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Metabolic and immune risk factors for dementia and their modification by flavonoids: New targets for the prevention of cognitive impairment?

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Abstract. A number of contributory factors have been implicated in the pathogenesis of Alzheimer's disease. One of these factors is chronic inflammation, with the over expression of pro-inflammatory cytokines and acute phase reactants consistently observed in the post mortem brain and plasma of AD patients. Furthermore, cardiovascular risk factors, such as hypertension, impaired vascular function and elevated LDL cholesterol, also appear to be predictive of increased dementia risk. Although classically associated with cardiovascular disease risk, both vascular and immune mediators may have direct deleterious effects on the brain, which contribute to the development of vascular dementia and Alzheimer's disease, as well as impairments in memory and neuro-cognitive function. Dietary agents previously noted for their ability to modulate these cardiovascular risk factors leading to reductions in chronic, low-grade inflammation and/or vascular dysfunction, may also possess an ability to moderate the progression of dementia. Flavonoid-rich foods such as tea, berries and cocoa have been reported to attenuate age-related deficits in memory and cognition, although the precise mechanisms of their action are unclear. As these flavonoid rich-foods/beverages also appear to mediate inflammatory processes, attenuate endothelial dysfunction and reduce hypertension, such actions may contribute to their efficacy in the brain. This review will explore these concepts with the view to further unravelling the actions of flavonoids and flavonoid-rich foods against brain disease and to highlight the importance measuring such factors in future clinical studies.

Keywords: Flavonoid, dementia, Alzheimer's disease, vascular function, immune system

1. Alzheimer's disease and dementia

Alzheimer's disease (AD) is the most common form of dementia, accounting for approximately 62% of all cases. Worldwide it is estimated that there are 35.6 million sufferers and, due to increased life expectancy, the number of sufferers has been predicted to rise to 65.7 million by 2030 and 115.4 million by 2050, with the sharpest rise incurring in low and middle income countries [1]. In addition to the personal and social burden of the disease, it is estimated that dementia costs the global economy in excess of £370 billion sterling per year with 70% of these costs incurred in Western Europe and North America. AD is a progressive, age-related neurodegenerative disorder with the majority of cases being late onset, primarily affecting individuals of 65 years and over [2] and often preceded by a condition known as 'mild cognitive impairment' (MCI). MCI can be described as a transitional state between normal aging and dementia, where cognitive decline is greater than expected for the individual's age

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but remaining distinct from dementia due to everyday activities remaining unaffected [3]. Afflicting between 3% and 19% of adults over the age of 65 it is estimated that more than half of MCI patient's progress to dementia within 5 years [4]. The neuropathology of MCI appears to be comparable to that apparent in early AD and is likely to occur at least a decade prior to the emergence of clinical symptoms [5, 6]. It is hoped that preventive treatments/drugs may be capable of reducing the number of MCI individuals that progress to AD through the effective modulation of the underlying pathology.

It is widely accepted that the brain areas initially affected in AD are located in the medial temporal lobes including the hippocampus, transentorhinal cortex, entorhinal cortex and the subiculum ll, [7]. The pathology is known to include the deposition of senile plaques (SP's) and neurofibrillary tangles (NFT's) composed of hyper-phosphorylated tau, which lead to significant neuronal/synaptic loss over time. Such changes may be triggered in part by changes in blood brain barrier permeability brought about by abnormal neuroinflammatory processes [8]. SP's are primarily composed of two isoforms of amyloid beta (Aβ), $A\beta_{40}$ and $A\beta_{42,}$ which are produced as a result of abnormal processing of amyloid precursor protein (APP), catalysed by beta-secretase 1 (BACE 1), followed by gamma-secretase cleavage [5]. Normal, processing of APP by alpha-secretase precludes Aβ production and is down-regulated in AD [9]. These events, contribute to the 'amyloid cascade hypothesis', which involves initial Aβ production, plaque formation and a downstream inflammatory response thought to induce tau hyper-phosphorylation and neurofibrillary tangles [10]. However, this mechanism has been questioned in that Aβ and NFT's may only represent end products of neurodegeneration and not it's cause [11].

It has been postulated that neuroinflammation may play a major contributory role in pathology of AD, as evidenced by an altered immune response in AD patients [12] and by a variety of immunohistochemical, biochemical and molecular data [13]. Microglia, the primary immune cells of the central nervous system (CNS), when activated, produce numerous inflammatory mediators including cytokines and chemokines [14]. Pro-inflammatory cytokines, such as tumour necrosis factor-alpha (TNF-α), appear to play a major role in neurodegeneration due to their ability to: 1) activate other pro-inflammatory mediators such as acute phase proteins, e.g. C-reactive protein (CRP); 2) up-regulate the expression of inducible nitric oxide synthase (iNOS) resulting in the neurotoxic levels of nitric oxide (NO); and 3) interact with inflammatory signalling pathways capable of inducing neuronal apoptosis [15]. In support of this, chronic or intermittent cerebral ischemia induces neuroinflammation, which may then directly contribute to vascular dementia and AD pathology by triggering the necrotic/apoptotic death of neurons or by rendering them more susceptible to subsequent pro-apoptotic stimuli [16]. Furthermore, chronic or intermittent hypo-perfusion of the brain appears to exert amyloidogenic effects by enhancing expression of APP, by up-regulating β-secretase and down regulating α-secretase [17, 18].

As well as these pro-inflammatory events, there is emerging evidence that the progression of atherosclerosis and neurodegeneration, in particular typical and atypical dementia may share common risk factors and gene associations, including the presence of the ε4 allele of the apolipoprotein E genotype, hypertension, endothelial dysfunction, elevated total cholesterol and type II diabetes mellitus (T2DM) [19, 20]. Although there is only limited data at present detailing the benefits of flavonoids with regard to neurodegenerative disease and dementia, there is extensive data collected on the ability of flavonoids to attenuate a number of vascular pathologies, including endothelial dysfunction, hypertension, hypercholesterolemia and type II diabetes. Such studies indicate that attenuation of such mediating factors may play a role in the potential of flavonoids to slow the progression of neurodegenerative pathologies and age-related deficits in cognitive decline. This review will attempt to give an overview of the involvement of such factors in the progression of dementia and will assess the potential role of flavonoids to influence dementia and AD development through their ability to modulate these same immune, vascular and lipid factors (Fig. 1).

2. Risk factors for dementia and AD

2.1. Apolipoprotein E

Apolipoprotein E (ApoE) is a major genetic risk factor for the development of AD [21, 22]. Synthesised primarily in the liver but also within the central nervous system (CNS) by microglia, astrocytes and to a smaller extent neurons, relatively little is known about the role

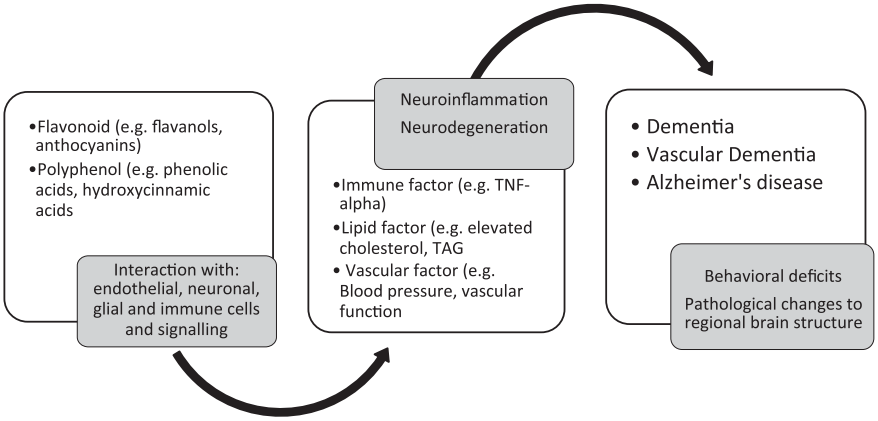

Fig. 1. Proposed associations between flavonoid intake immune and metabolic mediators and dementia.

of this 34-kDa secretory protein in the brain [23]. ApoE appears to be the principal lipid transport vehicle in cerebrospinal fluid (CSF) and is involved in the redistribution of lipids and cholesterol during membrane repair and synaptic plasticity, during development, or after injury, including injury caused by inflammation [24]. ApoE is encoded by a gene located on chromosome 19, within a region previously associated with familial late-onset Alzheimer's disease [25]. It is a polymorphic gene with two missense mutations resulting in 3 common isoforms, apoE ε2, apoE ε3 and apoE ε4, which engender 6 different genotypes (ε2/ε2, ε2/ε3, ε2/ε4, ε3/ε3, ε3/ε4 and ε4/ε4), with apoE ε3 being the ancestral isoform of the protein [26]. Approximately 25% of the Caucasian population carry one or more of the ε4 alleles and those individuals who inherit one or two copies of this allele have a greater risk (2 to 10 fold, respectively) of developing AD at an earlier age of onset [22, 27, 28] and an increased conversion of MCI to AD [6].

In addition, the ε4 allele is also associated with a 40–50% increased risk of developing cardiovascular disease which was traditionally attributed to its effects on higher circulating cholesterol and TAG levels [29] however, more recently it has been associated with increased inflammation [30–32]. Indeed, inflammatory gene expression is greater in apoE ε4/ε4 mice compared to apoE ε3/ε3 mice, in response to LPS injection, which may be due to incorrect regulation of the NF-kβ signalling cascade in apoE animals [33]. In support of this, apoE ε4/ε4 microglia, produce higher levels of pro-inflammatory cytokines and increased NO production relative to their apoE ε3/ε3 equivalents [30]. A similar elevated inflammatory response has been repeatedly observed in macrophages derived from apoE transgenic mice [34–36] and in macrophages derived from apoE ε4/ε4 AD patients compared to healthy, age matched individuals or to AD patients with an apoE ε3/ε3 genotype [37].

It has also been suggested that apoE4 may also exhibit a reduced neuronal repair, remodelling and protective ability relative to that of apoE3 and apoE2, with E3 stimulating normal neurite development and apoE4 inhibiting neurite growth [38, 39]. Alternatively, ApoE3 but not apoE4 has been found to interact with Tau, protecting it against hyper-phosphorylation and it's self-assembly into the paired helical filaments that form NFT's [40]. Collectively these data provide some explanation for the increased severity in neuropathological features of AD, particularly evident in carriers of the apoE ε4/ε4 genotype [41]. Clearly the ApoE genotype is not modifiable by diet. However, due to its involvement in lipid metabolism/transport, vascular responsiveness and immune homeostasis (individually detailed below), and due to its clear involvement in AD and dementia risk, it seems highly appropriate to screen individuals for this genotype for their inclusion in future clinical studies. Such a critical determinant of AD risk is likely to impact on pathophysiology on many levels and thus is important to take into account when studying the impact of any diet/dietary agent on medium to long-term cognitive impairment.

2.2. *Immune factors*

Elevated levels of tumour necrosis factor alpha (TNF-α) and other pro-inflammatory cytokines have

also been proposed to contribute to the neuronal injury observed in neurodegeneration, mainly through their ability to amplify inflammatory processes [42] (Table 1). In a cohort of 300 AD patient's, a high baseline plasma concentration of TNF-α was found to be associated with a 4-fold increase in the rate of cognitive decline over a 6-month period [43]. Furthermore, plasma levels of TNF-α have been observed to be elevated in MCI patients compared to healthy, age-matched individuals [44]. In support of these observations, TNF-α is over expressed in the affected regions of the AD brain [13] and is elevated in the cerebrospinal fluid (CSF) of AD patients [45]. It has also been suggested that a higher spontaneous production of IL-1 or TNF-α by peripheral blood mononuclear cells may be a marker of future risk of AD in older individuals [46]. The neurotoxicity of TNF-α and other immune factors is likely linked to their potential to induce microglial production, leading to the production of neurotoxic levels of nitric oxide [15] and/or their ability to stimulate Aβ production [47], which in turn stimulates the production of further pro-inflammatory cytokines [48].

Increased plasma levels of the acute phase protein, serum C-reactive protein (CRP), have also been reproducibly measured in AD [49] and MCI patients [50], whilst high circulating levels of CRP are associated with an increased risk of dementia [51–54] (Table 1). Furthermore, elevated CRP levels predict poorer memory performance in healthy older adults [55, 56] and are associated with accelerated cognitive decline and an increased risk of dementia in patients with MCI [57]. In support of this relationship, whilst CRP is not typically localised in the brain [58], it has been consistently observed to be co-localised with senile plaques and neurofibrillary tangles in the AD brain [58, 59]. Collectively, these data emphasize the pathophysiological role of inflammation in the development of AD and highlight potential targets for drugs and nutrients designed to slow AD pathology.

2.3. Vascular function

Recent observations regarding the involvement of vascular risk factors in cognitive decline has led to the so called 'vascular hypothesis' of AD, in which neuro-vasculature dysfunction contributes to the pathogenesis of AD and other dementias [60–62]. This observation has been supported by both neuroimaging and post-mortem histopathological studies, which have indicated that vascular pathology is evident in up to one-third of AD patients [63]. Vascular dysfunction occurs when the endothelium expresses changes in nitric oxide generation, increased vasoconstrictor release and a shift towards a more pro-inflammatory/pro-thrombotic status [64]. The function of the endothelium is known to be impaired with ageing [65], but is more strongly affected in AD patients [66, 67] and is associated with the severity of AD [66]. Vascular dysfunction undoubtedly contributes to the reduced level/volume of cerebrovascular blood flow (CBF) evident in AD patients [68, 69]. Indeed, imaging studies indicate that CBF is greatly reduced to specific brain regions, primarily the prefrontal and inferior paritetal cortices in AD patients compared to age-matched controls [69], whilst reduced CBF in the frontal lobe has also been observed in AD patients [68]. In the Rotterdam study (1730 subjects aged 55+) researchers investigated the relationship between CBF velocity, dementia and cognitive decline and found that subjects with a greater CBF velocity were less likely to go on to suffer from dementia. As such, it seems that cerebral hypoperfusion proceeds, and potentially contributes to, brain pathophysiology and the onset of clinical dementia [70].

2.4. Hypertension

Hypertension is the major clinical manifestation of impaired endothelial function and is a well-known risk factor for vascular dementia [71] and more recently has been implicated in cognitive decline and AD [62]. A number of longitudinal cohort studies have reported a strong association between hypertension (systolic blood pressure above 140 mmHg and/or a diastolic blood pressure above 90 mmHg) in middle age or late in life and an increased risk of AD [19, 72–74]. Notably, Odds Ratios for the risk of dementia were as follows: OR 3.8 (95% CI; 1.6–8.7) for DBP of 90–94 mmHg; OR 4.3 (95% CI; 1.7–10.8) for DBP >95 mmHg compared to those with DBP of 80–89 mmHg. Similar results were observed with a SBP of 160 mmHg or above: OR 4.8 (95% CI; 2.0–11.0), compared to those with SBP of 110 to 139 mmHg [72]. Furthermore, if patients with elevated blood pressure are effectively treated the association between hypertension and any form of dementia is eliminated [72]. This observation is supported by a

Table 1
Metabolic and immune factors and their association with Alzheimer's disease and dementia risk. OR: odds ratio; HR: hazard ratio; RR: relative risk; T2DM: type 2 diabetes mellitus; SBP: systolic blood pressure; DBP: diastolic blood pressure; NS: No studies

Biomarker	Epidemiology	Clinical evidence	Potential mechanism
TNF-α	NS	Over expressed in AD brain Elevated in plasma of MCI and AD patients	Stimulates neuroinflammation, NO production and neuronal apoptosis
CRP	OR 1.49; CI, 1.23–1.81	Over expressed in AD brain Elevated in plasma of MCI, AD and other dementias High levels predict poorer memory in healthy adults Found co-localised with senile plaques and NFT	Not clear but evident within plaques and tangles characteristic of AD
Hypertension	SBP↑ HR 1.6 SBP: >160 mmHg: OR 4.8 DBP: 90–94 mmHg: OR 3.8 DBP >95 mmHg: OR 4.3	Hypertension in mid and late life increases the risk of AD and other dementias Anti-hypertensive medication lowers AD risk in hypertensive patients	Damage to microvasculature and BBB resulting in hemodynamic changes, inflammatory response and Aβ deposition
Vascular dysfunction	NS	Classical vascular pathology observed in a third of AD patients at PM Compromised cerebral blood flow in AD	Ischaemia/reperfusion injury/apoptosis Restricted O_2 and nutrient supply
Type II diabetes	T2DM: RR: 1.9 Older T2DM: RR: 1.3 to 2.27 T2DM + Insulin: RR 4.3 T2DM: OR 1.69	Fasting insulin and 2-hour post load plasma glucose is associated with the SP Increased risk of dementia in T2DM is elevated by insulin treatment	Reduced sensitivity of insulin receptors Reduction in glucose utilisation IR receptor influence on neuronal plasticity
Hyper-cholesterolemia	200–239 mg/dl: HR 1.23 >240 mg/dl: HR 1.57	Elevated total cholesterol in mid life associated with increased risk of AD	Contributes to atherosclerosis which impedes CBF and promotes an amyloidogenic environment

number of trials with anti-hypertensive drugs, including diuretics, which have been found to reduce the incidence of AD (HR 0.57; 95% CI, 0.33–0.94) [75] and dihydropyridine, a calcium channel blocker, which reduces the risk of dementia by 55% [76].

Despite these convincing epidemiological evidence regarding the involvement of hypertension in the progression of AD, it is relatively unclear as to how hypertension is mechanistically linked to the disease pathology. It has been postulated that sustained increases in blood pressure result in damage to the micro-vascular structure in the brain [62], a process that over time may lead to hemodynamic changes, and the subsequent activation of microglia and chronic, low grade neuroinflammation [77]. Moreover, it has been hypothesised that hypertension causes an increase in the permeability of the blood brain barrier, something evident in AD patients compared to age matched controls [78]. Further support stems from neuropathological and imaging studies, which have revealed that

non-demented individuals with high blood pressure exhibit an increase in AD related pathologies prior to the onset of the disease, including increased NFT's, Aβ plaques, large areas of demyelination, tissue degeneration, cortical infarctions and hippocampal atrophy [60]. These processes may even be linked, in that hypertension-induced permeability of the blood brain barrier may be a causal factor for the increased deposition of Aβ [79].

2.5. Type II diabetes mellitus

Characterised by both hyperglycaemia and hyperinsulinemia, type II Diabetes Mellitus (T2DM) is a well-established risk factor for CVD [60] and more recently has been linked with both accelerated cognitive decline [80] and an increased risk of developing AD [81–85] (Table 1). Patients with T2DM have been found to have an almost doubled risk of dementia, RR 1.9 (95% CI; 1.3–2.8), with those patients treated with insulin having an even greater risk, RR 4.3 (95% CI; 1.7–10.5) [83]. In older, dementia free individuals, T2DM slightly increased dementia risk, RR 1.3 (95% CI; 0.8–1.9) [84] with men having a higher risk, RR 2.27 (95% CI;1.55–3.31) than women, RR 1.37 (95% CI: 0.94–2.01) [82]. Twin studies have also corroborated this increased dementia risk associated with T2DM, with an OR of 1.69 (95% CI; 1.16–2.36) reported for developing AD and that the risk was greater when T2DM occurred in mid life compared to in late life [85].

Accumulating evidence suggests that the reduced sensitivity of insulin receptors (IR's) measurable in T2DM may have multiple effects in the brain [86, 87]. In addition to its clear influence on glucose utilisation, IR's are also involved in neuronal growth, synaptic development and neurotransmitter release all of which are disturbed in T2DM [81]. Additionally, there is evidence to suggest that in combination with ApoE4, hyperinsulinemia and hyperglycemia induced by insulin resistance may accelerate senile plaque formation [88]. Hyperglycaemia itself has been proposed to be pro-apoptotic due to its potential to increase advanced glycation end product production, many of which have been shown to be neurotoxic [60]. Furthermore, T2DM increases the risk of ischemic cerebrovascular disease and accelerates cerebrovascular inflammation, thus contributing to AD pathology discussed above [89].

2.6. Hypercholesterolemia

Hypercholesterolemia has long been a risk factor for CVD, although more recent epidemiological data has suggested that elevated total plasma cholesterol may also be a risk factor for AD and other dementias [90–92]. For example, moderately high plasma cholesterol (200–239 mg/dl) has been associated with an increased risk of AD: Hazard Ratio (HR) 1.23 (95% CI; 0.97–1.55), whilst high cholesterol (>240 mg/dl) increases the risk further to HR 1.57 (95% CI; 1.23–2.01) [91]. It has been postulated that elevated cholesterol in midlife may represent an independent risk factor for AD with an OR of 2.8 (CI, 1.2 to 6.7) [92]. Brain cholesterol is largely synthesised in the CNS (as the BBB prevents it from entering from the peripheral blood), where it plays a vital role in maintaining neuronal function and plasticity [93]. However, if the BBB is compromised, due to vascular damage, hypertension or inflammation, an accumulation of cholesterol in the brain can occur [20], leading to arteriosclerosis of the cerebral vasculature, followed by an impairment of CBF and the deposition of Aβ [93].

2.7. Flavonoids and cognitive function

Many lifestyle factors, including diet have been postulated to reduce the risk of neurodegenerative diseases [42, 94–96] and to maintain normal cognitive function during ageing [97–99]. There has been much interest in a group of phytochemicals known as flavonoids, found in a wide variety of fruit and vegetables, as well as tea, red wine and cocoa, in reducing the risk of dementia [100, 101], attenuate cognitive decline [102], modify cardiovascular risk factors [103–105] and improve cognitive function [106–108]. Whilst the mechanisms of their action against neuropathophysiology are unknown, their actions against dementia may partly involve interactions with the vascular and immune systems. In the next two sections we will outline the evidence for the actions of flavonoids and flavonoid-rich foods against cognitive ageing and the progression of dementia.

2.8. Flavonoids and dementia

Prospective cohort studies have highlighted positive associations between the consumption of flavonoid-rich foods and a reduction in the risk of developing

dementia [100, 101, 109, 110]. In the Paquid study, which followed a cohort of 1367 healthy older adults (aged 65+) for 5 years, there was an age related RR for dementia of 0.49 (95% CI: 0.26–0.92; $p = 0.04$) for the two highest tertiles of flavonoid intake compared to the lowest (after adjustment for gender, education, weight and vitamin C intake) [100]. In addition, both total flavonoids and flavonol intake has been associated with lower population rates of dementia [101], whilst frequent flavonoid-rich fruit and vegetable consumption has been linked with a reduced risk of dementia and AD [109], something which was observed to be more pronounced in ApoE4 carriers. Indeed, the Hazard Ratio for AD has been calculated to be 0.24 (95% CI, 0.09–0.61) for individuals consuming fruit and vegetable juices at least 3 times per week and 0.84 (95% CI, 0.31–2.29) for individuals consuming 1–2 times per week, compared to those who consume less than one per week [110]. However, associations between flavonoid intake and reductions in dementia are not entirely consistent, with the Rotterdam study [111] and the Honolulu aging study [112] failing to show any associations. The reasons for these inconsistencies may relate to study design, measurement errors in reported dietary intake data and residual confounding bias by lifestyle factors. Further studies, including controlled intervention studies in patient populations are required to fully substantiate the efficacy of flavonoids in preventing dementia and AD.

2.9. Flavonoids and neuro-cognitive performance

Flavonoid-rich food/beverage intake has also been linked with a better cognitive test performance in healthy, older people [113, 114] and with an improved cognitive evolution over a 5 year period [102]. A number of dietary intervention studies have added to this data, with many showing flavonoid rich foods effective in improving cognitive function [106, 115–118]. Despite these positive findings, the Lothian Birth cohort failed to find an association between flavonoid intake and a variety of cognitive test scores after adjusting for confounding factors including childhood IQ [97]. Again, these inconsistencies are likely to be related to aforementioned differences in dietary intake methodology and the bias due to confounding lifestyle factors, although the differences in cognitive testing methods used in these studies make reliable comparisons between them difficult.

Despite two null findings [115, 117], positive cognitive outcomes have been reported following supplementation with isoflavone-rich foods, predominantly soy [116, 119–121] (Table 2). Multiple improvements in cognitive performance have been observed in response to soy intake, including processing speed, executive function and mood [116], sustained attention and episodic memory [119], improvements in verbal memory [119], improvements in episodic memory and executive function/working memory tasks [122] and improvements in MMSE score and attention [121] following interventions of varying length. Such effects have been suggested to be due to their ability to mimic the actions of oestrogen in the brain [123, 124], or to influence the synthesis of acetylcholine and neurotrophic factors such as BDNF [125, 126]. However, cognitive improvements have also been observed in young adults [127], suggesting alternative mechanisms independent of their oestrogen mimicking effects.

Intervention with the flavonoid-rich *Ginkgo biloba* extract, EGb 761, has also been found to result in improvements in general cognitive functioning in both MCI and AD patients [128] and improvements in episodic memory including free and delayed recall and recognition memory in cognitively intact older adults [129]. Furthermore, supplementation of healthy older adults with flavonoid-rich pine bark extracts also revealed memory improvements [130, 131]. Supplementation for 5 weeks (960 mg/day) resulted in improved response times in a spatial working memory tasks and a task of immediate recall [130] and supplementation for 3 months resulted in improvements in working memory [131]. With regards to more commonly consumed foods/beverages, a 12 week intervention with purple grape juice has been found to induce significant improvements in verbal learning in older adults with early memory decline [118], whilst blueberry intake improved paired, associate learning and word list recall [106]. In addition to these moderate term interventions, an acute intervention with flavanol-rich cocoa has also been shown to improve working memory (Serial Three's task) and at higher doses improve attention (reduction in response times in the RVIP Task) [108].

In support of this human data, animal studies have also indicated that pomegranate [132], blueberry [133, 134], strawberry and spinach [135], Concorde grape juice [136], blackberry [137], Vaccinium berries [138], Ginkgo biloba [139, 140], green tea catechins [141], pure (−)-epicatechin [142] and quercetin

Table 2
Cognitive improvements induced by intervention with flavonoid-containing foods

Flavonoid and intervention	Population	Cognitive improvement	Reference
60 mg/day; 24 weeks	$n = 78$; 44–54 yrs. Post menopausal women	Faster processing speed Improved executive function and mood	[116]
60 mg/day; 12 weeks	$n = 33$; 50–65 yrs. Post menopausal women	Improved episodic memory Sustained attention	[119]
60 mg/day; 6 weeks	$n = 50$; 51–66 yrs.	Improved episodic memory Improved executive function/working memory	[122]
79 mg/day; 16 weeks	$n = 79$; 48–65 yrs. Post menopausal women	No significant improvements	[115]
60 mg/day; 6 months	$n = 28$; 60+ yrs.	No significant improvements	[117]
110 mg/day; 6 months	$n = 53$; 55–74 yrs. Post menopausal women	Improved verbal memory	[120]
100 mg/day; 3 months	$n = 127$; 50–65 yrs.	Increase in general cognition (MMSE) Improved attention	[121]
100 mg/day; 10 weeks	$n = 27$; 22–30 yrs. Healthy adults	Improved episodic memory Improved executive function/working memory	[127]
Ginkgo biloba 120 mg/day (Egb 761); 12 months	$n = 236$; 45–90 yrs. AD patients	General improvements in ADAS-Cog score and GERRI scores	[128]
Ginkgo biloba 180 mg/day (Egb 761); 6 weeks	$n = 262$; 60+ yrs. Healthy	Improved episodic memory	[129]
Pine bark extract; 960 mg/day; 5 weeks	$n = 42$; 50–65 yrs. Healthy males	Increase in processing speed Enhanced visuospatial memory Improved spatial working memory	[130]
Pine bark extract; 150 mg/day; 3 months	$n = 101$; 60–85 yrs. Healthy	Improved working memory	[131]
Blueberry juice; 6–9 ml/kg BW; 12 weeks	$n = 9$; mean 76.2 yrs. Healthy with self reported memory decline	Improved episodic memory	[106]
Concorde grape juice; 6–9 ml/kg BW; 12 weeks	$n = 12$; mean 78.2 yrs. Healthy with self reported memory decline	Improved episodic memory	[118]
Cocoa flavanols 520 mg & 994 mg Acute 0–8 h	$n = 30$ mean age 21.9 y Healthy	Working memory (both doses) Attention and processing speed (994 mg only)	[108]

and rutin [143] are all capable of reversing age-related deficits in learning and memory. Mechanistic investigations have suggested that improvements in memory, normally assessed as increased spatial memory performance, may be linked to the potential of flavonoids/metabolites to induce hippocampal ERK-CREB-BDNF signalling [133–135, 144, 145] and potentially increase angiogenesis and neuronal spine density [142]. These observations are supported by *in vitro* experiments, which indicate that epicatechin at physiologically relevant concentrations stimulates ERK1/2 and PI3 kinase dependent phosphorylation of CREB [146]. Despite these direct actions of flavonoids and their metabolites on the brain, it is also possible that they may influence neuronal and glial function, brain ageing and cognitive function from actions in the periphery. As discussed above there are many vascular and lipid factors well reported to influence the progression of AD and vascular dementia. Concurrently, there is good evidence that intervention with flavonoid-rich foods/beverages can impact on many, if not all, of these factors. As such, the modification of such classical CVD risk factors, known also to be associated with AD pathology, by flavonoids may play a role in delaying, or even preventing, the progression of AD and other dementias (Fig. 1). In the following sections we

detail the evidence that flavonoid-rich foods by modulate the risk factors detailed earlier in the review and discuss how these may impact upon the development of dementia and cognitive impairments.

3. Modification of vascular and immune risk factors by flavonoids and implications for AD

As discussed above, although the precise cause of AD is unclear, chronic inflammation [44] and vascular pathology [60–62] have been implicated in the cause and progression of the disease. In the next sections, we present evidence that flavonoids and flavonoid-rich foods are capable of attenuating chronic, low grade inflammation and lowering risk factors associated with vascular pathology (Fig. 2). As such, it is conceivable that such interactions *in vivo* may in part be responsible for their potential to delay cognitive impairment and/or the onset and progression of AD.

3.1. Inflammatory mediators

A large cross sectional study ($n = 8332$) has indicated that total flavonoids ($P < 0.01$), as well as individual flavonols ($P < 0.01$), anthocyanidins ($P < 0.05$), isoflavones ($P < 0.01$) and the pure flavonoids, quercetin ($P < 0.01$), kaempferol ($P < 0.01$), malvidin ($P < 0.01$), peonidin ($P < 0.05$), daidzein ($P < 0.05$), and genistein ($P < 0.01$), are all inversely correlated with serum CRP concentrations [147]. In support of this, a number of dietary intervention studies have provided evidence that dietary flavonoids are capable of modulating TNF-α and CRP production [147–153]. Notably, intervention with green tea catechins (580 mg) in healthy male smokers [148] and a flavonoid rich grape extract in pre and postmenopausal woman [149] have highlighted the potential to significantly lower plasma TNF-α. Furthermore, interventions with flavanol rich red wine [151], flavanol-rich cocoa [152] and a chokeberry extract [153] all significantly reduce CRP levels in both healthy and diseased individuals.

In animals, both pure luteolin [150] and flavonoid-rich *Ginkgo biloba* [154] have been shown to inhibit TNF-α production after LPS stimulation. Plausible mechanisms exist for the anti-inflammatory effects of flavonoids with many flavonoids and flavonoid-rich foods having been shown to inhibit TNF-α production in activated microglia [155–157] through the modulation of both nuclear factor NF-kβ signalling pathway [154, 155] and the MAP kinase signalling pathway. Such a modulation of peripheral immune homeostasis by flavonoids may be important in light of studies suggesting that the activation of the peripheral immune system elicits a discordant central (i.e. in the brain) inflammatory response in aged but otherwise healthy subjects compared with younger cohorts [156]. As such, regulation of peripheral immune cells, and their production of pro-inflammatory cytokines by flavonoids may protect against neurodegeneration and cognitive deficits through their ability to inhibit low-grade, sustained peripheral immune system activation, such as occurs during systemic infections, cardiovascular disease, cancer or autoimmune diseases [162] (Fig. 2). Indeed, data suggests that flavonoids may be capable of influencing this immune-to-brain signaling pathway, thus exerting anti-inflammatory actions that are capable of mitigating microglial activation in the brain and thus limiting neuronal injury and cognitive losses with aging [165]. Such links between the peripheral and central immune systems, as well as associations between cognitive performance and immune dysfunction, are certainly worthy of further investigation, particularly in future chronic dietary intervention trials.

3.2. Vascular function

A large number of human intervention studies have provided evidence that a variety of flavonoid-rich foods promote vascular function. In particular, there is strong evidence for the vascular effects of flavanol-rich cocoa [104, 166, 167], black tea [168–171], green tea [171–175] and *Ginko Biloba* [176]. Flavonoid-induced improvements in endothelium-dependent vascular function, as indicated by increases in flow mediated dilation of the brachial artery and changes in pulse wave amplitude have been recorded in healthy subjects [104, 163, 164, 166–169], in older individuals [176, 178], in smokers [173, 174, 179] and in hypertensive individuals [166]. Such changes in vascular function have been linked to alterations in circulating nitric oxide species, suggesting that these effects are mediated by flavonoid/metabolite increases in NO production [104, 163]. This is supported by *in vitro* studies, which indicate that flavonoids increase NO production in endothelial cells by the activation of endothelial nitric oxide synthase (eNOS) through

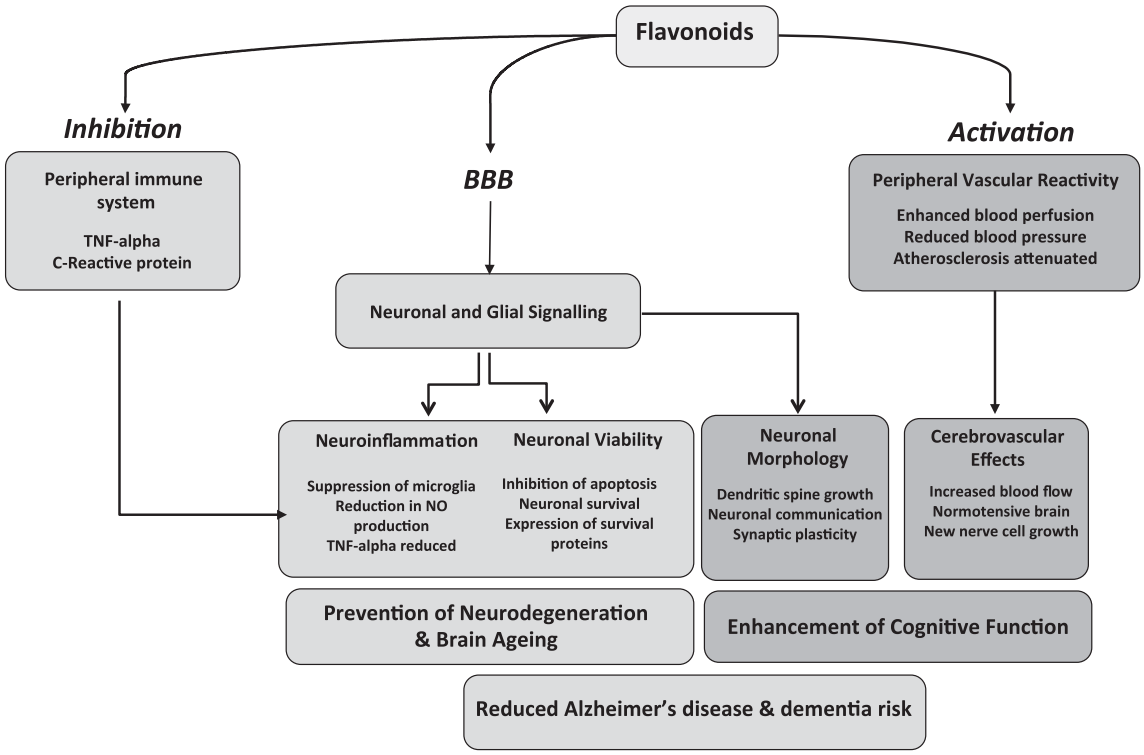

Fig. 2. The interactions of flavonoids and their metabolites with the immune system, the vascular system and the brain and how such interactions influence brain ageing, cognition and dementia.

the phosphatidylinositol 3-kinase pathway [180, 181]. In addition to these peripheral vasodilator effects, improvements in blood flow to the brain have been observed after consumption of flavanol-rich cocoa [182, 183]. Here, a weeks intervention with a high flavanol cocoa drink resulted in an increase in the mean cerebral blood flow (CBF), measured by transcranial Doppler ultrasound in healthy older adults [183]. In support of this, increased CBF velocity, and an increase in blood oxygenation level-dependent (BOLD) responses to a cognitive task measured by functional Magnetic Resonance (fMRI), has been observed after cocoa ingestion [182].

Collectively these data suggest that flavonoids may be capable of regulating endothelial function leading to acute changes in vascular function and blood perfusion and longer-term changes in blood pressure (Fig. 2). In doing so flavonoid-rich diets appear to be capable of inducing changes that may restore endothelial/vascular homeostasis to normal, healthy conditions, thus reducing the progression of atherosclerosis and/or lowering or maintaining blood pressure at healthy levels. Maintenance of normotensive conditions is critical, as hypertension is known to cause damage to the microvasculature, an event, which is left unchecked, is capable of inducing cognitive impairments by disrupting oxygen and nutrient delivery to specific brain areas. In addition, peripheral and cerebrovascular regulation by flavonoids may also limit vascular dementia via a potential to inhibit atherosclerosis and attenuate neuronal injury following a stroke (ischaemia/reperfusion injury). Alternatively, increased blood flow and enhanced cerebrovascular function are potentially significant as collectively they are thought to facilitate adult neurogenesis in the hippocampus, a process which may lead to enhanced cognition through the generation of new neuronal connections in the brain [184].

3.3. Hypertension

The interest in the effects of flavonoids against hypertension was principally reinvigorated with the Kuna Indian study of the San Blas islands, Panama

[185]. Although originally believed to be due to genetic factors, the low rates of hypertension in island dwelling Kuna (relative to those living on the mainland) was found to be associated with a high dietary intake of cocoa. Such observational data is supported by the Zutphen elderly study, which highlighted an association between cocoa intake and lower blood pressure [186]. In addition to cocoa, anthocyanins, apigenin and catechin [187], green tea [188] and black tea [189] have all been associated with a reduced risk of hypertension. Human intervention studies support this observational data, indicating blood pressure lowering effects of cocoa in hypertensive patients [103, 166, 190, 191] and in healthy volunteers [192]. Indeed, the blood pressure lowering effects of cocoa and dark chocolate are well reported in clinical studies where systolic BP is reduced by 5.88 mmHg (−9.55, −2.21; 5 studies), whilst diastolic BP reduces by 3.30 mmHg (−5.77, −0.83; 4 studies) [193]. A soy protein isolate (but not other soy products) have also been shown to reduce diastolic BP by a smaller degree: 1.99 mmHg (−2.86, −1.12), although it is unlikely that these effects were mediated entirely by flavonoids [193]. With regards to pure flavonoids, quercetin intake (730 mg/day for 28 days) has also been shown to lower BP in untreated hypertensive patients (systolic BP: -7 ± 2 mmHg; diastolic BP: -5 ± 2 mmHg) [194], although the BP lowering effects of tea appear to be more inconsistent [195].

Studies in animal models of hypertension, using a variety of flavonoid-rich foods, support these positive findings [196–198]. As mentioned above the mechanism of action is likely to be mediated be the actions of flavonoids and/or their metabolites on the bioavailability of NO and a reduction in the production of vasoconstrictors such as endothelin-1 [200, 201]. As mentioned above, flavonoid-induced reductions in blood pressure in hypertensive individuals may impact on dementia and cognitive decline by preventing vascular damage caused by excessive blood pressure in the brain (Fig. 2). Indeed, hypertension is an important predictor of acute ischaemic stroke and is associated with cognitive impairments. However, the situation is far from clear. Although lowering BP is beneficial in most patients with vascular risk factors, the effects of BP reduction on cognition remain unclear, in that low BP and antihypertensive treatment may be associated with cognitive impairment once cerebrovascular disease is established, raising questions surrounding the desirability of lowering of BP beyond a certain level in such patients. This is most likely as indiscriminate BP reduction may compromise cerebral perfusion and function in these patients, increasing the risk of cognitive decline and cerebrovascular disease progression. Given the predicted increase in the numbers of people with cognitive impairments, it seems appropriate that clinical trials designed to examine the relationship between cognitive function and hypertension are essential. Such trials, linking flavonoid intake to blood pressure and to cognitive outcomes should provide important information regarding the potential of such foods to impact on stroke rates and cognitive impairment long-term.

3.4. Type II diabetes mellitus

Studies with the Kuna also revealed that, in addition to the protective effect of cocoa in mediating hypertension, a similar protective effect on the development of T2DM may be plausible [202]. Indeed, epidemiology has suggested a reduced risk of developing T2DM following intake of flavonoid rich foods, including apple and tea [203]. Furthermore, dietary intervention studies have highlighted the ability of flavanol-rich chocolate to reduce insulin resistance, a major metabolic factor in T2DM [192, 204], whilst studies in animal models of T2DM show that the flavanol myricetin can reduce plasma glucose and improve insulin resistance [205, 206]. *In vitro* studies, suggest that these effects may occur through effects on GLUT-4 and an ability to prevent phosphorylation/activation of insulin receptor substrate-1 (IRS-1) [207]. It also seems feasible that flavonoids may positively influence insulin resistance due to their anti-inflammatory effects, in that inflammation is believed to play a distinct role in the development of insulin resistance [208]. This may be mediated by JNK- and ERK-induced phosphorylation of IRS-1, which blocks tyrosine phosphorylation and reduces the action of insulin [209]. Alternatively, TNF-α activated NF-kB signalling enhances the gene expression of protein tyrosine phosphatise (PTB)-1B, a protein which dephosphorylates tyrosine residues on IRS-1 and, therefore, blocks insulin signalling.

Unlike most other cells types, neurons and glia primarily rely on glucose for energy production, and as such, an acute interruption of this supply by systemic hypoglycemia produces marked cognitive impairment, whilst repeated severe hypoglycaemia similar to that

experienced in diabetes cause both significant neuronal death and cognitive impairment. Whilst the brain may respond by up-regulating the efficiency of glucose utilisation in response to hypoglycaemia, the reduced sensitivity of insulin receptors, known to be a feature in diabetes, may impact on brain function through the inadequate regulation of blood glucose [86, 87]. As such the ability of flavonoids and/or their metabolites to improve insulin resistance, through their effects on insulin receptor signalling may lead to better utilisation of brain glucose and thus a reduction in cognitive problems associated with hypoglycaemia. Lastly, as diabetes is intimately linked to vascular disease, including ischemic cerebrovascular disease and [89], the known impact of flavonoids on these conditions (outlined above) may act to limit the secondary vascular and immune damage associated with this disease.

3.5. Hypercholesterolemia

Epidemiology has suggested that both total flavonoid and pure quercetin intake may be associated with lower total and LDL cholesterol [210]. In a Meta analysis of 92 trials investigating the effects of flavonoids on CVD risk factors, only soy protein isolate and green tea were found to significantly lower LDL [193]. However, in a smaller Meta analysis of eight trials, cocoa intake was shown to lower blood cholesterol dependent on the dose given to the subjects and the health status of the population [211]. These data are supported by animal studies where flavonoid rich *Hypericum perforatum* L. has been shown to reduce total and LDL cholesterol in high cholesterol fed rabbits [212]. In the same animal model naringenin and naringin have been shown to decrease hepatic acyl-CoA: cholesterol acyltransferase (ACAT) activity [213], an enzyme involved in the formation of insoluble cholesterol esters and their subsequent accumulation in macrophages and vascular tissue. Pure quercetin intervention in mice has been shown to be protective against high cholesterol-induced neurotoxicity by activating AMP-activated protein kinase resulting in reduced fatty acid synthesis and thus brain cholesterol accumulation [214]. These beneficial effects on cholesterol biosynthesis have also been supported by experiments with HepG2 cells that have shown that naringenin, kaempferol and apigenin have the potential to reduce cholesterol biosynthesis at physiologically relevant quantities [215].

4. Summary and future insights

The large increases in life expectancy predicted in the 50 years is expected to lead to a large increase in the number of individuals suffering from both typical and atypical age-related cognitive impairment. In the absence of effective curative treatments for cognitive impairment and dementia, there is an urgent need for novel preventive approaches to delay the onset of, or avert completely, cognitive deficits in old age. This has led to an interest in the potential of diet and lifestyle to affect such disorders. Historically, this research derived from an understanding of the role oxidative stress plays in the deterioration of specific brain structures and function [216, 217] and an interest in the potential of *in vitro* classified 'antioxidants' to counteract this. More recently, these ideas have developed and evolved, predominantly through a better understanding of the absorption and metabolism of such compounds *in vivo* [218], to include other potential mechanisms of action (Fig. 2). These mechanistic lines of evidence have included, amongst other things, their direct interactions with neurons and glial cells post blood-brain-barrier transfer [144, 145, 219, 220], a 'scavenging' of toxic species including oxidants and an inhibition of neuroinflammation, through interactions with activated microglia [15].

Such concepts are reasonably well developed and probably explain, in part, the efficacy of flavonoid-rich foods in the brain following consumption. However, such mechanisms do not explain the totality of their brain activity, in particular cognitive effects occurring more acutely (2–8 h) after intake [107, 108]. A more likely mechanism for this activity is the acute activation of the peripheral vascular system by flavonoids and their metabolites leading to subsequent changes in blood perfusion, which also affects blood flow to, and in, the brain. Increased blood flow to the brain and perhaps even to specifics regions during activity, would facilitate the delivery of oxygen and nutrients thus enhancing signal processing and the encoding or recall of information. It is conceivable that such daily improvements in cerebrovascular blood flow over a prolonged period may be capable of influencing cognitive function through additional mechanisms, notably changes in adult neurogenesis in the hippocampus [221]. This is likely, as it has been observed that changes in blood flow may lead to increased vascularisation, which in turn may stabilise the presence of new neurons [222]. Thus the enhancement of blood

flow and vascular function by flavonoids in the periphery has the potential to impact on both immediate and medium to long-term cognitive function, independent of the bioavailability of these phytochemicals to the brain.

It is now relatively well established that chronic inflammation is a contributory factor in both the onset and progression of neurodegenerative diseases [42, 43, 49] and that flavonoids have the potential to reduce circulating levels of pro-inflammatory mediators such as TNF-α [148, 149] and CRP [151, 152]. Whilst these changes are unlikely to be clinically significant in the short term, small changes in immune factors such as TNF-α and CRP may be capable of reducing the neuronal destruction caused by neuroinflammation. Flavonoid-induced reductions in circulating cytokine levels (and other mediators of inflammation), especially in the context of disease has the potential to preserve cognitive function by lessening the activation of microglia and the damage they inflict on neurons through release of neurotoxic mediators such as high levels of nitric oxide. In the medium to long term, a reduction in inflammatory processes in both the brain and the next 50 years the periphery may act to promote healthy aging and delay the onset and progression of AD and other neurodegenerative diseases.

We propose that future intervention studies designed to investigate the impact of flavonoids, or indeed, other plant-based, polyphenol-rich foods on memory, learning or neuro-cognitive performance should also take account of the various metabolic and immune factors mentioned above. Firstly, measurement of how factors such as blood pressure, cytokines and cholesterol change in response to dietary interventions with flavonoid-rich foods and how these changing levels correlate with cognitive function, will help to build a casual relationship between intake of these foods (and individual components) and effects on brain activity. Secondly, understanding how these risk factors for dementia alter within the context of a human clinical study aimed at assessing the influence of flavonoid intake on cognition will provide a more complete understanding of the mechanisms of action of these pleiotropic compounds *in vivo* (Fig. 2). Such information is likely to establish better evidence regarding the potential of plant-based diets to counteract cognitive impairment and in the longer term may provide potential candidate compounds for a new class of preventive drugs effective against Alzheimer's disease, dementia and other neurodegenerative disorders.

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