Lecture 2c – Annex D Neurodegenerative disease: mitochondrial remedies

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Astaxanthin and AD, dementia or MCI

- In subjects with age-related forgetfulness, 12mg/day astaxanthin for 12 weeks improved cognitive function but the study size was too small to show a significant difference (Katagiri M, J Clin Biochem Nutr, 2012).
- In middle-aged and older subjects, 8mg/day astaxanthin for 8 weeks, improvement was seen only in those aged 45-54 (Hayashi M, J Clin Biochem Nutr, 2018).
- Combinations of astaxantin with sesamin and astaxanthin with Bacopa monnieri, phosphatidylserine and vitamin E improved cognitive function in subjects with mild cognitive impairment (Zanotta D, Neuropsychiatr Dis Treat, 2014; Ito N, J Alzheimers Dis, 2018).
- Studies of rodents with AD or impaired cognitive function show that astaxanthin improved cognitive function and reversed Aβ42 deposition, Tau formation, antioxidant loss and neurodegeneration through increasing microglial activation, upregulating Nrf2, increasing SOD and glutathione and decreasing inflammation (Feng Y, Front Pharmacol, 2018; Hongo N, Front Pharmacol, 2020; Taksima T, Mar Drugs, 2019).

Astaxanthin and PD

- No human studies.
- *In vitro* studies show that astaxanthin inhibited neuronal apoptosis, reduced the expression of α-synuclein, protected against oxidative stress and promoted cell viability (Shen DF, Neurosci Res, 2020; Ye Q, Mar Drugs, 2013; Ye Q, BMC Neurosci, 2012; Lee DH, Food Chem Toxicol, 2011).
- In rodent models of PD, astaxanthin reduced toxicity in dopaminergic neurons (Grimmig B, Oncotarget, 2017), inhibited apoptosis and lowered α-synuclein (Fernandez-Moriano C, Oxid Med Cell Longev, 2015).

B vitamins and AD, dementia or MCI

- The VITACOG trial showed that in subjects with mild cognitive impairment (MCI), treatment with folic acid and vitamins B6 and B12 to lower homocysteine slowed the rate of cognitive and clinical decline. The authors also found that when omega-3 fatty acid concentrations are low, B vitamin treatment has no effect on cognitive decline in MCI, but when omega-3 levels are in the upper normal range, B vitamins interact to slow cognitive decline. (Oulhaj A, J Alzheimers Dis, 2016)
- Higher intake of B vitamins throughout young adulthood was associated with better cognitive function in midlife, particularly B3, B6, B12 and folate (Qin B, Am J Clin Nutr, 2017). Among elderly Koreans with AD or MCI, total B vitamin intake was associated with stronger cognitive function (Kim H, Nutr J, 2014).
- In older patients with MCI and serum homocysteine ≥10.0 µmol/L, 500µg/day methylcobalamin and 400µg/day folic acid showed no effect on cognitive decline (Kwok T, Clin Nutr, 2019).
- Among French subjects, higher intake of folate was inversely associated with the risk of dementia, with a 50% lower risk for individuals in the highest compared to the lowest quintile of folate. No association was found for vitamins B6 and B12 (Lefèvre-Arbogast S, Nutrients, 2016).
- However, higher dietary intakes of riboflavin and folate in midlife were associated with a lower risk of cognitive impairment in later life in the Chinese population (Sheng LT, J Gerontol A Biol Sci Med Sci, 2020).
- A 2014 meta-analysis showed that homocysteine-lowering by using B vitamins had no significant effect on cognitive function or on cognitive ageing (Clarke R, Am J Clin Nutr, 2014).
- In elderly subjects with MCI, high-dose folic acid and vitamins B6 and B12 slowed the rate of accelerated brain atrophy (Smith AD, PLoS One, 2010).
- A 2016 health economics study found that in UK subjects with high levels (>13 µmol/L) of plasma homocysteine, treatment with B vitamins would save £60,021 per quality-adjusted life years gained (Tsiachristas A, Alzheimers Dement, 2016).

B vitamins and PD

- PD patients given 250mg/day vitamin B3 for 3 months altered macrophage polarisation from M1 (proinflammatory) to M2 (anti-inflammatory), decreased expression of the macrophage niacin receptor and improved patient quality of life.
- In PD patients taking L-dopa, high dose pyridoxal-5-phosphate (active vitamin B6) improved motor and activities of living scores.
- In PD patients with low serum vitamin B2, high doses of (30 mg riboflavin every 8 hours) and the elimination of dietary red meat normalised vitamin B2 levels and improved some motor functions (Coimbra CG, Braz J Med Biol Res, 2003).
- Two meta-analyses found that both plasma folate and vitamin B12 levels were lower in PD patients and PD patients with cognitive dysfunction. Others found that those with the lowest CSF and serum vitamin B12 levels had the lowest ambulatory capacity score, whereas a higher vitamin B12 level at diagnosis was associated with lower risk of future dementia. Low serum vitamin B1 is associated with PD development and intravenous treatment has been found to help PD motor disorders. Intake studies are largely inconclusive.
- In animal studies, pre-treatment with B vitamins prevented pesticide-induced accumulation of alpha-synuclein, oxidative stress and mitochondrial dysfunction, while treatment with vitamin B3 reduced neuroinflammation and improved behaviour and folic acid improved memory and motor coordination.

(Murakami K, Br J Nutr, 2010; Jia H, Neurobiol Aging, 2010; Chen H, Am J Epidemiol, 2004; Lu'o'ng Kv, J Neurol Sci, 2012; Motawi TK, Mol Cell Biochem, 2020; Wakade C, J Neuroimmunol, 2018; Tan EK, Am J Med Genet B Neuropsychiatr Genet, 2005; Christine CW, Mov Disord, 2020; McCarter SJ, Parkinsonism Relat Disord, 2020; Dong B, Clin Neurol Neurosurg, 2020; Christine CW, Mov Disord, 2018; Xie Y, Neurosci Lett, 2017; Shooshtari MK, Iran J Basic Med Sci, 2012)

B vitamins and MS

- A review found that despite limited clinical studies, the anti-inflammatory and re-myelinating attributes of vitamin B complex members are promising (Nemazannikova N, Med Chem. 2018).
- Supplemental high-dose vitamins B1, B6 and B12 were effective in improving visual function parameters in MS-related visual persistent disability (Mallone F, Drug Discov Ther. 2020).
- High dose thiamine (vitamin B1) improved fatigue in humans with MS (Costantini A, BMJ Case Rep. 2013).
- In mice, riboflavin (vitamin B2) is capable of suppressing the neurological disability mediated by BDNF and IL-6 but had no impact on disability status in humans (Naghashpour M, Iran J Basic Med Sci. 2016; Naghashpour M, Int J Vitam Nutr Res. 2013).
- In MS patients with high homocysteine, 5 mg/day folic acid and 3 injections of 1,000 mcg/day vitamin B12 lowered homocysteine and improved both physical and mental fields of quality of life (Nozari E, Clin Nutr Res. 2019). MS patients commonly have vitamin B12 (cobalamin) deficiency, regardless of homocysteine levels (Miller A, J Neurol Sci. 2005).

Berberine and AD, dementia and MCI

- No human studies.
- A 2020 systematic review of animal studies of diabetes-induced dementia found that berberine exerts beneficial effects directly in the brain: enhancing cholinergic neurotransmission, improving cerebral blood flow, protecting neurons from inflammation, limiting hyperphosphorylation of tau and facilitating Aβ peptide clearance (Shinjyo N, J Integr Med, 2020).
- A 2019 systematic review of studies of animal models of AD found that berberine improved memory by acting as an anti-inflammatory, antioxidant, inhibiting cholinesterase and removing amyloid (Yuan NN, BMC Complement Altern Med, 2019).
- In other forms of induced AD, berberine inhibited Aβ42 formation and downregulated Tau, iNOS and BACE gene expression in rats' hippocampus and improved learning and memory function (Saleh SR, Curr Clin Pharmacol, 2020; Chen Y, Biomed Pharmacother, 2020).
- A berberine and curcumin combination had a better effect than either substance alone in improving cognitive function, reducing soluble Aβ(1,42) production and decreasing inflammation and oxidative stress in AD mice (Lin L, Neurochem Res, 2020).

Butyrate and AD, dementia and MCI

- No human studies.
- In an early-onset AD mouse model, sodium butyrate lowered Aβ levels by 40% and improved associative learning and cognitive functioning (Fernando WMADB, J Alzheimers Dis, 2020).
- Sodium butyrate improved associative memory in AD mice even when administered at a very advanced stage of pathology. Recovery of memory function correlated with elevated hippocampal histone acetylation and increased expression of genes implicated in associative learning, with butyrate acting as a histone deacetylase inhibitor. (Govindarajan N, J Alzheimers Dis, 2011)
- Sodium butyrate attenuated diabetes-induced impairment of learning and memory in rats (Sharma B, Psychopharmacology, 2011).

Cannabinoids and AD, dementia and MCI

- Two 2020 systematic reviews of human studies found that there were no RCTs investigating the use of cannabinoids for the treatment of cognitive decline in dementia and those assessing cannabinoids for agitation and aggression found little evidence of efficacy, although a 2020 meta-analysis indicated that cannabinoids could reduce neuropsychiatric symptoms (Charernboon T, Clin Gerontol, 2020; Paunescu H, Am J Ther, 2020; Bahji A, Can J Psychiatry, 2020).
- In AD patients, PET scans showed significantly lower binding of the cannabinoid type 2 receptor (CB2R), expressed on microglia in the brain, compared to healthy controls (Ahmad R, Eur J Nucl Med Mol Imaging, 2016).
- In animals with AD, vascular dementia or cognitive impairment, CR2R receptor agonists, including cannabidiol, suppressed Aβ-induced microglial activation, apoptosis and inflammation, lowered intracellular calcium, improved learning and memory, rescued the cognitive deficit and protects synaptic plasticity (Wang DP, Psychiatry Res, 2018; da Silva VK, Transl Psychiatry, 2018; Martín-Moreno AM, Mol Pharmacol, 2011; Nuñez-Borque E, Mol Neurobiol, 2020; Li H, Eur J Med Chem, 2020; Hughes B, Neurochem Res, 2019).
- Cannabidiol could also inhibit Aβ-induced tau protein hyperphosphorylation, attenuate oxidative stress and mitochondrial dysfunction, reverse cognitive deficits, prevent memory loss and promote neurogenesis (Vallée A, Acta Biochim Biophys Sin, 2017; Watt G, Front Pharmacol, 2017; Cheng D, J Alzheimers Dis, 2014).

Cannabinoids in PD

- The endocannabinoid system, which involves cannabinoid receptors type 1 (CB1R), mainly expressed in neurons, and type 2receptors (CB2R), mainly expressed in glial cells, endogenous cannabinoids and the enzymes that catabolise these compounds are involved in the pathogenesis of PD. Yet, deletion of the cannabinoid CB2 receptors expressed in dopamine neurons enhances motor activities, modulates anxiety and depression-like behaviours. (Liu QR, Sci Rep, 2017; Basavarajappa BS, J Neurochem, 2017; Little JP, Mini Rev Med Chem, 2011).
- A 2020 systematic review of 5 RCTs found insufficient evidence to recommend cannabinoids for PD, although 1 found a reduction of l-dopa-induced dyskinesias, and another found a reduction in anxiety and tremor amplitude, with the remaining 3 without effect on motor and non-motor symptoms (Bougea A, Complement Ther Clin Pract, 2020).
- Animal studies showed that administration of cannabinoids or other CB2R agonists improved behaviour, increased the number of basal ganglia neurons, reduced pro-inflammatory mediators and astroglial reactivity and prevented degeneration of dopamine neurons, blood-brain barrier damage, infiltration of peripheral immune cells and production of inducible nitric oxide synthase (Burgaz S, Molecules, 2019; Garcia C, J Neuroinflammation, 2018; Chung YC, Exp Mol Med, 2016; Garcia C, Br J Pharmacol, 2011).
- Similarly, chronic administration of both CB1R and CBR2 agonists reversed the abnormal behavioural responses to L-Dopa (Song L, Drug Des Devel Ther, 2014; Martinez A, Neurosci Res, 2012; Walsh S, Brain Res, 2010).
- In principal, the neuroprotective, anti-inflammatory and antioxidant properties of cannabinoids and their ability to reduce excitotoxicity, control calcium influx and limit the toxicity of reactive microglia should protect the basal ganglia, which play a crucial role in controlling motor function (Antonazzo M, Int Rev Neurobiol, 2019).

Cannabinoids in MS

- In animals, CBD is effective in reducing the amounts of T-cell infiltrates in the spinal cord, suggesting that it has anti-inflammatory properties. This delays symptom onset in animal models of MS and slows disease progression. Importantly, combinations of CBD and Δ9-THC appear particularly effective in treating animal models of MS. In human studies, the results are less encouraging and conflict with the findings in animals. Drugs which deliver a combination of Δ9-THC and CBD in a 1:1 ratio appear to be only moderately effective in reducing spasticity scores, but appear to be almost as effective as current front-line treatments and cause less severe side effects than other treatments. Hence cannabinoids may help treat neuropathic pain in MS as an adjuvant therapy, although treatment with cannabinoid compounds may cause significant cognitive dysfunction. At the time of writing there had been no long term double-blind placebo-controlled studies. (Jones É, Molecules. 2020)
- A 2019 systematic review of RCTs in MS showed a consistent and sustained reduction in the spasticity score (Akgün K, J Cent Nerv Syst Dis. 2019).
- A 2020 RCT showed that an oromucosal spray containing cannabinoids applied for 12 weeks halved mean severity scores for spasticity and pain (Meuth SG, Int J Neurosci. 2020).

Capsaicin in AD, dementia and MCI

- In subjects aged >39, dietary capsaicin intake was independently positively associated with cognitive function and inversely associated with serum Aβ40 levels and total serum Aβ levels (Liu CH, J Alzheimers Dis, 2016).
- In AD mice, capsaicin improved spatial learning, memory and synaptic function, with reduced synapse loss (Chen L, J Alzheimers Dis, 2017).

Acetyl L-carnitine for AD, dementia and MCI

- A 2003 Cochrane Review of human RCTs showed that acetyl L-carnitine had little effect on measures of AD severity, although another 2003 meta-analysis found that 1.5-3.0g/day for at least 3 months induced significant improvement in clinical scales and psychometric tests in subjects with mild cognitive impairment (MCI) and mild AD (Hudson S, Cochrane Database Syst Rev, 2003; Montgomery SA, Int Clin Psychopharmacol, 2003).
- Since then, in patients with dementia associated with cerebrovascular disease, 1500mg/day acetyl L-carnitine for 28 weeks improved cognitive function (Yang Y, Dement Neurocogn Disord, 2018).
- An RCT showed that 4g/day acetyl L-carnitine for 90 days improved cognitive function in severe hepatic encephalopathy (Malaguarnera M, Metab Brain Dis, 2011).
- A study of centenarians given 2g/day levocarnitine found that it reduced severity of physical and mental fatigue and increased cognitive function (Malaguarnera M, Am J Clin Nutr, 2007).
- In early AD patients, cerebrospinal fluid levels of L-carnitine in non-apolipoprotein E4 carriers are decreased and correlated inversely with Aβ levels and mental state, suggesting that supplementation might be helpful in these patients (Lodeiro M, J Alzheimers Dis, 2014).
- In mild AD patients unresponsive to acetylcholinesterase inhibitors, 2g/day acetyl L-carnitine for 3 months improved symptoms (Bianchetti A, Curr Med Res Opin, 2003).
- A Russian study showed that doses from 2250-3000mg/day for 12 weeks in dementia patients showed a treatment effect of 2.8 times that of placebo on neuropsychological tests; the improvement was greater in those with AD compared to vascular dementia (Gavrilova S, Zh Nevrol Psikhiatr Im S S Korsakova, 2011).

Acetyl L-carnitine for PD

- No human treatment trials.
- PD patients had significantly lower levels of free and total carnitine compared with controls, but only in those without the c.95A > G mutation rendering the carnitine transporter less efficient (Crooks SA, Neurosci Lett, 2018). Nevertheless, decreased long-chain acylcarnitines from insufficient β-oxidation have been proposed as potential early diagnostic markers for PD (Saiki S, Sci Rep, 2017).
- *In vitro* studies have shown that acetyl L-carnitine enhances β-oxidation and promotes elimination of excess ammonia, thought to underlie many neurodegenerative diseases (Maldonado C, Curr Pharm Des, 2020). It can also reverse microglial activation and neuroinflammation (Gill EL, ACS Chem Neurosci, 2018) and increase mitochondrial biogenesis and lower ROS production (Fernandez-Moriano C, Oxid Med Cell Longev, 2015).
- A combination of R-alpha-lipoic acid and acetyl-L-carnitine worked synergistically to protect PD neuroblastoma cells by increasing mitochondrial biogenesis and decreasing ROS production (Zhang H, J Cell Mol Med, 2010).
- In rodent models of PD, acetyl L-carnitine improved memory and cognitive function and enhanced dopamine D1 receptor levels. It also reversed the reduction in tyrosine hydroxylase and reduced striatal malondialdehyde, dopamine transporter and astrocyte immunoreactivity, microglial activation, neuroinflammation and apoptosis and raising dopamine, catalase and glutathione levels. It could also enhance proliferation, long term survival and neuronal differentiation of neural progenitor cells and increase neural stem cells. (Burks S, Neurosci Lett, 2019; Afshin-Majd S, Biomed Pharmacother, 2017; Singh S, Neurochem Int, 2017; Singh S, Mol Neurobiol, 2018; Singh S, Mol Neurobiol, 2016)

Coenzyme Q10 (CoQ10) for AD, dementia and MCI

- Among 6000 Japanese subjects, serum CoQ10 was inversely and independently associated with dementia incidence (Yamagishi K, Atherosclerosis, 2014). There are no human studies of CoQ10.
- In rats with induced AD, CoQ10 improved learning, memory, synaptic plasticity and insulin signalling, decreased inflammation, APP, Aβ42, plaque area and number, lipid peroxides, apoptosis and neuronal degeneration and regulated cholinergic functioning (Attia H, J Biochem Mol Toxicol, 2020; Ibrahim Fouad G, Neurochem Res, 2020; Komaki H, Brain Res Bull, 2019; Singh A, Front Pharmacol, 2015; Dehghani Dolatabadi HR, Iran J Basic Med Sci, 2012; Dumont M, J Alzheimers Dis, 2011; Yang X, J Mol Neurosci, 2010).
- CoQ10 could improve learning and memory deficits induced by diabetes in older rats and improve cognitive performance in older healthy rats (Monsef A, Neuropsychobiology, 2019).
- In cognitively impaired rodents, CoQ10 reduced brain atrophy and amyloid plaque and induced improvement in behavioral tests and oxidative stress and increased BDNF (Li G, Biofactors, 2008; Yang X, J Mol Neurosci, 2010; Nagib MM, Neurotox Res, 2019).
- However, one study found that when young mice were given high dose CoQ10, they suffered impaired cognitive function in old age (Sumien N, J Nutr, 2009).

Coenzyme Q10 (CoQ10) for PD

- 2 meta-analyses found no evidence that CoQ10 helped PD patients (Zhu ZG, Neurol Sci, 2017; Negida A, CNS Neurol Disord Drug Targets, 2016).
- Despite this, several RCTs showed improvement. 300mg/day ubiquinol for 48 weeks and 360mg/day CoQ10 for 4 weeks significantly improved patient symptoms and visual symptoms (Yoritaka A, Parkinsonism Relat Disord, 2015; Müller T, Neurosci Lett, 2003) and a further study found improvement in several parameters at doses ranging from 400-1200mg/day but with 2400mg/day plasma F2-isoprostanes and serum phospholipase A2 were significantly increased; furthermore improvement was only observed in those with lower baseline plasma ubiquinol (Seet RC, Antioxid Redox Signal, 2014).
- A combination of 100mg/day CoQ10 and 5g/day creatine improved cognitive scores in PD patients (Li Z, Eur Neurol, 2015).
- PD patients were found to have significantly lower serum ubiquinol compared to healthy controls and a significant reduction CoQ10 concentration in the cortex region of the brain (Mischley LK; J Neurol Sci, 2012; Hargreaves IP, Neurosci Lett, 2008).
- Rodent studies found that CoQ10 improved behavioural test scores, decreased protein carbonyl content in the brain and blocked the progression of neurodegeneration (Attia HN, Behav Pharmacol, 2018; Muthukumaran K, BMC Neurosci, 2014).

Coenzyme Q10 (CoQ10) for MS

- In patients with no other treatment for MS, 500 mg/day improved fatigue and depression (Sanoobar M, Nutr Neurosci. 2016).
- 500 mg/day CoQ10 decreased markers of inflammatory and oxidative stress and increased markers of antioxidants in patients with MS (Sanoobar M, Nutr Neurosci. 2015; Sanoobar M, Int J Neurosci. 2013).
- In patients treated with interferon, the addition of CoQ10 for 3 months improved disability status, fatigue, depression, pain and disease biomarkers (Moccia M, Ther Adv Neurol Disord. 2019).
- In a mouse model of MS, CoQ10 promoted remyelination, alleviated oxidative stress and suppressed inflammatory markers (Khalilian B, J Mol Histol. 2021).

Creatine for AD, dementia and MCI

- In subjects with mild cognitive impairment, decline of cognitive function was predicted in part by decline in creatinine concentrations and was particularly marked in those who developed AD (Pilatus U, Psychiatry Res, 2009).
- A 2011 review found that higher levels of brain creatine was associated with improved neuropsychological performance; supplementation could improve cognitive processing. In elderly subjects, 20g/day for 1 week improved random number generation, forward number and spatial recall and long-term memory tasks. (Rawson ES, Amino Acids, 2011; McMorris T, Neuropsychol Dev Cogn B Aging Neuropsychol Cogn, 2007)
- A 2018 systematic review found that in healthy individuals, creatine could improve short term memory and intelligence/reasoning (Avgerinos KI, Exp Gerontol, 2018).
- A study of rats with induced AD showed that creatine supplementation reduces learning and memory impairment (Alimohammadi-Kamalabadi M, Iran J Basic Med Sci, 2016).

Creatine for PD

- A 2017 meta-analysis of 5 human RCTs found no benefit to creatine supplementation (Mo JJ, BMC Neurol, 2017). Similarly, a 2014 Cochrane Review found no effect on motor function, activities of daily living or quality of life (Xiao Y, Cochrane Database Syst Rev, 2014).
- In PD patients with the genotype GRIN2A, which encodes an NMDA-glutamate-receptor subunit, and a higher level of caffeine intake, supplementing creatine was associated with an increased rate of PD progression (Simon DK, J Neurol Sci, 2017).
- A meta-analysis found no evidence that creatine supplementation was protective against PD (Attia, CNS Neurol Disord Drug Targets, 2017).
- An RCT of a combination of 5g/day creatine monohydrate and 100 mg/day CoQ10 significantly delayed the cognitive decline in PD patients after 18 months (Li Z, Eur Neurol, 2015). A similar study in mice found a significant reduction in lipid peroxidation, DNA oxidative damage and alpha-synuclein accumulation in neurons and striatal lesion volumes, while improving glutathione homeostasis, motor performance and survival (Yang L, J Neurochem, 2009).
- Rodent and *in vitro* studies show that creatine reduces oxidative stress and is neuroprotective in a PD model (Cunha MP, ASN Neuro, 2014).

Ginkgo biloba for AD, dementia and MCI

- A 2019 meta-analysis showed that 240mg/day EGb761 (a commercial ginkgo biloba preparation) for a minimum of 22 weeks showed no treatment benefit compared to placebo (Thancharoen O, Drugs Aging, 2019). Despite this, a 2018 meta-analysis found that in dementia patients, 240mg/day EGb761 for 20 or 22 weeks was effective in reducing numerous behavioural and psychological symptoms (Savaskan E, Int Psychogeriatr, 2018). Numerous earlier reviews had drawn the same conclusion.
- A 2019 expert consensus concluded that EGb761 induced significant improvement in cognitive function, neuropsychiatric symptoms, activities of daily living (ADL) and quality of life in patients with mild-to-moderate dementia or mild cognitive impairment. It demonstrated the same strength of evidence as acetylcholinesterase inhibitors and NMDA antagonists such as memantine but increased strength of evidence in improving cognition, behaviour and ADL in both AD and vascular dementia patients. (Kandiah N, CNS Neurosci Ther, 2019)
- A 2018 meta-analysis found that EGb761 reduced incidence of tinnitus and dizziness (Spiegel R, Clin Interv Aging, 2018).
- Specifically in AD patients aged >79, there was no significant difference in cognitive decline between Aricept and EGb761, but there were more adverse events in the Aricept group (Rapp M, Int J Clin Pharmacol Ther, 2018).
- A population study of subjects aged >64 showed that ginkgo biloba extract consumers had a lower risk of dying before suffering dementia and a longer lifetime without dementia than participants taking other drugs for the same indication (Dartigues JF, J Prev Alzheimers Dis, 2017). However an earlier meta-analysis had found no evidence that ginkgo biloba could prevent dementia (Charemboon T, J Med Assoc Thai, 2015).
- In rats with vascular dementia, EGb761 promoted proliferation of endogenous neural stem cells (Wang J, Neural Regen Res, 2013).

Ginseng for AD, dementia and MCI

- A 2016 meta-analysis of the use of ginseng in AD showed that most studies were small, of poor quality and provided inconclusive results (Wang Y, Curr Top Med Chem, 2016).
- Since then, a study of Korean AD patients showed that 4.5g/day Panax ginseng for 12 weeks improved cognitive function (Heo JH, J Altern Complement Med, 2016).
- In Korean subjects with mild cognitive impairment, 3g/day Panax ginseng for 6 months significantly enhanced cognition (Park KC, Transl Clin Pharmacol, 2019).
- Among elderly Korean subjects, long term supplementation (>4 years) with ginseng significantly improved neuropsychological scores (Lho SK, Alzheimers Res Ther, 2018).
- Animal studies show that in induced AD, vascular dementia or cognitive impairment, ginseng significantly improves Aβ deposition, gliosis, neuronal injury or loss, deficits in hippocampal neurogenesis and cognitive deficits (Shin SJ, Int J Mol Sci, 2019; Zhu JD, Neural Regen Res, 2018; Tu TT, Planta Med, 2017).

Supplementary ketones and MCTs for AD, dementia and MCI

- An imaging study showed that in AD and MCI, the brain undergoes structural atrophy with lower brain glucose metabolism; there is no reduction, however, in ketone metabolism (Croteau E, Exp Gerontol, 2018). A study of blood ketones in AD suggested that patients have impaired ketogenesis (Ciavardelli D, Neurobiol Aging, 2016).
- A 2020 meta-analysis of MCT administration may improve cognition in patients with mild cognitive impairment and Alzheimer's disease (Avgerinos KI, Ageing Res Rev, 2020).
- Since then an RCT of APOE4-/- patients with mild to moderate AD given 17.3g/day MCT oil for 30 days showed improved cognitive ability (Xu Q, Clin Nutr, 2020).
- A further imaging study showed that in AD patients given MCTs, brain ketone consumption doubled, with the slope of the relationship between plasma ketones and brain ketone uptake being the same as in healthy young adults (Croteau E, J Alzheimers Dis, 2018).
- Animal studies showed that supplementary ketones induced higher concentrations of citrate and α-ketoglutarate (TCA cycle intermediates) in the hippocampus compared with controls, blocked Aβ42 entry into neurons, reduced hyperphosphorylated tau deposition, oxidative stress and anxiety and improved mitochondrial Complex I activity, synaptic plasticity and learning and memory (Pawlosky RJ, Int J Mol Sci, 2020; Yin JX, Neurobiol Aging, 2016; Kashiwaya Y, Neurobiol Aging, 2013).

Lipoic acid for AD, dementia and MCI

- In AD patients, 600mg/day alpha lipoic acid improved cognitive decline, with a greater improvement in those with T2D (Fava A, J Neurodegener Dis, 2013).
- A combination of alpha lipoic acid and omega-3 fats for 12 months in AD patients resulted in slowed cognitive and functional decline (Shinto L, J Alzheimers Dis, 2014).
- In animal AD and vascular dementia studies, lipoic acid protected against cognitive dysfunction, decreased oxidative stress, improved cognitive impairment, neuronal antioxidant status, insulin signalling and synaptic function and plasticity, restored central cholinergic system functioning and increased hippocampal cell survival (Park JH, Eur Rev Med Pharmacol Sci, 2019; Rodriguez-Perdigon M, Biochim Biophys Acta, 2016; Zhao RR, Neurosci Lett, 2015; Sancheti H, PLoS One, 2013; Sharma M, Eur Neuropsychopharmacol, 2003; Fernandez-Moriano C, Oxid Med Cell Longev, 2015; Head E, Exp Neurol, 2009).

Lipoic acid and PD

- No human studies.
- The disruption of neuronal iron homeostasis and oxidative stress are related to the pathogenesis of PD, while α-lipoic acid is an antioxidant and iron chelator and has neuroprotective effects against PD. In vitro and rat studies showed that α-lipoic acid could protect against cell damage by decreasing the levels of intracellular ROS and iron by increasing iron efflux from cells. It also promoted the survival of dopaminergic neurons in rat models of PD and ameliorated motor deficits by inhibiting the decrease in tyrosine hydroxylase expression and SOD activity in the substantia nigra. α-lipoic acid also attenuated induced iron accumulation both in vivo and in vitro. (Tai S, Front Neurosci, 2020; Cai T, Xi Bao Yu Fen Zi Mian Yi Xue Za Zhi, 2018; Li YH, Metab Brain Dis, 2015; Karunakaran S, FASEB J, 2007)
- In animal studies, α-lipoic acid decreased body rotations and improved motor performance. It was also protective, had antioxidant effects and maintained membrane potential, preventing damage induced by chronic use of L-DOPA in dopaminergic neurons (de Araújo DP, Evid Based Complement Alternat Med, 2013; Fernandez-Moriano C, Oxid Med Cell Longev, 2015).
- In vitro studies showed that R-lipoic acid increased cell viability and decreased apoptosis, intracellular ROS and cytotoxicity and induced cell autophagy in PD. It also reversed the induced decreased dopamine and increased α-synuclein expression, upregulated PGC-1α and downregulated expression levels of autophagy-related proteins, including Parkin and PINK1, prevented depletion of glutathione and preserved mitochondrial Complex I activity. (Zhao H, Int J Biochem Cell Biol, 2017; Bharat S, Neurotoxicol, 2002)
- A combination of α-lipoic acid and acetyl L-carnitine improved motor performance, mitochondrial dysfunction, oxidative damage and accumulation of alpha-synuclein and ubiquitin, reduced the level of ROS and lipid peroxides and increased mitochondrial biogenesis. When combined, they were effective at 100-1000-fold lower concentrations was required individually. (Zaitone SA, Pharmacol Biochem Behav, 2012; Zhang H, J Cell Mol Med, 2010)

Lipoic acid and MS

- There has only been one clinical trial to assess physical improvement in MS patients: 1200 mg/day for 2 years improved walking performance, particularly in those with lower baseline disability (Loy BD, Complement Ther Med. 2018).
- 1200 mg/day alpha-lipoic acid for 12 weeks decreased asymmetric dimethylarginine (ADMA), a marker for oxidative stress, and inflammatory cytokines and increased antioxidant production (Khalili M, Electron Physician. 2017; Khalili M, Neuroimmunomodulation. 2014; Khalili M, Nutr Neurosci. 2014).
- Patients taking 1200 mg/day for 14 days showed a decrease in MMP-9 and sICAM-1 levels (Yadav V, Mult Scler. 2005).
- In vitro studies showed that lipoic acid reduced inflammation by inhibiting monocyte secretion of cytokines and inhibited monocyte phagocytosis via increased cAMP levels. It also inhibited monocyte and B cell migration. (Fiedler SE, Immunol Cell Biol. 2021; George JD, J Neuroimmunol. 2018).

Magnesium for AD, dementia and MCI

- No human clinical trials.
- A 2016 systematic review showed that patients with AD had significantly lower magnesium in cerebrospinal fluid and in hair but no differences between AD patients and controls were evident for serum magnesium (Veronese N, Am J Alzheimers Dis Other Demen, 2016).
- Since then, two cross-sectional studies showed that magnesium intake and serum magnesium were inversely associated with cognitive impairment and a prospective study found that subjects who supplemented magnesium oxide (as a laxative) had a significantly lower risk of developing dementia. However another prospective study showed that both low (≤0.79 mmol/L) and high (≥0.90 mmol/L) serum magnesium levels were associated with dementia risk after 7.8 years. (Peeri NC, Eur J Nutr, 2020; Al-Ghazali K, Front Aging Neurosci, 2020; Tzeng NS, Curr Med Res Opin, 2018; Kieboom BCT, Neurology, 2017)
- Animal AD studies have found that magnesium improved recognition and spatial memory by reducing synaptic loss and restoring the NMDA signalling pathway. In particularly, magnesium-threonate enhanced clearance of Aβ and prevented synapse loss and memory decline. (Huang Y, CNS Neurosci Ther, 2018; Yu X, FASEB J, 2015; Li W, Mol Brain, 2014)

Melatonin for AD, dementia and MCI

- A 2017 meta-analysis showed that melatonin improved sleep time in AD patients but had no effect on cognitive ability (Wang YY, Int J Geriatr Psychiatry, 2017).
- In elderly surgical patients, 1mg/day melatonin for 5 days prevented postoperative cognitive decline (Fan Y, J Clin Anesth, 2017).
- In elderly subjects, 2.5 mg/day melatonin for 15 months adversely affected mood and increased withdrawn behaviour (Riemersma-van der Lek RF, JAMA, 2008).
- Supplementation of DHA-phospholipids containing melatonin and tryptophan for 12 weeks in elderly patients suffering from mild cognitive impairment resulted in improved cognitive function and verbal fluency (Rondanelli M, Nutr Neurosci, 2012).
- A population study of elderly subjects found that higher serum melatonin levels were associated with lower cognitive decline and depression (Obayashi K, J Clin Endocrinol Metab, 2015).
- Disruption of the circadian rhythms is a frequent preclinical and clinical manifestation of AD; a *post mortem* study showed that the melatonin receptor type 1A gene, which modulates APP metabolism, was linked to AD in old age, with expression of both pineal and cortical melatonin receptors MT1 and MT2 being decreased in AD (Sulkava S, Sleep, 2018; Brunner P, Eur J Histochem, 2006).
- Decreased cerebral spinal fluid melatonin levels may be an early event in the development of AD (Zhou JN, J Pineal Res, 2003).
- In animal studies, melatonin prevents cognitive decline in tau-related AD, reduced Aβ accumulation, anxiety, depression-like behaviour oxidative stress, neuroinflammation, tau hyperphosphorylation and apoptosis and restored autophagic flux and memory (Luengo E, J Pineal Res, 2019; Nie L, Biofactors, 2017; Rudnitskaya EA, J Alzheimers Dis, 2015).

Melatonin for PD

- Insomnia, sleep fragmentation and excessive daytime sleepiness are common in PD and may contribute to the reduction of cognition and alertness in those patients. They have been linked to a dysregulation of the circadian cycle and clock genes. Melatonin is involved in the regulation of sleep and circadian biological rhythmicity; decreased melatonin secretion has been associated with circadian disruptions and also with hypothalamic volume loss and PD severity. In PD patients, there were correlations between serum melatonin level and sleep dysfunction. (Delgado-Lara DL, Biomed Pharmacother, 2020; Kataoka H, Sleep Med, 2020; Hadoush H, NeuroRehabilitation, 2020; Breen DP, Moc Disord, 2016)
- Plasma melatonin levels were significantly higher in PD patients and were associated with the levodopa daily dose. Higher plasma melatonin concentrations were positively correlated with disease severity but an inverse association with glutathione levels. Studies are divided over whether lower or higher melatonin levels in PD are associated with sleep disorders but 1 showed that higher melatonin levels correlated with fewer cardiovascular symptoms and gastrointestinal dysfunction. (Li L, Front Neurosci, 2020; Wei HJ, Zhongguo Yi Xue Ke Xue Yuan Xue Bao, 2019; Lin L, Brain Res, 2014; Bordet R, Clin Neuropharmacol, 2003)
- A trials giving 2 mg/day melatonin improved non-motor symptoms, quality of life, chromic fatigue, sleep quality, REM sleep behaviour disorders, daytime sleepiness, anxiety and depression (Ahn JH, Parkinsonism Relat Disord, 2020; Daneshvar Kakhaki R, Clin Neurol Neurosurg, 2020; Lyashenko EA, Zh Nevrol Psikhiatr Im S S Korsakova, 2015; Datieva VK, Zh Nevrol Psikhiatr Im S S Korsakova, 2013; Medeiros CA, J Neurol, 2007; Dowling GA, Sleep Med, 2005).
- Nevertheless, in PD patients with sleep disorders, RCTs giving 4mg before bedtime or 25mg melatonin at noon and 30 min before bedtime for 2 or 3 months showed no significant difference between melatonin and placebo (Delgado-Lara DL, Biomed Pharmacother, 2020; Gilat M, Mov Disord, 2020).
- In animals, melatonin can improve synaptic dysfunction, motor symptoms, behaviour, long-term memory deficits, depression and Complex I activity, protect neurons from oxidative damage, maintain nigrostriatal integrity, inhibit striatal degeneration and nigral dopamine loss, inflammation and neuronal apoptosis, maintain mitochondrial membrane potential, decrease calcium concentrations and increase antioxidant production. (Ran D, Biomed Rep, 2018; Rasheed MZ, J Environ Pathol Toxicol Oncol, 2018; Paul R, Life Sci, 2018; Li Y, Chin Med J, 2017; Sun X, Mol Med Rep, 2016; Carriere CH, Brian Res, 2016; Bassani TB, Brain Res, 2014; Yildirim FB, Neurochem Int, 2014; Tapias V, J Neurosci Res, 2010; Fernandez-Moriano C, Oxid Med Cell Longev, 2015).

N-acetyl cysteine (NAC) for AD, dementia and MCI

- No human trials for AD, dementia or MCI.
- In patients with psychosis, 2g/day NAC for 24 weeks had significantly higher working memory performance (Rapado-Castro M, Psychol Med, 2017).
- Animal studies showed NAV improved depressive and anxiety-like behaviour and cognitive and spatial learning deficits, reversed hippocampal pathological alterations and inhibited microglia activation; it also prevented neuronal degeneration by minimising the neurofibrillary tau accumulation (Chakraborty S, Neurochem Int, 2020; Joy T, Neurosci J, 2019; Joy T, Brain Sci, 2018; Shahidi S, Brain Res Bull, 2017). NAC may have more effect in young animals (Ikonne US, J Nutr, 2019).

NAD and precursors for AD, dementia and MCI

- An open label trial of NADH for 8-12 weeks in 17 AD patients showed improvement in cognitive dysfunction (Birkmayer JG, Ann Clin Lab Sci, 1996).
- An RCT of 10mg/day NADH for 6 months in AD patients found that it prevented further cognitive deterioration and showed significantly improved scores on the dementia rating scale for verbal fluency and visual-constructional ability but there was no effect on attention, memory or dementia severity; an earlier trial had shown no improvements in any measurement (Demarin V, Drugs Exp Clin Res, 2004; Rainer M, J Neural Transm, 2000).
- Animal AD studies showed that nicotinamide riboside (NR) improved contextual fear memory, neuroinflammation, hyperphosphorylated tau, APP levels, DNA damage, synaptic dysfunction and neuronal degeneration and loss and inhibited Aβ accumulation (Hou Y, Proc Natl Acad Sci U S A, 2018; Xie X, Metab Brain Dis, 2019; Gong B, Neurobiol Aging, 2013; Lee HJ, Int J Mol Sci, 2019).
- In aged mice, NR also improved the short-term spatial memory and inhibited the activation of astrocytes and the elevation of serum NAMPT (Xie X, Metab Brain Dis, 2019).
- Nicotinamide mononucleotide (NMN) restored mitochondrial respiratory function and SIRT1 activation and induced a shift from fission to fusion proteins in AD rodents and improved age- or T2D-induced cognitive impairment, particularly spatial working memory, and gait coordination, prevented neuronal loss and restored learning and memory deficits (Long AN, BMC Neurol, 2015; Chandrasekaran K, Int J Mol Sci, 2020; Wang X, Brain Res Bull, 2020; Tarantini S, Redox Biol, 2019; Johnson S, NPJ Aging Mech Dis, 2018).

Omega 3 fatty acids for AD, dementia and MCI

- A 2016 meta-analysis of trials of omega 3 fats in the elderly showed that doses of 400-1800mg/day for at least 3 months reduced the rate of cognitive decline (Zhang XW, Aging Clin Exp Res, 2016). A 2019 systematic review had shown that omega 3 fats improved at least one aspect of cognitive function and another in 2018, despite finding little evidence of benefit, suggested that there may be a positive effect in subjects with very mild AD (Martí Del Moral A, Nutr Hosp, 2019; Canhada S, Nutr Neurosci, 2018).
- However a 2016 Cochrane Review found no evidence for omega 3 fats in the treatment of mild-moderate AD (cognitive function, severity of dementia, mental health or quality of life) (Burckhardt M, Cochrane Database Syst Rev, 2016).
- A 2012 Cochrane Review found no evidence of omega 3 fats for prevention of cognitive decline or dementia (Sydenham E, Cochrane Database Syst Rev, 2012).
- A trial of omega 3 fats in patients with MCI found increased cerebral blood flow and volume, with upregulation of cytoprotective genes, decreased proapoptotic genes and improved Aβ immune clearance cognitive function in ApoEe3/e3 vs. ApoEe3/e4 patients(Schwarz C, J Prev Alzheimers Dis, 2018; Olivera-Perez HM, FASEB J, 2017).
- In elderly subjects followed up after 7 years, baseline plasma levels of EPA and DHA were associated with slower decline of visual retention performances in ApoE-ε4 carriers only. A cross-sectional study found that a lower ratio of omega-6 to omega-3 fatty acid intake strongly predicted improved spatial memory, learning and higher cognitive status overall. (Samieri C, Neurobiol Aging, 2011; Andruchow ND, Neuropsychology, 2017).

Omega-3 fatty acids for PD

- In PD patients with major depression, 12 weeks of fish oil induced a decrease in depression scores (da Silva TM, J Affect Disord, 2008).
- In PD patients, a combination of 1000 mg/day omega-3 fatty acids from flaxseed oil plus 400 IU/day vitamin E for 12 weeks improved rating on the UPDRS, decreased markers of inflammation and increased total antioxidant capacity (Taghizadeh M, Neurochem Int, 2017; Tamtaji OR, Clin Neurol Neurosurg, 2019).
- In rodents with severe PD, docosahexaenoic acid (DHA) protected against the core symptoms of PD, including deficits in postural stability, gait integrity and dopamine neurochemistry in motor areas of the striatum; it also improved rotational behaviour, suggesting neuroprotection from dyskinaesia. DHA also increased striatal dopamine synthesis and reversed dopamine loss in the nigrostriatal pathway, reduced the density of iNOS-immunoreactive cells and microglia and astrocyte reactivity. In a partial lesion model of PD, DHA administration decreased astrogliosis and microgliosis and upregulated Nrf2; there was a trend toward improved behaviour. DHA also protected against apoptosis of dopaminergic neurons and prevented loss of tubulin and synaptophysin, proteins relevant to synaptic transmission. (Chitre NM, Neuropharmacology, 2020; Hernando S, Neurobiol Dis, 2019; Serrano-García N, Neurchem Int, 2018; Mori MA, Nutr Neurosci, 2018; Delattre AM, Neurosci Res, 2010; Bousquet M, FASEB J, 2008)
- Human and animal studies have shown that omega-3 PUFAs may improve PD by inhibiting proinflammatory cytokine release, promoting neurotrophic factor expression, recovering mitochondrial function and membrane fluidity, decreasing the levels of oxidant production, maintaining α-synuclein proteostasis, calcium homeostasis and axonal transport and reducing endoplasmic reticulum stress. They may also blunting microglial iNOS induction (Li P, Nutr Neurosci, 2020;).

Omega 3 fatty acids in MS

- A 2021 systematic review of 7 RCTs found that fatty acid supplementation reduced the relapsing rate, lowered inflammatory markers and improved the quality of life of MS patients (AlAmmar WA, Nutr Neurosci. 2021).
- A 2020 Cochrane Review found that PUFA administration has little impact with regards to relapse rate, disability worsening or overall clinical status in people with MS (Parks NE, Cochrane Database Syst Rev. 2020).
- A 2019 meta-analysis showed that omega 3 fatty acids had no impact on the disability status scale but reduced TNF-α, a pro-inflammatory cytokine (Sedighiyan M, CNS Neurol Disord Drug Targets. 2019). It similarly had no significant effect on depression (Shinto L, PLoS One. 2016).
- 1350 mg/day of EPA and 850 mg/day of DHA for 6 months had no effect on the number of MRI lesions and there was no difference in relapse rate or fatigue or quality-of-life scores (Torkildsen O, Arch Neurol. 2012).
- Omega-3 fish oils for 1 year reduced fatigue and relapse rate (Weinstock-Guttman B, Prostaglandins Leukot Essent Fatty Acids. 2005).
- In a population study, those consuming fish more frequently or taking omega-e supplements had an improved quality of life and less disability (Jelinek GA, Int J Neurosci. 2013).
- An *in vitro* study showed that omega-3 fatty acids significantly decreased MMP-9 protein levels and activity and significantly inhibited human T cell migration, indicating an effect as an immune modulator (Shinto L, Autoimmune Dis. 2011; Shinto L, Prostaglandins Leukot Essent Fatty Acids. 2009).

Selenium for AD, dementia and MCI

- In elderly subjects with MCI, 288.75 µg/day selenium for 6 months improved some cognitive functions (Rita Cardoso B, Eur J Nutr, 2016).
- A 2017 meta-analysis showed that AD patients had significantly lower circulatory, erythrocyte and cerebral spinal fluid selenium levels (Reddy VS, J Trace Elem Med Biol, 2017). However, since then a cross-sectional study found that in older subjects or AD/dementia patients, plasma selenium was not associated with cognitive performance, inflammatory markers or neurotrophic factors (Cardoso BR, Nutrients, 2018).
- A 2019 meta-analysis found that AD subjects had significantly decreased brain tissue selenium levels (Varikasuvu SR, Biol Trace Elem Res, 2019).
- An NHANES study showed that selenium intake was inversely associated with low cognitive function (Li S, J Alzheimers Dis, 2019).
- Animal studies show that selenomethionine restored synapses, dendrites and spines, leading to improved synaptic plasticity and cognitive function in AD by inhibiting NMDA receptors; it also inhibited Aβ aggregation and tau pathologies, enhanced antioxidant capacity and improved cognitive decline (Zhang ZH, Antioxid Redox Signal, 2020; Vicente-Zurdo D, Anal Bioanal Chem, 2020; Zhang ZH, Food Funct, 2018).

Taurine for AD, dementia and MCI

- In elderly women with dementia, 3g/day taurine for 4 weeks induced positive changes in language and executive function (Gao R, Adv Exp Med Biol, 2019).
- In elderly subjects with and without dementia, those without dementia had consumed significantly more taurine-rich foods over their lifetime than those with dementia; cognitive function scores were positively correlated with past taurine intake (Bae ME, Adv Exp Med Biol, 2017).
- In animal studies, taurine can reverse cognitive impairment, reduce inflammatory cytokines, raise endogenous antioxidant activity and protect from neuronal damage and nucleus shrinkage through binding to oligomeric Aβ (Kim HY, Sci Rep, 2014; Javed H, Neurol Sci, 2013; Tu DG, Food Funct, 2018; Jang H, Adv Exp Med Biol, 2017; Reeta KH, Neurochem Int, 2017).

Vitamin A for AD, dementia and MCI

- No human clinical trials.
- A 2018 meta-analysis found that patients with AD had significantly lower plasma levels of α-carotene, β-carotene and vitamin A (Mullan K, J Alzheimers Dis, 2018). Serum levels of retinol were also lower in MCI and dementia patients (Huang X, J Nutr Health Aging, 2020; Raszewski G, Ann Agric Environ Med, 2016).
- Both serum and brain β-carotene concentrations were positively associated with improved cognition in healthy octogenarians and centenarians (Johnson EJ, J Aging Res, 2013).
- Peripheral blood mononuclear cells from AD patients which were treated with all-trans-retinoic acid (ATRA) showed downregulation of the spontaneous in vitro production of NO and decreased expression of iNOS, which was associated with decreased inflammation (Behairi N, Neuroimmunomodulation, 2015).
- A 6-year prospective study of elderly diabetics found that lower baseline intake of carotene in part predicted cognitive decline in males but not females (Araki A, Geriatr Gerontol Int, 2017).
- In animals with induced AD or dementia, ATRA treatment significantly decreased activation of microglia and astrocytes, attenuated neuronal degeneration, improved spatial learning and memory, decreased Aβ deposition and APP and tau phosphorylation and proved to be anti-cholinesterase, anti-oxidative and anti-inflammatory (Sodhi RK, Prog Neuropsychopharmacol Biol Psychiatry, 2013; Ding Y, J Neurosci, 2008).

Vitamin A for MS

- 25,000 IU/day retinyl palmitate (RP) for 6 months followed by 10,000 IU/day RP for another 6 months showed significant improvement in fatigue and depression in MS (Bitarafan S, Iran J Allergy Asthma Immunol. 2016).
- 25,000 IU/day RP for 6 months followed by 10,000 IU/day RP for another 6 months did not affect the expanded disability status scale (EDSS), relapse rate or brain active lesions on MRI but did improve the multiple sclerosis functional composite (MSFC) index (Bitarafan S, Arch Iran Med. 2015).
- 25,000 IU/day RP in MS patients could reduce T cell stimulation (Jafarirad S, J Neurosci Rural Pract. 2012).
- MS patients that received 25,000 IU/day RP showed upregulated TGF-β and FoxP3 gene expression (Saboor-Yaraghi AA, J Mol Neurosci. 2015).
- MS patients generally have lower plasma levels of vitamin A, which leads to loss of immune tolerance and induces pathogenic immune cell production. Vitamin A is thought to ameliorate MS through a reduction in inflammatory cytokines by re-establishing the balance between pathogenic (Th1, Th17, Th9) and immunoprotective cells (Th2, Tregs), modulating B cell and dendritic cell function as well as increasing tolerance of autoimmunity and regeneration in the CNS. (Reza Dorosty-Motlagh A, J Mol Neurosci. 2016)

Vitamin D for AD, dementia and MCI

- In older adults with AD, 800 IU/day vitamin D for 12 months showed significant improvements in levels of plasma Aβ42 and APP and several measures of cognitive function and increased IQ, however a similar study comparing 2000 and 800 IU/day over 24 months found that the improvement in cognitive performance with 800IU/day was not increased with 2000 IU/day (Jia J, J Neurol Neurosurg Psychiatry, 2019; Schietzel S, Am J Clin Nutr, 2019).
- In older African Americans, vitamin D given with calcium improved serum levels but failed to show a difference in cognition between the group given calcium only (Owusu JE, J Am Geriatr Soc, 2019). A further study of vitamin D with calcium failed to have an impact on cognitive impairment (Rossom RC, J Am Geriatr Soc, 2012), suggesting that vitamin D should be given alone for neurodegenerative disease.
- 100,000 IU vitamin D given as a bolus dose followed by 20,000 IU/week for four months in healthy middle-aged or older adults did not improve cognitive function (Jorde R, J Neurol Sci, 2019).
- A 2019 meta-analysis found that vitamin D insufficiency (serum 25(OH)D = 25-50 nmol/l) was not associated with dementia or AD but vitamin D deficiency (<25 nmol/l) was associated with dementia but not AD. Serum 25(OH)D of 62.5 nmol/l was associated with lower risk for dementia and AD risk decreased continuously as serum 25(OH)D increased up to 87.5 nmol/l. (Jayedi A, Nutr Neurosci, 2019)
- Another 2019 meta-analysis found that 25(OH)D levels >50 nmol/l was associated with both AD and dementia incidence (Chai B, BMC Neurol, 2019).

Vitamin D for PD

- A 2016 systematic review and later studies show that PD patients have lower vitamin D levels and that concentrations are inversely correlated with PD risk, severity, delayed gastric emptying and balance and are positively associated with cognitive function and mood in PD patients; sunlight exposure and outdoor working, but not vitamin D supplementation, was associated with reduced PD risk (Lv L, Transl Neurodegener, 2020; Bivona G, Clin Chim Acta, 2019; Zhou Z, Med Sci Monit, 2019; Luo X, Front Neurol, 2018; Sleeman I, J Parkinsons Dis, 2017; Wang J, Nutrients, 2016; Rimmelzwaan LM, J Parkinsons Dis, 2016; Kwon KY, Neurodegener Dis, 2016; Shen L, Nutrients, 2015; Peterson AL, J Parkinsons Dis, 2013; Peterson AL, Mov Disord, 2013).
- Observational studies of vitamin D supplementation have generally failed to show an association with improvement in PD symptoms (Zhou Z, Med Sci Monit, 2019, Luthra NS, J Clin Mov Disord, 2018).
- An pilot study of 10,000 IU/day vitamin D3 for 16 weeks showed no effect overall but did induce an improvement in sensory organisation in those of younger age; however, baseline mean vitamin D levels were around 75nmol/l (Hiller AL, PLoS One, 2018). [It may be that vitamin D is preventive and does not have much of the treatment effect and also that this population had a healthy baseline vitamin D level, suggesting that the PD was not due to low vitamin D concentrations.]
- Animal studies show that vitamin D supplementation attenuated the loss of tyrosine hydrlase-positive neuronal cells, microglial cell activation, inducible nitric oxide synthase (iNOS) and TLR-4 expression, typical hallmarks of the pro-inflammatory (M1) activation of microglia. It could also decrease pro-inflammatory cytokine mRNA expression in certain brain areas and upregulated anti-inflammatory cytokine mRNA expression, indicating substantial neuroprotective effects (Calvello R, J Neuroimmune Pharmacol, 2017).

Vitamin D for MS

- Two 2021 meta-analyses found that administration of vitamin D in dosages ranging from 2,857 to 14,007 IU/day and treatment periods ranging from 6 to 24 months did not affect the clinical outcomes or relapse rate in patients with MS (Yuan X, Neuroimmunomodulation. 2021; Hanaei S, Int J Prev Med. 2021).
- Another systematic review found that disease measures improved to a greater extent overall in those with lower baseline serum 25(OH)D levels (Berezowska M, Int J Mol Sci. 2019).
- Nevertheless, a further meta-analysis showed that there was a significant inverse correlation between 25(OH)D levels and extent of disability in MS patients (Moosazadeh M, AIMS Neurosci. 2021).

Baicalin/Baicalein for AD, dementia and MCI

- No human trials.
- In animals with AD or cognitive impairment, baicalein and baicalin can improve behavioural dysfunction, energy metabolism and neurotransmission, reduce brain Aβ concentration, the number of activated microglia and associated neuroinflammation, decrease proinflammatory cytokines and oxidative stress, prevent neuronal apoptosis, tau phosphorylation and Aβ-induced impairments in the hippocampus and restore spine number, synaptic plasticity and memory deficits (Zhou L, Neuropsychiatr Dis Treat, 2016; Gu XH, Behav Brain Res, 2016; Wei D, Curr Alzheimer Res, 2014; Qi Z, Int J Clin Exp Med, 2015; Jin X, CNS Neurosci Ther, 2019; Ma P, Mol Med Rep, 2015).
- *In vitro* studies showed that baicalein significantly reduced the production of Aβ by increasing APP α-processing (Zhang SQ, J Neurosci Res, 2013).

Baicalin/Baicalein for PD

- No human studies.
- A systematic review of animal studies found that baicalein offered a protective effect for induced PD, focusing mainly on its antioxidative, anti-apoptotic and anti-inflammatory actions. Later studies showed that baicalein reversed induced motor dysfunction, tremor, loss of dopaminergic neurons and elevation of pro-inflammatory cytokines. It also inhibited apoptosis and the activation and proliferation of disease-associated proinflammatory microglia. (Zhu Q, Phytomedicine, 2019; Rui W, Int J Neuropsychopharmacol, 2020; Mu X, Pharmacol Biochem Behav, 2009)
- Baicalein also inhibits α-synuclein oligomer formation, prevents progression of α-synuclein accumulation, promotes neurogenesis, neuroblast proliferation, neurotrophin signalling pathways, walking and locomotor behaviours and inhibits dopamine metabolism to prevent its breakdown. It attenuated astroglial activation and the upregulation of striatal basal glutamatergic strength by decreasing the presynaptic glutamate release and recovering the insertion of postsynaptic glutamate receptor subunit GluR1. It also inhibited apoptosis and prevented toxin-induced dysfunction and loss of membrane potential (Hu Q, Biochim Biophys Acta, 2016; Zhang X, Sci Rep, 2017; Gao L, Pharmacol Biochem Behav, 2015; Xue X, Brain Res Bull, 2014; Li E, J Neurosci Res, 2014; Fernandez-Moriano C, Oxid Med Cell Longev, 2015).
- Similarly, baicalin protected dopaminergic neurons against oxidative damage and α-synuclein expression, improving behavioural performance, reducing apoptosis and dopaminergic neuron loss in the substantia nigra and inactivating proinflammatory cytokines and oxidative stress. (Lei K, Oxid Med Cell Longev, 2020; Tu L, Neuropsychiatr Dis Treat, 2019; Zhai H, J Integr Neurosci, 2019)
- Baicalin also acts to remove iron from various brain regions and had a protective effect on dopaminergic neurons (Xiong P, Neural Regen Res, 2012).

Curcumin for AD, dementia and MCI

- A 2019 systematic review of 6 trials found that in older adults curcumin improved memory but not depression, while in AD patients it did not improve cognitive function (Zhu LN, Phytother Res, 2019).
- An open label study of curcumin combined with huperzine A (a cholinesterase inhibitor and glutamic acid receptor antagonist) showed that patients with AD, dementia or MCI showed improved cognitive function (Tabira T, J Alzheimers Dis, 2018).
- In AD animals, curcumin downregulated expression of immune system genes controlling pro-inflammatory activation of microglia and promoted phagocytosis of amyloid plaques (Teter B, Neurobiol Dis, 2019). It effectively decreased neuroinflammation, neuronal degeneration, oxidative stress and tau and amyloid pathology and improved cognitive function (Sundaram JR, J Alzheimers Dis, 2017; Sevastre-Berghian AC, Oxid Med Cell Longev, 2017).
- In *in vitro* studies, curcumin protected against oxidative toxicity, prevented tau aggregation, disassembled tau structures and reduced production of Aβ40 and Aβ42). It also enhanced mitochondrial fusion and reduced fission, while increasing mitochondrial biogenesis and synaptic proteins, increasing neuronal viability; curcumin was even more effective as a preventive. (Morales I, J Alzheimers Dis, 2017; Reddy PH, J Investig Med, 2016; Xiong Z, Pharmacol Rep, 2011)
- Aerosol curcumin delivery (via inhalation) also improved cognitive function (McClure R, J Alzheimers Dis, 2017).

Curcumin for PD

- No human studies.
- *In vitro* studies have shown that curcumin protected against neurotoxicity, increased the number of surviving dopamine neurons, increased proliferation and endogenous antioxidants, inhibited apoptosis and decreased nuclear damage and protein and mRNA expression of α-synuclein; curcumin also acts as an iron chelator (Wu Y, Zhejiang Da Xue Xue Bao Yi Xue Ban, 2018; Sang Q, Cell Physiol Biochem, 2018; Pandareesh MD, Neurochem Res, 2016; van der Merwe C, Mol Neurobiol, 2017; Du XX, Neurosci Bull, 2020).
- A 2017 systematic review of animal studies found that curcumin was neuroprotective, with an anti-inflammatory and antioxidant effect in substantia nigra neurons, reduced neuronal apoptosis and improved striatal dopamine levels and functional outcome (Wang XS, BMC Complement Altern Med, 2017).
- Since then rodent studies have shown that curcumin improved abnormal motor behaviour, protected against the reduction of dopaminergic neurons, normalised tyrosine hydroxylase, the dopamine transporter and antioxidants, prevented iron deposition in dopaminergic neurons, lowered the increase in α-synuclein, inflammation, oxidative stress, caspases and DNA fragmentation and protected against astroglial and dopaminergic neurotoxicity (El Nebrisi E, Int J Mol Sci, 2020; Motawi TK, Mol Cell Biochem, 2020; Abbaoui A, Acta Histochem, 2018; Wang YL, Cell Physiol Biochem, 2017; Sharma N, Inflammopharmacology, 2018; Abbaoui A, Neurosci Lett, 2017).

Epigallocatechin-3-gallate (EGCG) for AD, dementia and MCI

- There are no human clinical trials for AD, dementia or cognitive impairment.
- A clinical trial of EGCG and cognitive training for Fragile X syndrome, an inherited condition causing learning disability, found an improvement in visual episodic memory and functional competence (de la Torre R, Clin Nutr, 2020). A similar trial for Down's syndrome found improvement in visual recognition memory, inhibitory control and adaptive behaviour (de la Torre R, Lancet Neurol, 2016).
- In AD animal studies, EGCG reduced Aβ plaques, behavioural symptoms and cognitive deficits, improved dendritic integrity and expression levels of synaptic proteins, lowered inflammation through reducing microglia activation, prevented hyperphosphorylation of tau, acetylcholinesterase activity and oxidative stress and reduced mitochondrial dysfunction (Bao J, Curr Med Sci, 2020; Guo Y, Neuroreport, 2017; Biasibetti R, Behav Brain Res, 2013; Dragicevic N, J Alzheimers Dis, 2011; Rasoolijazi H, Iran Biomed J, 2007).
- In animals with diabetes-induced AD, EGCG increased synaptic markers and decreased the unfolded protein response, Aβ production and plaque formation, neuroinflammation and astrocyte reactivity (Ettcheto M, Mol Neurobiol, 2020).
- An *in vitro* study of iron-induced plaque formation in human neurons, EGCG significantly reduced APP (Reznichenko L, J Neurochem, 2006).
- In AD mice, the addition of EGCG to curcumin did not reduce Aβ any further and the authors warn that interactions between nutraceuticals might result in counterproductive outcomes (Sharman MJ, Neurobiol Dis, 2019).

Epigallocatechin-3-gallate (EGCG) for PD

- No human clinical trials.
- Among Singapore Chinese, green tea drinking was unrelated to Parkinson's disease risk (Tan LC, Am J Epidemiol, 2008).
- Nevertheless, *in vitro* studies showed that EGCG prevented α-synuclein aggregation (Xu Y, Neurochem Res, 2016).
- Other studies show neuroprotective effects against oxidative stress, neuroinflammation, protein aggregation, autophagy and neuronal apoptosis, with maintenance of mitochondrial membrane potential, lowering calcium levels and ROS production (Fernandez-Moriano C, Oxid Med Cell Longev, 2015).
- In rodents, EGCG restored impaired movement, protected tyrosine hydroxylase-positive cells in the substantia nigra and reduced inducible nitric oxide synthase expression, immune activation and inflammation. It was neuroprotective against oxidative stress, protein aggregation, autophagy and neuronal cell death, reversed behavioural changes (decreased rotational behaviour, increased locomotor activity), was anti-depressive and improved cognitive dysfunction. (Zhou T, Mol Med Rep, 2018; Renaud J, Rejuvenation Res, 2015; Bitu Pinto N, Evid Based Complement Alternat Med, 2015; Al-Amri JS, Indian J Exp Biol, 2013; Kim JS, J Clin Neurosci, 2010; Guo S, Biol Psychiatry, 2007)
- Insect models show that EGCG could reverse behavioural deficits and improve PD symptoms, dopamine production and neuron survival through modulation of gut bacteria (Xu Y, FASEB J, 2020).

Icariin for AD, dementia and MCI

- No human studies.
- In rodent AD studies, icariin significantly improved spatial learning and memory retention, promoted neuronal cell activity, enhanced ATP production, reversed axon and dendritic atrophy and synaptic loss, reduced neuronal inflammation, APP, Aβ plaque deposition and levels of Aβ42 and protected against neuronal apoptosis and mitochondrial fragmentation (Chen YJ, CNS Neurosci Ther, 2016; Urano T, Phytother Res, 2010; Wu J, Neuroreport, 2020; Li F, Life Sci, 2019; Zhu T, Clin Interv Aging, 2019; Li WX, Pharmacol Biochem Behav, 2015).
- Icariin has been shown to protect against AD by reducing hyperphosphorylation of tau protein, acting as an anti-inflammatory and regulating intracellular calcium homeostasis (Cui Z, Int J Mol Sci, 2016).

Luteolin for AD, dementia and MCI

- No human studies.
- In animals, luteolin could reverse spatial learning and short-term memory dysfunction, microglia over-activation, astrogliosis, neuroinflammation, neuronal insulin resistance and oxidative stress, decrease acetylcholinesterase, hyperphosphorylated tau protein and Aβ deposition and increase synaptic plasticity, BNDF production, choline acetyl transferase levels and antioxidant production

(Yao ZH, Neurochem Res, 2018; Wang H, Mol Med Rep, 2016; Yu TX, Int J Clin Exp Pathol, 2015; Fu X, Pharmacol Biochem Behav, 2014; Liu Y, Behav Brain Res, 2014; Choi JS, Arch Pharm Res, 2014; Sawmiller D, Int J Mol Sci, 2014; Xu B, Eur J Pharmacol, 2010).

Naringin/Naringenin for AD, dementia and MCI

- No human studies.
- A 2017 meta-analysis of the use of naringin for oxidative stress-induced neurological disorders in rodents found that it could significantly inhibit physical- and chemical-induced neurological disturbances mediated through oxidative stress and restored levels of brain oxidative and nitrosative free radicals, enzymes and mitochondrial complexes (Viswanatha GL, Biomed Pharmacother, 2017).
- Specifically, naringin can improve learning and memory, increase antioxidant status, insulin signalling and mitochondrial Complex I, II and III activity, upregulate AMPK and reduce neuronal oxidative stress, inflammation, acetylcholinesterase activity and apoptosis (Liu X, Iran J Basic Med Sci, 2016; Qi Z, Mol Med Rep, 2015; Wang D, Cell Mol Neurobiol, 2015; Kumar A, Food Chem Toxicol, 2010; Mahdavinia M, Int J Mol Cell Med, 2019; Sachdeva AK, Pharmacol Biochem Behav, 2014).
- Naringenin can also improve learning, memory and mitochondrial function and lower tau hyperphosphorylation, Aβ deposition, oxidative stress, neuronal inflammation and apoptosis in rodents with induced AD, dementia or cognitive impairment (Ghofrani S, Eur J Pharmacol, 2015; Yang W, Neurol Sci, 2014; Krishna Chandran AM, Environ Toxicol Pharmacol, 2019; Hua FZ, Int J Mol Med, 2016; Khan MB, Neurochem Int, 2012)

Nobiletin for AD, dementia and MCI

- No human studies.
- *In vitro* studies showed that in neurons with induced AD, nobiletin upregulated neprilysin, an Aβ peptide-degrading enzyme, and decreased intraneuronal Aβ content (Kimura J, Biol Pharm Bull, 2018).
- In cognitively impaired rodents, nobiletin improved cognitive function (learning and short-term and recognition memory), reduced soluble Aβ levels, hippocampal plaques and tau phosphorylation and had antioxidant, anti-inflammatory and anti-apoptotic effects (Bi J, Mol Med Rep, 2016; Nakajima A, Behav Brain Res, 2015; Nakajima A, Behav Brain Res, 2013; Onozuka H, J Pharmacol Exp Ther, 2008).

Quercetin for AD, dementia and MCI

- In early-stage AD patients, quercetin-rich onion powder for 4 weeks significantly improved memory recall (Nakagawa T, Neuroreport, 2016).
- In a population study of healthy individuals, quercetin had no effect on cognitive functioning (Broman-Fulks JJ, Ther Adv Psychopharmacol, 2012).
- A 2020 systematic review of studies of animals with induced AD showed that quercetin was neuroprotective (Zhang XW, Int J Mol Sci, 2016).
- In addition, quercetin given to aged, AD or cognitively impaired rodents reduced learning and memory deficits, ROS production, Aβ42 cytotoxicity, senile plaques, phosphorylated tau-mediated neurofibrillary tangles, neuronal apoptosis and oxidative stress, including from AGEs. It also restored neuroplasticity, mitochondrial membrane potential and ATP levels through upregulating PGC-1α, AMPK and Nrf2. (Wang DM, Neurochem Res, 2014; Ansari MA, J Nutr Biochem, 2009; Aggarwal A, J Nutr Biochem, 2020; Qi Y, Drug Deliv, 2020; Yang S, J Food Biochem, 2020; Li YL, Mol Med Rep, 2017; Wang D, Nutr Neurosci, 2018)

Quercetin for PD

- No human studies.
- In rodents, quercetin attenuated induced motor deficits, balance and coordination, behavioural impairment, spatial memory and biochemical and neurotransmitter alterations, augmented autophagy and reduced apoptosis and oxidative stress. It also reversed cognitive impairment, striatal dopamine depletion and loss of tyrosine hydroxylase and other neuronal cells and protected against toxin-induced mitochondrial defects, lowering ROS production and maintaining membrane potential. (Sharma S, Neurotox Res, 2020; Ay M, J Neurochem, 2017; El-Horany HE, J Biochem Mol Toxicol, 2016; Karuppagounder SS, Neuroscience, 2013; Lv C, Evid Based Complement Alternat Med, 2012; Sriraksa N, Evid Based Complement Alternat Med, 2012; Fernandez-Moriano C, Oxid Med Cell Longev, 2015) However, 1 study showed that quercetin had no effect on tyrosine hydoxylase-positive cells or dopamine levels (Zbarsky V, Free Radic Res, 2005)
- *In vitro* studies showed that quercetin glycosides upregulated the tyrosine hydroxylase gene (important in dopamine biosynthesis) but did not affect its expression; they also upregulated ion transport and antiapoptotic genes (J Mol Neurosci, 2015).
- Quercetin combined with piperine significantly enhanced the neuroprotective, antioxidant and anti-inflammatory effect in rats compared with quercetin alone (Sharma S, Neurotox Res, 2020).
- Quercetin with omega-3 fish oil was more neuroprotective than either alone. The combination attenuated behavioural impairments, reduced oxidative stress and restored dopamine levels in the striatum (Denny Joseph KM, Neurochem Res, 2015).

Resveratrol for AD, dementia and MCI

- A 2018 meta-analysis of RCTs found that resveratrol had a significant effect on delayed recognition and negative mood but not on any other cognitive measures, while another found that resveratrol had no significant impact on factors related to memory and cognitive performance, including learning ability, delayed recall, retention, and recognition, but had the potential to enhance mood (Marx W, Nutr Rev, 2018; Farzaei MH, Pharmacol Res, 2018).
- Since then an RCT of 1000mg/day for 90 days given to sedentary, older adults showed improved psychomotor speed but no improvement in other cognitive measures; a dose of 300mg/day had no effect (Anton SD, J Altern Complement Med, 2018), while in postmenopausal women, 150mg/day trans-resveratrol for 12 months resveratrol improved overall cognitive performance and attenuated the decline in cerebrovascular responsiveness to cognitive stimuli (Thaung Zaw JJ, Nutrients, 2020).
- An RCT of subjects with mild-moderate AD given 10g/day resveratrol, dextrose and malate for 12 months showed improvements in all AD scores but these were not significantly different from the control group (Zhu CW, Alzheimers Dement, 2018). [Note the very small resveratrol dose]
- In subjects with MCI, 200 mg/day resveratrol for 26 weeks induced no improvement in memory but hippocampal resting-state functional connectivity was improved, leading to moderate preservation of left anterior hippocampus volume (Köbe T, Front Neurosci, 2017). In healthy adults resveratrol (250 or 500mg) induced dose-dependent increases in cerebral blood flow during task performance (Kennedy DO, Am J Clin Nutr, 2010).
- An RCT of older adults with normal cognitive function given 3000mg/day omega-3 PUFAs, 10µg/day vitamin D3, 150mg/day resveratrol and 8g/day whey protein isolate for 6 months showed no significant difference in overall cognitive function, although there were improvements in task completion time (Moran C, J Prev Alzheimers Dis, 2018).
- A 2019 systematic review of animal studies showed that resveratrol demonstrated consistent neuroprotective effects in AD models, confirmed by a further 2020 review and can improve cognition in vascular dementia by reducing oxidative stress (Chen JY, Pharmacol Res, 2019; Sousa JCE, Arq Neuropsiquiatr, 2020; Ma X, Neural Regen Res, 2013; Gocmez SS, Physiol Behav, 2019).

Genistein for AD, dementia and MCI

- In children with San Fillipo disease (a genetic metabolism disorder in which the body is unable to break down certain carbohydrates, leading to serious developmental disability), genistein administered for 1 year could inhibit or slow behavioral and cognitive problems after a further 2 years (Piotrowska E, Med Sci Monit, 2011).
- In middle-aged Asian women, dietary intake of genistein up to 6,788mcg/day showed no associations with measures of cognitive performance (Huang MH, Menopause, 2006).
- In AD rodent studies, a high dose of genistein activated autophagy, degraded neuronal Aβ and hyperphosphorylated tau protein and improved behaviour to the level of healthy animals (Pierzynowska K, Neuropharmacology, 2019). Other studies of rodents with AD or or cognitive impairment showed similar results, with decreased neuronal apoptosis, inflammation and ROS generation, increased antioxidant production and improved learning and memory (Ye S, Neural Regen Res, 2017; Wang Y, Neural Regen Res, 2016; Bagheri M, Neurobiol Learn Mem, 2011; Lee B, J Med Food, 2020; Lu C, Phytother Res, 2020; López P, Mol Nutr Food Res, 2018; Mirahmadi SM, Cytokine, 2018).
- However 1 study showed that tofu ingestion itself leads to cognitive impairment through accumulation of APP (Chatterjee G, Aging Dis, 2015).

Puerarin for AD, dementia and MCI

- No human studies.
- In animal models of AD, dementia or cognitive impairment, puerarin enhanced memory and learning, increased number of hippocampal cells, decreased Aβ levels, expression of phosphorylated tau, oxidative stress, neuronal inflammation, apoptosis, hypoxia inducible factor-1α, erythropoietin and endothelial nitric oxide synthase and protected neurons (Zhang H, Exp Gerontol, 2011; Wang HQ, Chin J Integr Med, 2018; Zhang J, Int J Clin Exp Pathol, 2015; Wu H, Neural Regen Res, 2012; Tao J, Oncotarget, 2017; Mei ZR, Zhongguo Zhong Yao Za Zhi, 2016; Liu X, Metab Brain Dis, 2016).
- In an AD rodent model, puerarin is able to penetrate the blood brain barrier, inhibit acetylcholinesterase activity and restore antioxidant defences through induction of Nrf2 (Liu S, Food Funct, 2019; Zhou Y, Int J Neuropsychopharmacol, 2014).