ginkgo biloba extract EGb 761

The Ginkgo biloba extract referred as EGb 761 (IPSEN laboratories, France) is a standardized extract that is widely prescribed in Europe for the treatment of patients with AD, vascular dementia or age-associated memory impairment. A meta-analysis performed by the Cochrane Collaboration concluded that EGb 761 is effective to treat memory loss and cognitive impairment in demented patients, compared with placebo (40). The mechanisms of action of EGb 761 likely include a vasodilatory action as well as antioxidant properties of flavonoid components found in the total extract. In support of this hypothesis, we have reported that the flavonoid fraction may account, at least in part, for the protective effects of the total extract against toxicity induced by β-amyloid in hippocampal cells (41).

3.4. Acetyl-l-carnitine

Acetyl-l-carnitine (ALC) is an amino acid derived from carnitine that possesses several properties including antioxidant activities and enhancing mitochondrial function. A meta-analysis indicated that a 3- to 6-month treatment with ALC improves clinical global impression on AD patients, although it does not seem to show benefit on cognition or the severity of dementia (42,43). Clinical use of ALC remains controversial and further controlled clinical trials are now required in order to confirm its potential beneficial effects.

3.5. Alpha-lipoic acid

Alpha lipoic acid (ALA) is an endogenous antioxidant that interrupts cellular oxidative processes in both its oxidized and reduced forms (44). In the absence of randomized double-blind placebo-controlled trials, there is no evidence suggesting that ALA may be helpful in treating patients with dementia (45).

4. PROPOSED MECHANISMS OF ACTION UNDERLYING THE NEUROPROTECTIVE EFFECTS OF THE NATURAL ANTIOXIDANTS

Numerous *in vitro* and animal studies reported on the neuroprotective effects of natural antioxidants (i.e. vitamin E, EGb 761, alpha-lipoic acid, acetyl-l-carnitine, red wine- and green tea-derived polyphenols) in models of toxicity induced by oxidative stress or β-amyloid (22-28,41,46-53). Other natural antioxidants such as curcumin, lycopene and β-carotene have yet to be properly tested in clinical trials but are known to display protective effects in *in vitro* models of Aß- or oxidative stress-induced toxicities (54,55). It is well established that the neuroprotective effects of these antioxidant compounds involve their radical scavenging and metal chelating activity and/or the regulation of antioxidant enzymes. Most interestingly, however, emerging evidence suggest that various intracellular signalling pathways, in addition to free radical scavenging properties, play a central role in the neuroprotection induced by natural products. These signalling molecules include the mitogen-activated protein (MAP) kinases, extracellular signal-regulated kinases 1 and 2 (ERK1/2), protein kinase C (various isoforms), phophatidylinositol-3-kinase-Akt (PI3/Akt), and the transcription factor NF- ?B (24,28,48,49,51,56-59). Moreover, molecular biology studies suggested that natural antioxidants were able to modulate the expression of genes that encode for apoptosis-related molecules such as caspases, p53, Bcl-2 or bax (26,60,61,62). Finally, it has been shown that some natural molecules/extracts such as EGb 761, curcumin or polyphenols inhibit the formation, extension, and destabilization of beta-amyloid fibrils, amyloid-beta aggregation or beta-amyloid-derived diffusible neurotoxic ligands (60,63-65).

5. CONCLUSION

Natural antioxidants appear to be promising molecules/extracts to prevent or delay the occurrence of neurodegenerative diseases. Although accumulating evidence on the health properties of natural antioxidants is associated with their well-known antioxidant properties, other mechanisms involving modulatory effects on signal transduction pathways and gene expression likely also play predominant roles. These multiple mechanisms of actions – that may be synergistic or additive – likely explain the variability of their clinical efficacy. To date, vitamin E and EGb 761 appear the most effective natural antioxidants in AD, while vitamin E failed to show significant benefit in reducing the incidence of stroke. Randomized controlled trials are now urgently needed to confirm or investigate the clinical efficacy of molecules such as acetyl-l -carnitine, alpha-lipoic acid and polyphenols (e.g. epigallocatechin gallate, resveratrol etc.) in various neurodegenerative diseases.

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7. REFERENCES

1. Barnham K J, C. L. Masters & A. I. Bush: Neurodegenerative diseases and oxidative stress. *Nat Rev Drug Discov* 3, 205-214 (2004)

2. Mattson M P: Excitotoxic and excitoprotective mechanisms: abundant targets for the prevention and treatment of neurodegenerative disorders. *Neuromolecular Med* 3, 65–94 (2003)

3. Uversky V N, J. Li & A. L. Fink: Metal-triggered structural transformations, aggregation, and fibrillation of human α-synuclein. A possible molecular NK between Parkinson's disease and heavy metal exposure. *J Biol Chem* 276, 44284–44296 (2001)

4. Double K L, M. Gerlach, M. B. Youdim & P. Riederer: Impaired iron homeostasis in Parkinson's disease. *J Neural Transm Suppl* 60, 37-58 (2000)

5. Renaud S C: Diet and stroke. *J Nutr Health Aging* 5, 167-172 (2001)

6. Commenges D, V. Scotet, S. Renaud, H. Jacqmin-Gadda, P. Barberger-Gateau & J. F. Dartigues: Intake of flavonoids and risk of dementia. *Eur J Epidemiol* 16, 357-363 (2000)

7. Keli S O, M. G. Hertog, E. J. Feskens, & D. Kromhout: Dietary flavonoids, antioxidant vitamins, and incidence of stroke: the Zutphen study. *Arch Intern Med* 156, 637-642 (1996)

8. Johnsen S P, K. Overvad, C. Stripp, A. Tjonneland, S. E. Husted, & H. T. Sorensen: Intake of fruit and vegetables and the risk of ischemic stroke in a cohort of Danish men and women *Am J Clin Nutr* 78, 57-64 (2003)

9. Knekt P, S. Isotupa, H. Rissanen, M. Heliovaara, R. Jarvinen, S. Hakkinen, A. Aromaa & A. Reunanen: Quercetin intake and the incidence of cerebrovascular disease. *Eur J Clin Nutr* 54, 415-417 (2000)

10. Joshipura K J, A. Ascherio, J. E. Manson, M. J. Stampfer, E. B. Rimm, F. E. Speizer, C. H. Hennekens, D. Spiegelman & W. C. Willett: Fruit and vegetable intake in relation to risk of ischemic stroke. *JAMA* 282, 1233-1239 (1999)

11. Sauvaget C, J. Nagano, N. Allen & K. Kodama: Vegetable and fruit intake and stroke mortality in the Hiroshima/Nagasaki Life Span Study. *Stroke* 34, 2355-2360 (2003)

12. Orgogozo J M, J. F. Dartigues, S. Lafont, L. Letenneur, D. Commenges, R. Salomon, S. Renaud & M. B. Breteler: Wine consumption and dementia in the elderly: a prospective community study in the Bordeaux area. *Revue Neurologique* 153, 185-192 (1997)

13. Obisesan T O, R. Hirsh, O. Kosoko, L. Carlson & M. Parrott M: Moderate wine consumption is associated with decreased odds of developing age-related macular degeneration in NHANES-1. *J Am Ger Soc* 46, 1-7 (1998)

14. Leibovici D, K. Ritchie, B. Ledesert & J. Touchon: The effects of wine and tobacco consumption on cognitive performance in the elderly: a longitudinal study of relative risk. *Int J Epidemiol* 28, 77-81 (1999)

15. Mukamal K J, W. T. Longstreth Jr, M. A. Mittleman, R. M. Crum & d. S. Siscovick DS: Alcohol consumption and subclinical findings on magnetic resonance imaging of the brain in older adults: the cardiovascular health study. *Stroke* 32, 1939-1946 (2001)

16. Ruitenberg A, J. C. van Swieten, J. C. Witteman, K. M. Mehta, C. M. van Duijn, A. Hofman & M. M. Breteler: Alcohol consumption and risk of dementia: the Rotterdam Study. *Lancet* 359, 281-286 (2002)

17. Luchsinger J A, M. X. Tang, M. Siddiqui, S. Shea & R. Mayeux: Alcohol intake and risk of dementia. *J Am Geriatr Soc* 52, 540-546 (2004)

18. Elias P K, M. F. Elias, R. B. D'Agostino, H. Silbershatz & P. A. Wolf: Alcohol consumption and cognitive performance in the Framingham Heart Study. *Am J Epidemiol* 150, 580–589 (1999)

19. Pan T, J. Jankovic J & W. Le: Potential therapeutic properties of green tea polyphenols in Parkinson's disease. *Drugs Aging* 20, 711-721 (2003)

20. Tan E K, C. Tan, S. M. Fook-Chong, S. Y. Lum, A. Chai, H. Chung, H. Shen, Y. Zhao, M. L. Teoh, Y. Yih, R. Pavanni, V. R. Chandran & M. C. Wong MC: Dose-dependent protective effect of coffee, tea, and smoking in Parkinson's disease: a study in ethnic Chinese. *J Neurol Sci* 216, 163-167 (2003)

21. Joseph J A, B. Shukitt-Hale, N. A. Denisova, D. Bielinski, A. Martin, J. J. McEwen & P. C. Bickford: Reversals of Age-Related Declines in Neuronal Signal Transduction, Cognitive, and Motor Behavioral Deficits with Blueberry, Spinach, or Strawberry Dietary Supplementation *J Neurosci* 19, 8114-8121 (1999)

22. Inanami O, Y. Watanabe, B. Syuto, M. Nakano, M. Tsuji & M. Kuwabara: Oral administration of (-)catechin protects against ischemia-reperfusion-induced neuronal death in the Gerbil. *Free Rad Res* 29, 359-365 (1998)

23. Virgili M & A. Contestabile: Partial neuroprotection of in vivo excitotoxic brain damage by chronic administration of the red wine antioxidant agent, trans-resveratrol in rats. *Neurosci Lett* 281, 123-126 (2000)

24. Bastianetto S, W. H. Zheng & R. Quirion: Neuroprotective abilities of resveratrol and other red wine constituents against nitric oxide-related toxicity in cultured hippocampal neurons. *Br J Pharmacol* 131, 711-720 (2000)

25. Levites Y, O. Weinreb, G. Maor, M. B. Youdim & S. Mandel: Green tea polyphenol (-)-epigallocatechin-3-gallate prevents N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced dopaminergic neurodegeneration. *J Neurochem* 78, 1073-1082 (2001)

26. Choi Y T, C. H. Jung, S. R. Lee, J. H. Bae, W. K. Baek, M. H. Suh, J. Park, C. W. Park & S. I. Suh: The green tea polyphenol (-)-epigallocatechin gallate attenuates beta-amyloid-induced neurotoxicity in cultured hippocampal neurons. *Life Sci* 70, 603-614 (2001)

27. Conte A, S. Pellegrini & D. Tagliazucchi: Synergistic protection of PC12 cells from beta-amyloid toxicity by resveratrol and catechin. *Brain Res Bull* 62, 29-38 (2003)

28. Han Y S, W. H. Zheng, S. Bastianetto, J. G. Chabot & R. Quirion Neuroprotective effects of resveratrol against beta-amyloid-induced neurotoxicity in rat hippocampal neurons: involvement of protein kinase C. *Br J Pharmacol* 141, 997-1005 (2004)

29. Voko Z, M. Hollander, A. Hofman, P. J. Koudstaal & M. M. Breteler: Dietary antioxidants and the risk of ischemic stroke: the Rotterdam Study. *Neurology* 61, 1273-1275 (2003)

30. Ascherio A, E.B. Rimm, M. A. Hernan, E. Giovannucci, I. Kawachi, M. J. Stampfer & W. C. Willett: Relation of consumption of vitamin E, vitamin C, and carotenoids to risk for stroke among men in the United States. *Ann Intern Med* 130, 963-970 (1999)

31. Hirvonen T, J. Virtamo, P. Korhonen, D. Albanes & P. Pietinen: Intake of flavonoids, carotenoids, vitamins C and E, and risk of stroke in male smokers. *Stroke* 31, 2301-2306 (2000)

32. Leppala J M, J. Virtamo, R. Fogelholm, J. K. Huttunen, D. Albanes, P. R. Taylor & O. P. Heinonen: Controlled trial of alpha-tocopherol and beta-carotene supplements on stroke incidence and mortality in male smokers. *Arterioscler Thromb Vasc Biol* 20, 230-235 (2000)

33. Leppala J M, J. Virtamo, R. Fogelholm, D. Albanes, P. R. Taylor & O. P. Heinonen: Vitamin E and beta carotene supplementation in high risk for stroke: a subgroup analysis of the Alpha-Tocopherol, Beta-Carotene Cancer Prevention. *Study Arch Neurol* 57, 1503-1509 (2000)

34. De Rijk M C, M. M. Breteler, J. H. den Breeijen, L. J. Launer, D. E. Grobbee, F. G. van der Meche & A. Hofman: Dietary antioxidants and Parkinson disease. The Rotterdam Study. *Arch Neurol* 54, 762-765 (1997)

35. Zandi P P, J. C. Anthony, A. S. Khachaturian, S. V. Stone, D. Gustafson, J. T. Tschanz, M. C. Norton, K. A. Welsh-Bohmer & J. C. Breitner: Reduced risk of Alzheimer disease in users of antioxidant vitamin supplements: the Cache County Study. *Arch Neurol* 61, 82-88 (2004)

36. Luchsinger J A, M. X. Tang, S. Shea & R. Mayeux: Antioxidant vitamin intake and risk of Alzheimer disease. *Arch Neurol* 60, 203-208 (2003)

37. Morris M C, D. A. Evans, J. L. Bienias, C. C. Tangney, D. A. Bennett, N. Aggarwal, R. S. Wilson & P. A. Scherr: Dietary intake of antioxidant nutrients and the risk of incident Alzheimer disease in a biracial community study. *JAMA* 287, 3230-3237 (2002)

38. Sano M, C. Ernesto, R. Thomas, M. Klauber, K. Schafer, M. Grundman, P. Woodbury, J. Growdon, C. Cotman, E. Pfeiffer, L. Schneider & L. Thal L: A controlled trial of selegiline, alpha-tocopherol, or both as treatment for Alzheimer's disease. The Alzheimer's disease cooperative study. *New Eng J Med* 336, 1216–1222 (1997)

39. Grundman M: Vitamin E and Alzheimer's disease: the basis for additional clinical trials. *Am J Clin Nutr* 71, S630–S636 (2000)

40. Birks J, E. V. Grimley & M. Van Dongen: Ginkgo biloba for cognitive impairment and dementia. *Cochrane Database Syst Rev* CD003120 (2002)

41. Bastianetto S, C. Ramassamy, S. Doré, Y. Christen, J. Poirier & R. Quirion The ginkgo biloba extract (EGb 761) protects hippocampal neurons against cell death induced by β-amyloid. *Eur J Neurosci* 12, 1-9 (2000)

42. Hudson S & N. Tabet: Acetyl-L-carnitine for dementia. *Cochrane Database Syst Rev* CD003158 (2003)

43. Montgomery S, L. Thal & R. Amrein: Meta-analysis of double blind randomized controlled clinical trials of acetyl-L-carnitine versus placebo in the treatment of mild cognitive impairment and mild Alzheimer's disease. *Int Clin Psychopharmacol* 18, 61-71 (2003)

44. Packer L, H. Tritschler & K. Wessel: Neuroprotection by the metabolic antioxidant a-lipoic acid. *Free Radical Biol & Med* 22, 359-378 (1997)

45. Sauer J, N. Tabet & R. Howard: Alpha lipoic acid for dementia. *Cochrane Database Syst. Rev.* CD004244 (2004)

46. Panigrahi M, Y. Sadguna, B. Shivakumar, S. Kolluri, S. Roy, L. Packer & V. Ravin-dranath: Alpha-Lipoic acid protects against reperfusion injury following cerebral ischemia in rats. *Brain Research* 717, 184–188 (1996)

47. Yamada K, T. Tanaka, D. Han, K. Senzaki, T. Kameyama & T. Nabeshima: Protective effects of idebenone and -tocopherol on beta-amyloid-(1-42)-induced learning and memory deficits in rats: implication of oxidative stress in -amyloid-induced neurotoxicity in vivo. *Eur J Neurosci* 11, 83-90 (1999)

48. Bastianetto S, W. H. Zheng & R. Quirion: The ginkgo biloba extract (EGb 761) protects and rescues hippocampal cells against nitric oxide-induced toxicity: involvement of its flavonoid constituents and protein kinase C. *J Neurochem* 74, 2268-2277 (2000)

49. Behl C: Vitamin E protects neurons against oxidative cell death in vitro more effectively than 17-ß estradiol and induces the activity of the transcription factor NF - ?B. *J Neural Transmission* 107, 393–407 (2000)

50. Virmani L, V. Caso, A. Spadoni, S. Rossi, F. Russo & F. Gaetani: The action of acetyl-L-carnitine on the neurotoxicity evoked by amyloid fragments and peroxide on primary rat cortical neurones. *Ann NY Acad Sci* 939, 162–178 (2001)

51. Zhang L, G. Xing, J. Barker, Y. Chang, D. Maric, W. Ma, B. Li & D. Rubinow: Alpha-lipoic acid protects rat cortical neurons against cell death induced by amyloid and hydrogen peroxide through the Akt signalling pathway. *Neurosci Lett* 12, 125–128 (2001)

52. Dhitavat S, D. Ortiz, T. Shea & E. Rivera: Acetyl-L-carnitine protects against amyloid-beta neurotoxicity: roles of oxidative buffering and ATP levels. *Neurochem Res* 27, 501–505 (2002)

53. Lovell M, C. Xie, S. Xiong & W. Markesbery: Protection against amyloid beta peptide and iron/hydrogen peroxide toxicity by alpha lipoic acid. *J Alzheimers Disease* 5, 229–239 (2003)

54. Lowe G M, L. A. Booth, A. J. Young & R. F. Bilton: Lycopene and beta-carotene protect against oxidative damage in HT29 cells at low concentrations but rapidly lose this capacity at higher doses. *Free Radic Res* 30, 141-151 (1999)

55. Kim D S, S. Y. Park & J. K. Kim: Curcuminoids from Curcuma longa L. (Zingiberaceae) that protect PC12 rat pheochromocytoma and normal human umbilical vein endothelial cells from betaA(1-42) insult. *Neurosci Lett* 303, 57-61 (2001)

56. Miloso M, A. A. Bertelli, G. Nicolini & G. Tredici: Resveratrol-induced activation of the mitogen-activated protein kinases, ERK1 and ERK2, in human neuroblastoma SH-SY5Y cells. *Neurosci Lett* 264, 141-144 (1999)

57. Chen C, R. Yu, E. D. Owuor & A. N. Kong: Activation of antioxidant-response element (ARE), mitogen-activated protein kinases (MAPKs) and caspases by major green tea polyphenol components during cell survival and death. *Arch Pharm Res* 23, 605-12 (2000)

58. Levites Y, T. Amit, M. B. Youdim & S. Mandel: Involvement of protein kinase C activation and cell survival/ cell cycle genes in green tea polyphenol (-)-epigallocatechin 3-gallate neuroprotective action. *J Biol Chem* 277, 30574-30580 (2002)

59. Mandel S, L. Reznichenko, T. Amit & M. B. Youdim: Green tea polyphenol (-)-epigallocatechin-3-gallate protects rat PC12 cells from apoptosis induced by serum withdrawal independent of P13-Akt pathway. *Neurotox Res* 5, 419-424 (2003)

60. Luo Y, J. V. Smith, V. Paramasivam, A. Burdick, K. J. Curry, J. P. Buford, I. Khan, W. J. Netzer, H. Xu & P. Butko: Inhibition of amyloid-beta aggregation and caspase-3 activation by the Ginkgo biloba extract EGb761. *Proc Natl Acad Sci U. S. A.* 99, 12197-12202 (2002)

61. Chung J H, J. H. Han, E. J. Hwang, J. Y. Seo, K. H. Cho, K. H. Kim, J. I. Youn & H. C. Eun: Dual mechanisms of green tea extract (EGCG)-induced cell survival in human epidermal keratinocytes. *FASEB J* 17, 1913-1915 (2003)

62. Massieu L, J. Moran & Y. Christen: Effect of Ginkgo biloba (EGb 761) on staurosporine-induced neuronal death and caspase activity in cortical cultured neurons. *Brain Res* 1002, 76-85 (2004)

63. Yao Z, K. Drieu & V. Papadopoulos: The Ginkgo biloba extract EGb 761 rescues the PC12 neuronal cells from beta-amyloid-induced cell death by inhibiting the formation of beta-amyloid-derived diffusible neurotoxic ligands. *Brain Res* 889, 181-190 (2001)

64. Ono K, K. Hasegawa, H. Naiki & M. Yamada: Curcumin has potent anti-amyloidogenic effects for Alzheimer's beta-amyloid fibrils in vitro. *J Neurosci Res* 75, 742-750 (2004)

65. Ono K, Y. Yoshiike, A. Takashima, K. Hasegawa, H. Naiki & M. Yamada: Potent anti-amyloidogenic and fibril-destabilizing effects of polyphenols in vitro: implications for the prevention and therapeutics of Alzheimer's disease. *J Neurochem* 87, 172-181 (2003)

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