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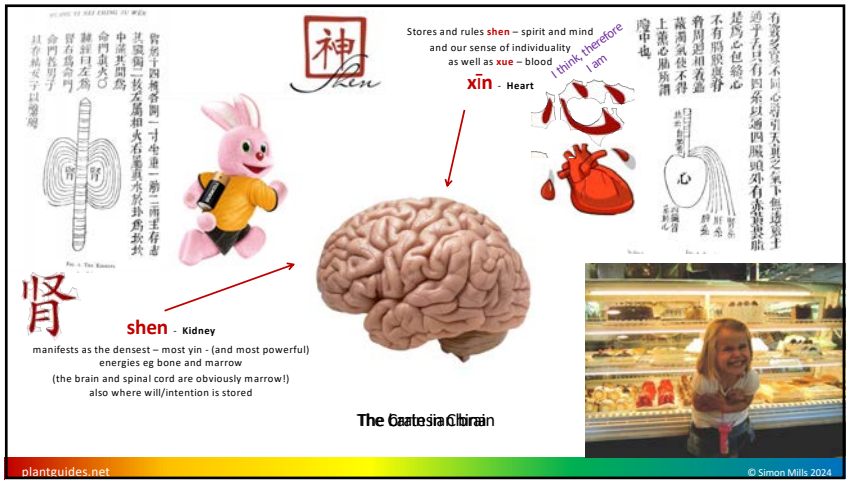

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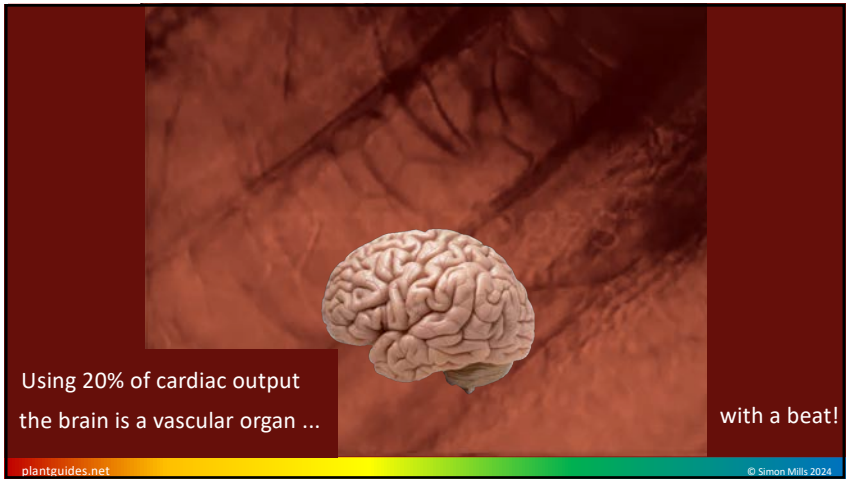

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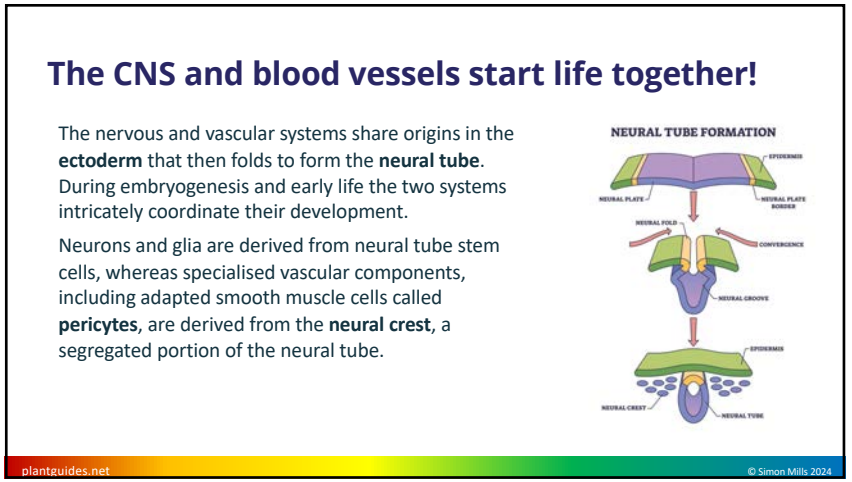
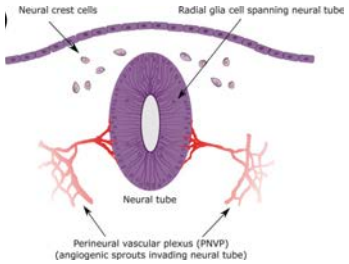


8

The CNS and blood vessels start life together!

In an early form of **angiogenesis** vessel sprouts invade the developing brain and spinal cord from the outset. Here they migrate alongside neural progenitor cells (**radial glia**) that form long cell extensions along the neural tube.

Radial glial cells mitose into daughter cells that differentiate into **neurons**, **microglia**, the macroglia **astrocytes** and **oligodendrocytes** and **ependymal cells**. Invading vessel sprouts form interconnections with these new cells.



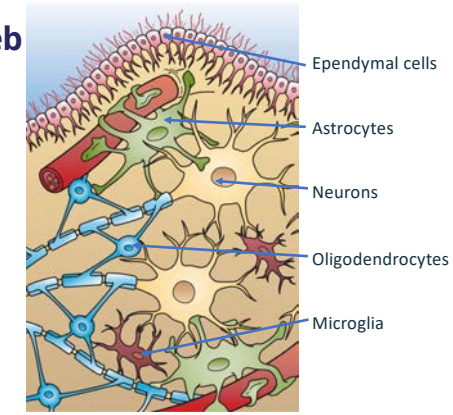
Vogenstahl J et al. Vascular Regulation of Developmental Neurogenesis. *Front Cell Dev Biol*. 2022;10:890852. doi: 10.3389/fcell.2022.890852

9

The neurovascular web

All CNS glial cells continue through adult life to form a web that intimately connects neurons and vascular cells.

There's a lot of hand holding in there!



10

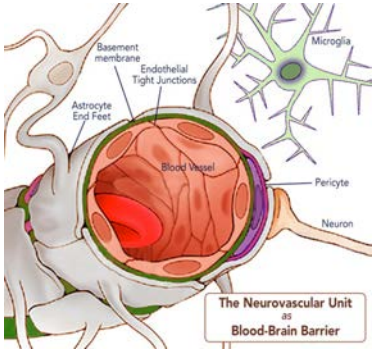
The frontline: the neurovascular unit

***aka*: the blood-brain barrier**

To deliver that 20% of cardiac output to neuronal and glial cells, the mammalian brain uses the neurovascular unit (NVU), a cell complex that connects the brain tissues to the cerebral endothelium.

This is also the key interface between the brain and body.

It is not a simple barrier!



Ward NL & Lamanna JC. The neurovascular unit and its growth factors: coordinated response in the vascular and nervous systems. *Neurol Res*. 2004; 26(8): 870-83. doi: 10.1179/016164104X3798

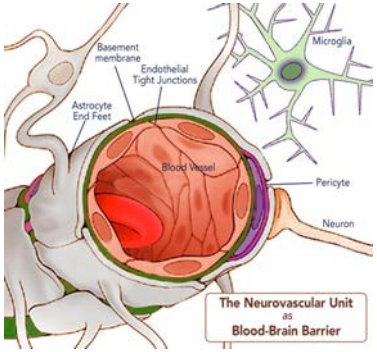
11

The frontline: the neurovascular unit

***aka*: the blood-brain barrier**

Instead the NVU is a **dynamic regulatory interface between the central nervous, vascular and immune systems**.

When provoked it transports cytokines and other inflammatory substances and even allows diapedesis of immune cells into the CNS. This is a key factor in 'neuroinflammation' in which microglia and other glial cells are activated and become disruptive.



Erickson MA, Dohi K, Banks WA. (2012) Neuroinflammation: a common pathway in CNS diseases as mediated at the blood-brain barrier. *Neuroimmunomodulation*. 19(2): 121-30. PMID: 22248728

12

The frontline: the neurovascular unit

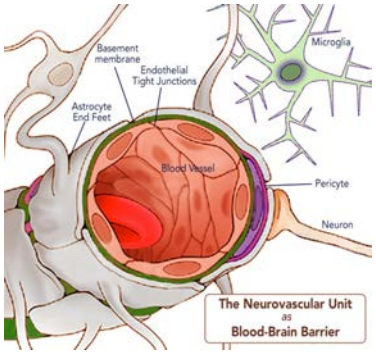
aka: the blood-brain barrier

BBB permeability increases with age.

It is further increased

- in patients with both vascular or Alzheimer's dementia
- in neuroinflammatory disorders

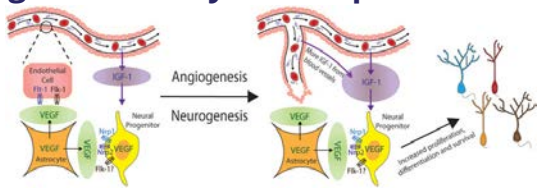
Brain problems start as vascular problems!



Erickson MA, Dohi K, Banks WA. (2012) Neuroinflammation: a common pathway in CNS diseases as mediated at the blood-brain barrier. *Neuroimmunomodulation*. 19(2): 121-30. PMID: 22248728

13

Angiogenesis always accompanies neurogenesis



Healthy angiogenesis remains an essential feature of neurogenesis through into late life, spurred by **endothelial** trophic factors, including brain-derived neurotrophic factor (BDNF), matrix metalloproteinases (MMPs), and notably **vascular endothelial growth factor (VEGF).**

In 'niche' neurogenesis regions the BBB is incomplete, with gaps between pericytes and astrocytic endfeet to allow **direct contact by neural stem cells with the endothelium.**

Kim TA et al. The interplay of neurovasculature and adult hippocampal neurogenesis. *Neurosci Lett*. 2021; 760: 136071. doi: 10.1016/j.neulet.2021.136071

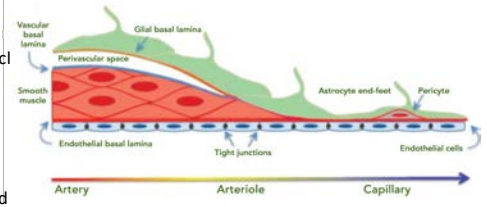
Sawada M et al. Vascular regulation of adult neurogenesis under physiological and pathological conditions. *Front Neurosci*. 2014; 8:53. doi: 10.3389/fnins.2014.00053

14

The glymphatic system

The brain has no lymphatic circulation, so waste metabolites (incl β-amyloid) are picked up by the cerebrospinal fluid (CSF).

CSF enters the brain parenchyma alongside capillaries (in perivascular spaces formed by astroglial cells) and that brain interstitial fluid is cleared along paravenous drainage pathways.



Besides waste elimination, the glymphatic system also facilitates brain-wide distribution of several compounds, including glucose, lipids, amino acids, growth factors, and neuromodulators.

It is most active during **sleep!**

Hablitz LM, Nedergaard M. (2021) The Glymphatic System: A Novel Component of Fundamental Neurobiology. *J Neurosci*. 41(37): 7698-7711. PMID: 34526407

15

PlantGuides

There is however a counter view to the vascular approach to brain health

16

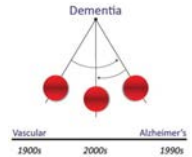
The Dementia Pendulum

In 1901 Dr Alois Alzheimer identified a distinctive case of senile dementia, with the assumption that it was caused by 'hardening of the arteries' (arteriosclerotic dementia). Vascular factors were considered the main cause of dementia well into the 20th century.

In the 1980s amyloid deposits were identified as critical elements of Alzheimer's disease, with amyloid beta (Aβ) peptide as the main component. Shortly after, mutations in the amyloid precursor protein (APP) gene were identified in familial forms of AD.

Since then, the emphasis has shifted away from vascular dementia: the "Alzheimerization of dementia."

Most dementia cases have mixed pathology, with amyloid plaques and neurofibrillary tangles as well as ischaemic lesions. Vascular factors are contributory to all.



Iadecola C. The pathobiology of vascular dementia. *Neuron*. 2013; 80(4): 844-66. doi: 10.1016/j.neuron.2013.10.008

Cortes-Canteli M, Iadecola C. Alzheimer's Disease and Vascular Aging: JACC Focus Seminar. *J Am Coll Cardiol*. 2020;75(8): 942-951. doi: 10.1016/j.jacc.2019.10.062

Neuropathology Group. Medical Research Council Cognitive Function and Aging Study. *Pathological correlates of late-onset dementia in a multicentre, community-based population in England and Wales. Lancet*. 2001; 357(9251): 169-75. doi: 10.1016/s0140-6736(00)03589-3

17

The Amyloid Mafia?

"the potential to mislead an entire field of research"

BLOTS ON A FIELD?

A neuroscience image sleuth finds signs of fabrication in scores of Alzheimer's articles, threatening a reigning theory of the disease By Charles Piller

In August 2021, Matthew Schrag, a neuroscientist and physician at Vanderbilt University, got a call that would plunge him into a maelstrom of possible scientific misconduct. A colleague wanted to connect him with an attorney investigating an experimental drug for Alzheimer's disease called Simufilam. The drug's developer, Cassava Sciences, claimed it improved cognition, partly by repairing a protein that can block sticky brain deposits of the protein amyloid beta (Aβ), a hallmark of Alzheimer's. The attorney's clients—two prominent neuroscientists who are also short sellers who profit if the company's stock falls—believed some research related to Simufilam may have been "fraudulent," according to a petition later filed on their behalf with the U.S. Food and Drug Administration (FDA).

Schrag, 37, a softspoken, nonchalantly rumpled junior professor, had already gained some notoriety by publicly criticizing the controversial FDA approval of the anti-Aβ drug Aduhelm. His own research also contradicted some of Cassava's claims. He feared volunteers in ongoing Simufilam trials faced risks of side effects with no chance of benefit.

So he applied his technical and medical knowledge to interrogate published images about the drug and its underlying science—for which the attorney paid him $18,000. He identified apparently altered or duplicated images in dozens of journal articles. The attorney reported many of the discoveries in the FDA petition, and Schrag sent all of them

Neuroscientist and physician Matthew Schrag found suspect images in dozens of papers involving Alzheimer's disease, including Western blots (projected in green) measuring a protein linked to cognitive decline in rats.

358 22 JULY 2022 • VOL 377 ISSUE 6604

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18

The Dementia Pendulum

The criteria for diagnosis of both vascular dementia and AD include memory impairment, irreversibility of the deficits, and impaired activities of daily living.

Cerebrovascular lesions have additional cognitive deficits such as executive dysfunction and psychomotor slowing >>

'Vascular cognitive impairment' (VCI) was introduced to better reflect the full range of cognitive alterations resulting from vascular factors: "*a syndrome with evidence of clinical stroke or subclinical vascular brain injury and cognitive impairment affecting at least one cognitive domain*".

Vascular dementia is the most severe form of VCI.

Gorelick PB et al. Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2011; 42(9): 2672-713. doi: 10.1161/STR.0b013e3182299496

19

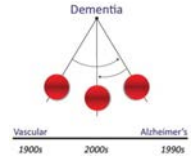
The Dementia Pendulum

'Cerebral microvascular pathology precedes and accompanies age-related cognitive dysfunction and neurodegeneration'.

Brown WR & Thore CR. Review: cerebral microvascular pathology in ageing and neurodegeneration. *Neuropathol Appl Neurobiol*. 2011; 37(1): 56-74. doi: 10.1111/j.1365-2990.2010.01139.x

Let's swing the pendulum back!

We will find that looking at neuroprotection and neurodegeneration from a vascular perspective can help reconfigure the research effort and point to many promising leads for plants in food and medicine.



Iadecola C. The pathobiology of vascular dementia. *Neuron*. 2013; 80(4): 844-66. doi: 10.1016/j.neuron.2013.10.008

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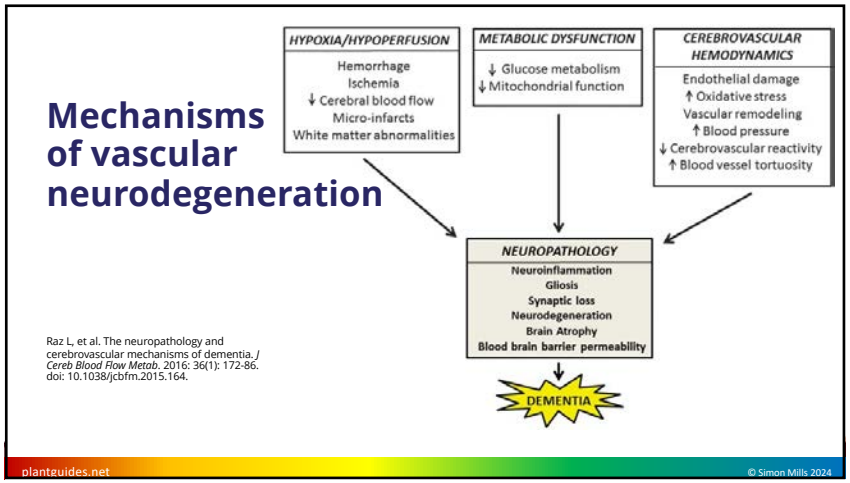

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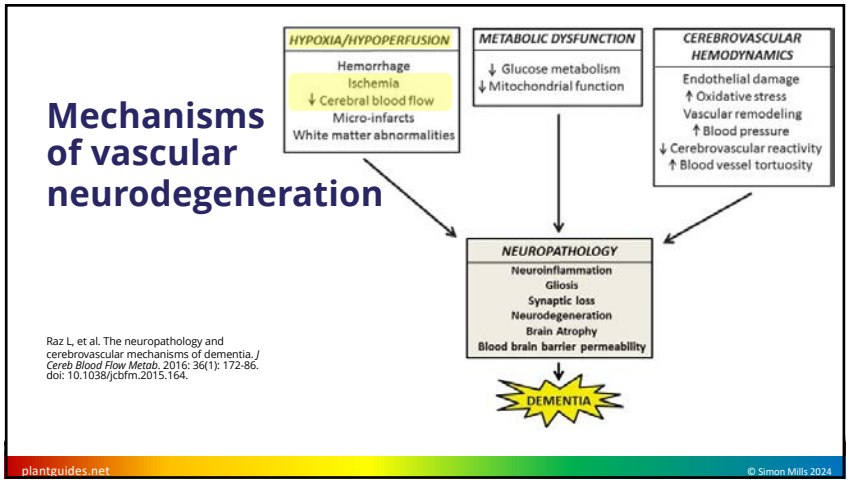

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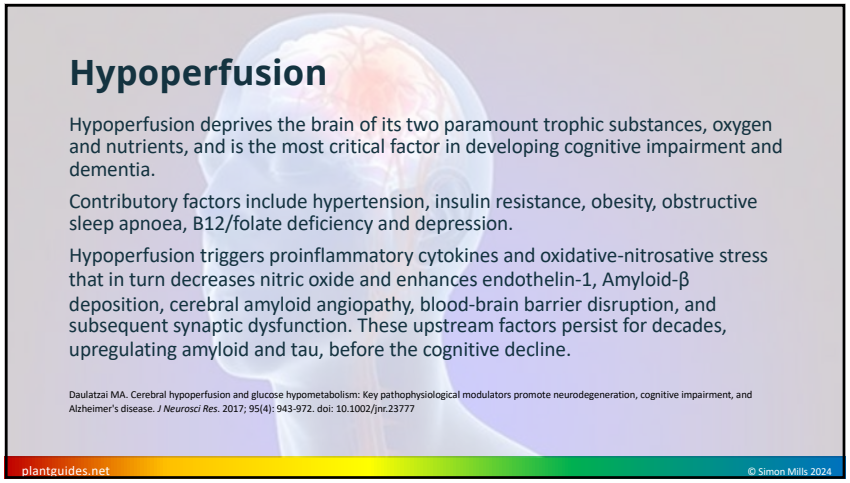


24

Hypoxia as Foe

As the human brain accounts for 20 % of resting oxygen consumption it is exceptionally vulnerable to hypoxia!

Hypoxia is implicated in

- reduced Amyloid-β degradation
- altered expression of A-β precursor, APP
- the secretase enzymes which cleave A-β from APP.

Peers C et al. Hypoxia and neurodegeneration. *Ann N Y Acad Sci*. 2009; 1177: 169-77. doi: 10.1111/j.1749-6632.2009.05026.x

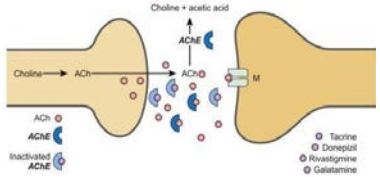
25

Cholinesterase inhibitors?

Chronic hypoperfusion leads to cholinergic deficits. Ischaemia of cholinergic nuclei can result in neuron loss in both vascular dementia and AD.

In vascular dementia (as well as Alzheimer's), cholinergic reductions are correlated with cognitive impairment.

Cholinesterase inhibitors can restore cerebral blood flow.



Kavirajan H & Schneider LS. Efficacy and adverse effects of cholinesterase inhibitors and memantine in vascular dementia: a meta-analysis of randomised controlled trials. *Lancet Neurol*. 2007; 6(9): 782-92. doi: 10.1016/S1474-4422(07)70195-3.

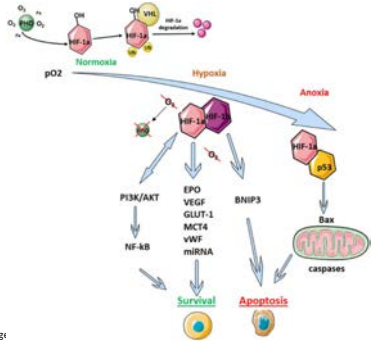
26

Hypoxia Inducible Factors (HIFs)

Cellular responses to hypoxia are associated with a family of transcription factors called hypoxia-inducible factors.

HIF-1α and HIF-1β modulate the expression of genes encoding **vascular endothelial growth factor** (VEGF), erythropoietin and genes that are involved in glucose transport or glycolysis.

In the CNS these genes regulate both neuro**genesis**, nerve cell differentiation, and neuronal **apoptosis**.



Mitroshina EV, et al. Hypoxia-Inducible Factor (HIF) in Ischemic Stroke and Neurodege *Cell Dev Biol*. 2021: 9: 703084. doi: 10.3389/fcell.2021.703084

27

Hypoxia as Friend

However, reducing environmental oxygen can reduce aging and mortality; controlled hypoxia is a treatment strategy for age-related neurological disorders.

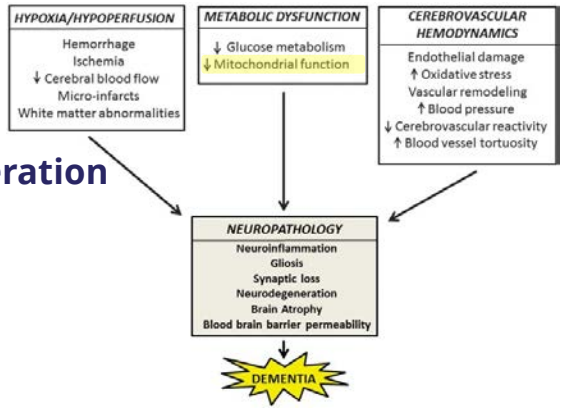
Aerobic metabolism is associated with the production of reactive O_2 species (ROS). Lowering oxygen levels **after** the sustained generation of ROS may be helpful.

The balancing act of avoiding both O_2 deprivation and O_2 toxicity has been compared to Ulysses' perilous navigation between *Scylla* and *Charybdis*.

Burtscher J, et al. Hypoxia and brain aging: Neurodegeneration or neuroprotection? *Ageing Res Rev*. 2021; 68: 101343. doi: 10.1016/j.arr.2021.101343

28

Mechanisms of vascular neurodegeneration



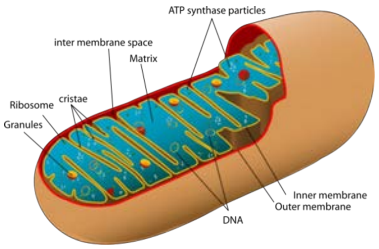
Raz L, et al. The neuropathology and cerebrovascular mechanisms of dementia. *J Cereb Blood Flow Metab*. 2016: 36(1): 172-86. doi: 10.1038/jcbfm.2015.164.

29

Mitochondria

Because of their high energy requirements, neurons are especially vulnerable to injury and death from dysfunctional mitochondria.

Impaired mitochondrial function and dynamics play crucial roles in aging and pathogenesis of neurodegenerative diseases.



Golpich M et al. Mitochondrial Dysfunction and Biogenesis in Neurodegenerative diseases: Pathogenesis and Treatment. *CNS Neurosci Ther*. 2017; 23(1): 5-22. doi: 10.1111/cns.12655

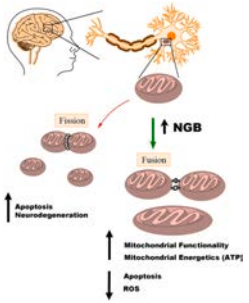
30

Mitochondria and Neuroglobin

Dysfunctional mitochondria generate Reactive Oxygen Species (ROS) and activate apoptotic pathways. The effects on neurons are closely linked with neurodegeneration.

Compensation is provided by **neuroglobin,** related to haemoglobin and myoglobin. This is localised to neuron mitochondria and fuses them for improved performance.

High levels of neuroglobin are protective against brain injuries, including neurodegeneration, hypoxia, ischaemia and nutrient deprivation.



Fiocchetti M et al. Neuroglobin and mitochondria: The impact on neurodegenerative diseases. *Arch Biochem Biophys*. 2021; 701: 108823. doi: 10.1016/j.abb.2021.108823

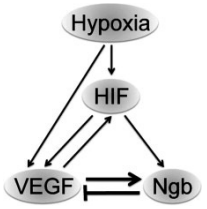
31

Mitochondria and Neuroglobin

Neuroglobin is in a feedback loop with **vascular endothelial growth factor** (VEGF), which promotes angiogenesis, neurogenesis and exerts neuroprotective effects as well as HIF.

This is a joint response to **hypoxia**.

Erythropoietin, produced by interstitial fibroblasts in the kidney under hypoxic conditions, also up-regulates neuroglobin expression in cerebral cortex and hippocampus.

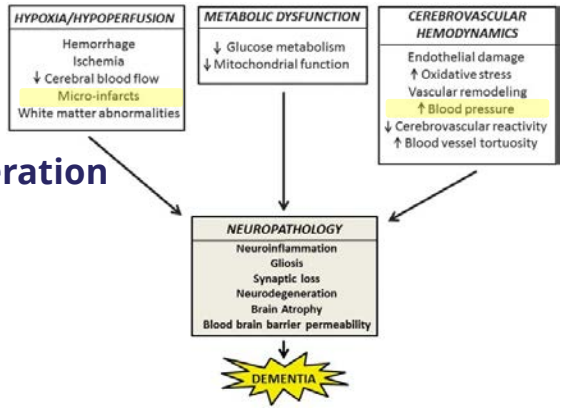


Jin K et al. Interactions between vascular endothelial growth factor and neuroglobin. *Neurosci Lett*. 2012; 519(1): 47-50. doi: 10.1016/j.neulet.2012.05.018.

Fiocchetti M et al. Neuroglobin and mitochondria: The impact on neurodegenerative diseases. *Arch Biochem Biophys*. 2021; 701: 108823. doi: 10.1016/j.abb.2021.108823

32

Mechanisms of vascular neurodegeneration



Raz L, et al. The neuropathology and cerebrovascular mechanisms of dementia. *J Cereb Blood Flow Metab*. 2016; 36(1): 172-86. doi: 10.1038/jcbfm.2015.164.

33

Hypertension

Hypertension is a shared risk factor for Alzheimer's and vascular dementia.

It is associated with significant memory impairments in late life.

Gupta A et al. Mid-life Cardiovascular Risk Impacts Memory Function: The Framingham Offspring Study. *Alzheimer Dis Assoc Disord*. 2015; 29(2): 117-23. doi: 10.1097/WAD.0000000000000059.

Pires PW, et al. The effects of hypertension on the cerebral circulation. *Am J Physiol Heart Circ Physiol*. 2013; 304(12): H1598-614. doi: 10.1152/ajpheart.00490.2012.

34

Hypertension

High BP may provoke **micro-infarcts** in the brain.

In a widescale autopsy study the presence of more than two microinfarcts, but no other pathological change, was independently associated with systolic BP in participants aged 65-80, but not in older participants.

- ***Significant associations were not observed in participants being successfully treated for hypertension***.

Wang LY, et al. Blood pressure and brain injury in older adults: findings from a community-based autopsy study. *J Am Geriatr Soc*. 2009; 57(11): 1975-81. doi: 10.1111/j.1532-5415.2009.02493.x.

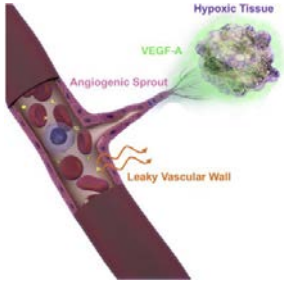
35

Vascular Endothelial Growth Factor (VEGF)

In the brain, VEGF is a key regulator of angiogenesis and neurogenesis, and in the recovery from stroke VEGF has a neuroprotective effect.

However, when over activated in acute damage it leads to increased BBB permeability and neuroinflammation.

Because it also leads to angiogenesis in cancer most pharmaceutical research has been into anti-VEGF agents!



Pauty J et al.. EBioMedicine. 2018; 27:225-236. doi: 10.1016/j.ebiom.2017.12.014.

Geiseler SJ & Morland C. The Janus Face of VEGF in Stroke. *Int J Mol Sci*. 2018; 19(5): 1362. doi: 10.3390/ijms19051362

36

Nitric Oxide (NO)

Endothelium-derived NO is key to neurogenesis by modulating the proliferation of progenitor neurons. However it also has two sides to its activity.

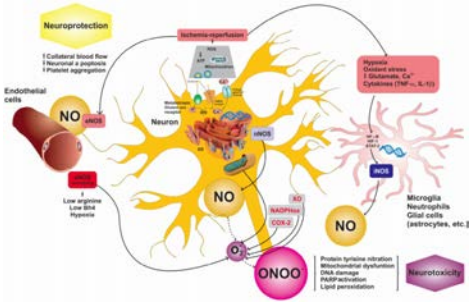
- It is a mediator of blood vessel dilation with antihypertensive, antithrombotic, anti-atherosclerotic and anti-obesogenic properties.
- On the other hand elevated production of NO, with increased nitrosative/oxidative stress, is a feature of many pathologies, such as neurodegenerative diseases, inflammation, and ischemia,
- Nitric oxide synthase (NOS) is therefore a pharmaceutical target.

Matarredona ER, et al. Role of nitric oxide in subventricular zone neurogenesis. *Brain Res Brain Res Rev.* 2005; 49(2): 355-66. doi: 10.1016/j.brainresrev.2005.01.001

Tewari D et al. Role of Nitric Oxide in Neurodegeneration: Function, Regulation, and Inhibition. *Curr Neuropharmacol.* 2021; 19(2):114-126. doi: 10.2174/1570159X18666200429001549

37

Nitric Oxide (NO)



Tewari D et al. Role of Nitric Oxide in Neurodegeneration: Function, Regulation, and Inhibition. *Curr Neuropharmacol.* 2021; 19(2):114-126. doi: 10.2174/1570159X18666200429001549

38

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So what do we need to do?

39

A New Research Agenda?

Previous dementia research has identified promising leads. However there remain bioavailability and other challenges, and few breakthroughs.

Can we take a more accessible starting point, looking at the strong evidence for vascular impacts on neurodegeneration and leverage the emerging effect of plants on these?

This will work even better if we can identify dietary influences.

A new focus?

➢ **plants that could**

- **reduce hypoperfusion**
- **moderate hypoxia**
- **maintain endothelial and BBB integrity**
- **reduce insulin resistance**
- **support mitochondria/neuroglobin**
- **reduce cholinesterase activity**
- **mobilise microbiome-gut-brain axis?**

40

Striking a balance – the hormetic zone

Physiological concentrations of an agent above or below homeostasis may adversely affect an organism, where the hormetic zone is a region of balanced nutrition. In pharmacology the hormetic zone is the therapeutic window.

In relation to brain health we have seen that key influences can be either helpful or harmful:

- hypoxia
- mitochondria
- HIF-1α / VEGF
- NO

Fortunately there is evidence that plant and dietary ingredients which impact on these influences can strike the right balance:

- their consumption has already been associated with improved long term brain health
- they appear evolutionarily to find the 'hormetic zone' between dangerous or ineffective biphasic responses

Calabrese, E.J., Mattson, M.P. (2017) How does hormesis impact biology, toxicology, and medicine?. *npj Aging Mech Dis* 3, 13 doi.10.1038/s41514-017-0013-zx

41

Lifestyle and Neurogenesis

Multiple studies have demonstrated the relation of diet and exercise with cognition in aging.

- Calorie restriction can influence brain plasticity and preclude the decline of memory.
- Exercise can increase brain-derived growth factor (BDGF) and vascular endothelial growth factor (VEGF) to enhance brain plasticity and neurogenesis.

Maharjan R et al. Role of Lifestyle in Neuroplasticity and Neurogenesis in an Aging Brain. *Cureus*. 2020; 12(9): e10639. doi: 10.7759/cureus.10639.

42

Diet and Neurogenesis

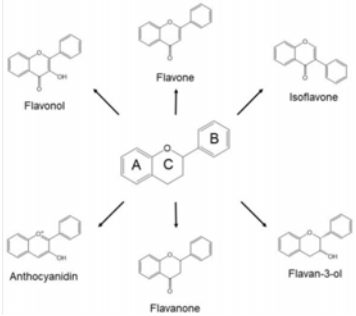
Many dietary components such as curcumin, resveratrol, blueberry polyphenols, sulforaphane, polyunsaturated fatty acids (PUFAs), and diets enriched with polyphenols and PUFAs have been shown to induce neurogenesis in adult brains.

Poulose SM et al. Nutritional Factors Affecting Adult Neurogenesis and Cognitive Function. *Adv Nutr.* 2017; 8(6): 804-811. doi: 10.3945/an.117.016261 .

Lewis JE, et al. The effects of twenty-one nutrients and phytonutrients on cognitive function: A narrative review. *J Clin Transl Res*. 2021; 7(4): 575-620. PMID: 34541370

43

Polyphenols



There is evidence to suggest that flavonoids and other shikimate derivatives may be capable of preventing many forms of cerebrovascular disease, including those associated with stroke and dementia, with powerful evidence for the beneficial effects of flavonoids on **endothelial function and peripheral blood flow**.

Vauzour D et al.The neuroprotective potential of flavonoids: a multiplicity of effects. *Genes Nutr.* 2008; 3(3-4): 115-26. doi: 10.1007/s12263-008-0091-4

44

Polyphenols

1. enhance the production of vasodilating factors: NO, endothelium-derived hyperpolarizing factor (EDHF) and prostacyclin
2. inhibit the synthesis of vasoconstrictor endothelin-1 in endothelial cells; and
3. inhibit the over expression of two major pro-angiogenic factors, VEGF and MMP-2 in smooth muscle cells.

Stoclet JC et al. Vascular protection by dietary polyphenols. *Eur J Pharmacol.* 2004; 500(1-3): 299-313. doi: 10.1016/j.ejphar.2004.07.034

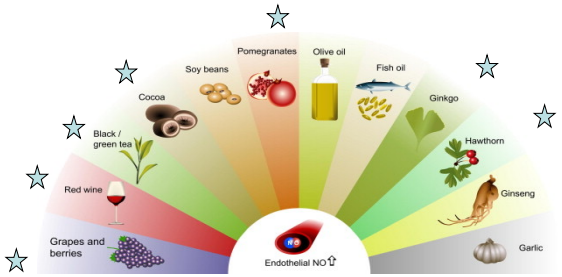
One proposition is that flavonols (notably metabolites of (-)-catechin from green tea) increase endothelial NO levels with reduction in NADPH oxidase activity.

A moderate level of endothelial NADPH oxidase is essential for angiogenesis and wound healing, but risks endothelial dysfunction when upregulated by proinflammatory agonists. Dietary polyphenols may contribute to maintain safe NADPH oxidase activity.

Schewe T et al. How do dietary flavanols improve vascular function? A position paper. *Arch Biochem Biophys.* 2008; 476(2): 102-6. doi: 10.1016/j.abb.2008.03.004

45

Polyphenols Say NO!



Schmitt CA , Dirsch VM. *Nitric Oxide* 2009; **21**(2): 77 - 91

☆ Predominately polyphenols

46

Polyphenols

Flavonoids demonstrate direct benefits on neural **mitochondria** and **neuroglobin** activity.

Fiocchetti M, et al. Neuroglobin and mitochondria: The impact on neurodegenerative diseases. *Arch Biochem Biophys.* 2021; 701: 108823. doi: 10.1016/j.abb.2021.108823

Schaffer S et al. Effects of polyphenols on brain ageing and Alzheimer's disease: focus on mitochondria. Mol Neurobiol. 2012; 46(1): 161-78. doi: 10.1007/s12035-012-8282-9.

Polydatin, genistein, daidzein, biochanin A, and formononetin upregulate human neuroglobin (Ngb) promoter activity, increasing Ngb mRN expression in primary neurons.

The flavonoid naringenin and the stilbene resveratrol up-regulate Ngb levels and increase its levels in mitochondria of human neuroblastoma cells.

Sandoval-Acuña C et al. Polyphenols and mitochondria: an update on their increasingly emerging ROS-scavenging independent actions. *Arch Biochem Biophys.* 2014; 559: 75-90. doi: 10.1016/j.abb.2014.05.017

47

Polyphenols

However many polyphenols do not reach the CNS, and it will be worth considering indirect ways in which they could influence brain structure and function.

Schaffer S & Halliwell B Do polyphenols enter the brain and does it matter? Some theoretical and practical considerations. *Genes Nutr* 2012; 7: 99-109 doi: 10.1007/s12263-011-0255-5

Productive crosstalk in the gut?

Polyphenols interact with intestinal microbiota to activate SCFA production, intestinal immune function, and other protective physiological processes.

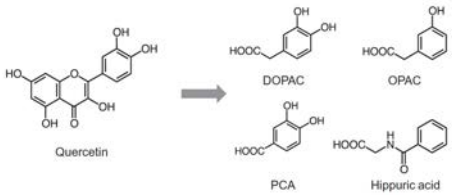
Kawabata K, et al. Role of Intestinal Microbiota in the Bioavailability and Physiological Functions of Dietary Polyphenols. *Molecules.* 2019; 24(2): 370. doi: 10.3390/molecules24020370.

"This interplay provides the central explanation as to the stupefying pleiotropic biological/clinical actions and functions of "parent'' polyphenols even though their systemic bioavailability is incredibly limited"

Koudoufio M et al. Insight into Polyphenol and Gut Microbiota Crosstalk: Are Their Metabolites the Key to Understand Protective Effects against Metabolic Disorders? *Antioxidants (Basel).* 2020; 9(10):982. doi: 10.3390/antiox9100982.

48

Polyphenols



Murota K et al. Flavonoid metabolism: the interaction of metabolites and gut microbiota. *Biosci Biotechnol Biochem.* 2018; 82(4): 600-610. doi: 10.1080/09168451.2018.1444467.

The microbiome metabolises non-absorbable polyphenol molecules to more available simple phenolics.

Quercetin is 'C-ring cleaved' to bioactive simple phenols which strongly inhibit the formation of advanced glycation end-products and oxidative stress-induced neuronal cell death.

49

Plants to watch ...

Tea

Although a large number of studies have shown that tea polyphenols have neuroprotective and neurogenerative effects, they have low bioavailability *in vivo*. However, tea flavanols (such as epigallocatechin gallate - EGCG) are metabolised by gut microbiota into metabolites (eg **g-valerolactones**) with significant neuroprotective effects.

Tea polyphenols and their metabolites may also provide neuroprotective benefits by restoring dysbiosis.

Zhang Z et al. The Neuroprotective Effect of Tea Polyphenols on the Regulation of Intestinal Flora. *Molecules.* 2021; 26(12): 3692. doi: 10.3390/molecules26123692.

Murota K et al. Flavonoid metabolism: the interaction of metabolites and gut microbiota. *Biosci Biotechnol Biochem.* 2018; 82(4): 600-610. doi: 10.1080/09168451.2018.1444467

50

Plants to watch ...

Cocoa

Cocoa contains very high quantities of flavon-3-ol catechins and epicatechins, along with theobromine, an alkaloid with vasodilative properties.

The stereoisomer (−)-epicatechin is relatively well absorbed, readily crosses the blood-brain barrier, and can be detected in the brain.

Cognitive benefit has been seen in human trials and may derive from **improved vascular function** and neurovascular coupling that result in better cerebral blood flow, **insulin resistance, blood pressure**, interactions with signalling pathways linked to neurogenesis and neuroprotection, and reductions in neural inflammation.

Baker LD, et al; COSMOS-Mind Research Group. Design and baseline characteristics of the cocoa supplement and multivitamin outcomes study for the Mind: COSMOS-Mind. *Contemp Clin Trials.* 2019; 83: 57-63. doi: 10.1016/j.cct.2019.06.019

51

Plants to watch ...

Grapes (and Resveratrol)

Resveratrol has confirmed **NO-mediated** vasodilatory and endothelial protective activity.

Access to brain and through the BBB has been established for major resveratrol **metabolites** reservatrol-3-sulfate and resveratrol-3-O-glucuronide.

Studies suggest that resveratrol may improve cognitive performance and delay the onset of cognitive impairment and dementia through control of peripheral **glucose** metabolism.

Studies also suggest that grape polyphenols other than resveratrol may also exert neurological health benefits.

Xia N et al. Resveratrol and endothelial nitric oxide. *Molecules.* 2014; 19(10): 16102-21. doi: 10.3390/molecules191016102

Pasinetti GM et al. Roles of resveratrol and other grape-derived polyphenols in Alzheimer's disease prevention and treatment. *Biochim Biophys Acta.* 2015; 1852(6): 1202-8. doi: 10.1016/j.bbadis.2014.10.006.

52

Plants to watch ...

Soy

Soya isoflavone daidzein is metabolised by gut microbiota to **S-equol**. This is the most **antiatherogenic** of isoflavones.

Several short-duration RCTs document that soy isoflavones improve arterial stiffness. The evidence associates both atherosclerosis and arterial stiffness with cognitive decline and dementia and points to the benefit of S-equol especially in preventing these.

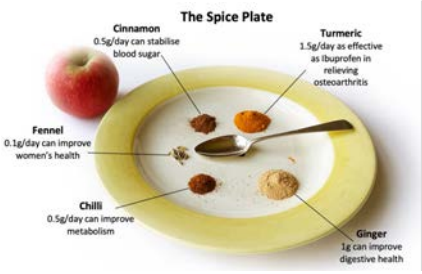
Sekikawa A, et al. Effect of S-equol and Soy Isoflavones on Heart and Brain. *Curr Cardiol Rev*. 2019; 15(2): 114-135. doi: 10.2174/1573403X15666181205104717

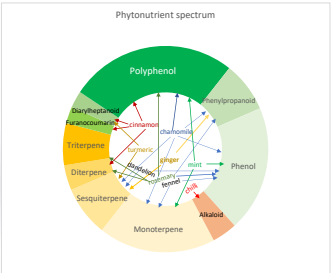
53

Kannappan R et al. Neuroprotection by spice-derived nutraceuticals: you are what you eat! *Mol Neurobiol*. 2011; 44(2): 142-59. doi: 10.1007/s12035-011-8168-2.

Spices

Culinary spices pack more phytochemical power (and circulatory stimulation!) than other plants and their consumption is widely associated with neuroprotective benefits.





54

Plants to watch ...

Ginger

The most widely used circulatory stimulant in human history!

Constituents with **cholinesterase-inhibiting** and neuroprotective properties have been shown to cross the BBB.

Preliminary studies show improvements in cognitive functions, including a dose-dependent effect in a placebo-controlled study of a standardized ginger extract.

Arcusa R et al. Potential Role of Ginger (*Zingiber officinale* Roscoe) in the Prevention of Neurodegenerative Diseases. *Front Nutr*. 2022; 9: 809621. doi: 10.3389/fnut.2022.809621.

Schepici G et al. Ginger, a Possible Candidate for the Treatment of Dementias? *Molecules*. 2021; 26(18): 5700. doi: 10.3390/molecules26185700.

55

Plants to watch ...

Turmeric

A range of studies shows oral curcumin consumption improved cognitive performance and increased neurogenerative activity.

For example, elderly Singaporeans who ate curry with turmeric had higher Mini Mental State Examination scores than those who ate the curry without turmeric.

Sarker MR & Franks SF. Efficacy of curcumin for age-associated cognitive decline: a narrative review of preclinical and clinical studies. Geroscience. 2018; 40(2): 73-95. doi: 10.1007/s11357-018-0017-z.

Berry A et al. *Curcuma Longa*, the "Golden Spice" to Counteract Neuroinflammaging and Cognitive Decline-What Have We Learned and What Needs to Be Done. *Nutrients*. 2021;13(5): 1519. doi: 10.3390/nu13051519.

Voulgaropoulou SD, et al. The effect of curcumin on cognition in Alzheimer's disease and healthy aging: A systematic review of pre-clinical and clinical studies. *Brain Res*. 2019 ;1725: 146476. doi: 10.1016/j.brainres.2019.146476.

56

Plants to watch ...

Turmeric

Benefits may not depend on the bioavailability of curcumin:

- curcumin and its metabolites may act indirectly on the CNS by correcting dysbiosis of gut microbiome to influence the microbiota-gut-brain axis.
- curcumin is subject to bacterial enzymatic modifications, forming pharmacologically more active metabolites than curcumin.

There is also evidence for the benefits of *ar*-tumerone.

Di Meo F, et al. Gut Microbiota, and Neuroprotection. *Nutrients*. 2019; 11(10): 2426. doi: 10.3390/nu11102426

Lopresti AL. The Problem of Curcumin and Its Bioavailability: Could Its Gastrointestinal Influence Contribute to Its Overall Health-Enhancing Effects? *Adv Nutr*. 2018; 9(1): 41-50. doi: 10.1093/advances/nmx011.

Hucklenbroich J, et al. Aromatic-turmerone induces neural stem cell proliferation in vitro and in vivo. *Stem Cell Res Ther*. 2014;5(4): 100. doi: 10.1186/scrt500.

57

Plants to watch ...

Cayenne

Several studies have shown the neuroprotective role of capsaicin in neurological disorders.

Cayenne has long been recognised as the most effective circulatory stimulant and vasodilator.

One factor may be its confirmed action on transient receptor potential vanilloid 1 (TRPV1) with evidence that this modulates neuroinflammatory processes.

Tyagi S et al. Protective Role of Capsaicin in Neurological Disorders: An Overview. *Neurochem Res*. 2022; 47(6): 1513-1531. doi: 10.1007/s11064-022-03549-5

Yang D et al. Activation of TRPV1 by dietary capsaicin improves endothelium-dependent vasorelaxation and prevents hypertension. *Cell Metab*. 2010;12(2):130-41. doi: 10.1016/j.cmet.2010.05.015.

Kong WL, et al. Modulation of neuroinflammation: Role and therapeutic potential of TRPV1 in the neuro-immune axis. *Brain Behav Immun*. 2017; 64: 354-366. doi: 10.1016/j.bbi.2017.03.007

58

Plants to watch ...

Cinnamon

Multiple activities across metabolic and vascular functions, with a particular prospect for improving cognitive performance and neuroprotection through **reducing insulin resistance**, eg in prediabetics.

Yulug B & Cankaya S. Translational perspective: is cinnamon a suitable agent for cognitive impairment and Alzheimer's disease associated with brain trauma? *Neural Regen Res*. 2019; 14(8): 1372-1373. doi: 10.4103/1673-5374.253518

Wahlqvist ML, et al. Cinnamon users with prediabetes have a better fasting working memory: a cross-sectional function study. *Nutr Res*. 2016; 36(4): 305-310. doi: 10.1016/j.nutres.2015.12.005

59

Plants to watch ...

Sage

"*Sage will retard the rapid progress of decay that treads upon our heels so fast in latter years of life, will preserve faculty and memory more valuable to the rational mind than life itself*" John Hill 'Family Herbal' 18thC

Sage (and rosemary) extracts exhibit **cholinesterase inhibition**, with 1 µL essential oils being more potent than the recommended daily dose of donepezil.

This was attributed to the presences of di- and triterpenes.

Kennedy DO & Scholey AB. The psychopharmacology of European herbs with cognition-enhancing properties. *Curr Pharm Des*. 2006; 12(35): 4613-23. doi: 10.2174/138161206779010387

60

Plants to watch ...

Rosemary

"There's rosemary; that's for remembrance". Shakespeare

Rosemary has demonstrated **anticholinesterase activity**, enhanced Nrf2 processes and **endothelial modulation**.

Diterpene carnosic acid exerted protective effects upon neuronal cells more intensely than resveratrol or sulforaphane.

Our own clinical trial pointed to rosemary improving cognition in the elderly.

Habtemariam S. The Therapeutic Potential of Rosemary (Rosmarinus officinalis) Diterpenes for Alzheimer's Disease. *Evid Based Complement Alternat Med*. 2016; 2016: 2680409. doi: 10.1155/2016/2680409.

de Oliveira MR. The Dietary Components Carnosic Acid and Carnosol as Neuroprotective Agents: a Mechanistic View. *Mol Neurobiol*. 2016; 53(9): 6155-6168. doi: 10.1007/s12035-015-9519-1

Pengelly A et al. Short-term study on the effects of rosemary on cognitive function in an elderly population. J Med Food. 2012; 15(1): 10-7. doi: 10.1089/jmf.2011.0005

61

Plants to watch ...

Ginkgo

The standardised 50:1 extract EGb761 is the paramount circulatory prescription in German medicine, often used in recovery from stroke, in vascular tinnitus and other heart and circulatory disorders. Also used widely in psychiatric medicine. It is very rich in flavonoids as well as unique ginkgolides.

EGb761 at 240 mg/day is able to stabilize or slow decline in cognition, function, behaviour, and global change at 22-26 weeks in cognitive impairment and dementia, especially for patients with neuropsychiatric symptoms.

Tan MS et al. Efficacy and adverse effects of ginkgo biloba for cognitive impairment and dementia: a systematic review and meta-analysis. *J Alzheimers Dis*. 2015; 43(2): 589-603. doi: 10.3233/JAD-140837.

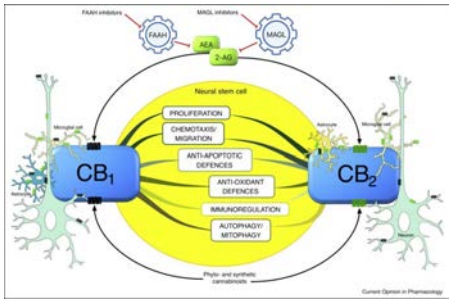
62

Herbs to watch ...

Echinacea (and ...)?

The endocannabinoid system is highly expressed in the hippocampus and controls biological processes including neuronal proliferation, migration and differentiation, intimately linked with embryonal neurogenesis.

Selective CB_1 and CB_2 agonism produces pro-neurogenic effects in different models of brain insults.



Oddi S et al. Endocannabinoid system and adult neurogenesis: a focused review. *Curr Opin Pharmacol*. 2020; 50: 25-32. doi: 10.1016/j.coph.2019.11.002

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