Natural Compounds and Plant Extracts as Therapeutics Against Chronic Inflammation in Alzheimer's Disease – A Translational Perspective

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Abstract: Alzheimer's disease (AD) is a progressive neurodegenerative disorder, characterized by deposition of amyloid beta, neurofibrillary tangles, astrogliosis and microgliosis, leading to neuronal dysfunction and loss in the brain. Bio- and histochemical evidence suggests a pivotal role of central and peripheral inflammation in its aetiopathology, linked to the production of free radicals. Numerous epidemiological studies support that the long-term use of non-steroidal anti-inflammatory drugs is preventive against AD, but these medications do not slow down the progression of the disease in already diagnosed patients. There are a number of studies focusing on traditional herbal medicines and small molecules (usually plant secondary metabolites) as potential anti-inflammatory drugs, particulary in respect to cytokine suppression. For instance, ω-3 polyunsaturated fatty acids and a number of polyphenolic phytochemicals have been shown to be effective against inflammation in animal and cell models. Some of these plant secondary metabolites have also been shown to possess antioxidant, anti-inflammatory, anti-amyloidogenic, neuroprotective, and cognition-enhancing effects. This review will provide an overview the effects of catechins/proanthocyanidins from green tea, curcumin from turmeric, extracts enriched in bacosides from Brahmi (*Bacopa monnieri*), flavone glycosides from *Ginkgo biloba*, and ω-3 polyunsaturated fatty acids. They do not only counteract one pathophysiological aspect of AD in numerous *in vitro* and *in vivo* studies of models of AD, but also ameliorate several of the above mentioned pathologies. The evidence suggests that increased consumption of these compounds might lead to a safe strategy to delay the onset of AD. The continuing investigation of the potential of these substances is necessary as they are promising to yield a possible remedy for this pervasive disease.

Keywords: Alzheimer's disease, inflammation, non-steroidal anti-inflammatory drugs, plant secondary metabolites, reactive oxygen species, treatment.

ALZHEIMER'S DISEASE – A GLOBAL BURDEN

Alzheimer's disease (AD) is a complex and heterogeneous progressive disorder of the central nervous system (CNS) [1, 2]. Although the familial early-onset form of AD caused by mutations in the amyloid precursor protein, or presenilin 1 and 2, has received substantial attention, the sporadic, late-onset form of AD accounts for 50-70% of all cases of dementia, including those caused by drug-induced conditions, alcoholism, stroke, Parkinson's disease, Huntington's disease, subdural hematoma, brain tumours, hydrocephalus, vitamin B_{12} deficiency, hypothyroidism, neurosyphilis, and HIV (human immunodeficiency virus) infection, and is therefore the most common neurodegenerative disease in the aging population [3-5]. The prevalence of AD is about 35 million people worldwide which accounts for 10-15% of people aged 65 or older and 35% of those 85 years and older. With increased expectation of life and aging population, it is estimated that this number will triple within the next 40 years, resulting in increased healthcare costs globally [4, 6, 7]. AD not only puts a tremendous strain on patients, their families and carers, but also represents an enormous financial burden on the society and the economy believed to be greater than that for stroke, heart conditions or cancer [4, 7, 8]. While to date there is no cure or treatment, which is able to reliably prevent AD or slow down its progression, there are symptomatic therapeutic strategies currently available for the disease including acetylcholine esterase (AChE) inhibitors and NMDA (N-methyl-d-aspartate)-type glutamate receptor antagonists [6, 8, 9]. Lacking an equivalent clinical representation in the animal kingdom, AD seems to be a uniquely human disease, which might be attributable to our long life and highly pronounced (episodic) memory functions making us more vulnerable to age-related memory dysfunctions [10]. Both, epigenetic and genetic factors are associated with an increased risk of developing the sporadic late-onset form of AD including increasing age, vascular risk factors such as hypertension or diabetes, head trauma, and carrying the AD susceptibility allele ApoE (apolipoprotein E) ε4 [11-13].

PATHOPHYSIOLOGY OF ALZHEIMER'S DISEASE

AD is characterised by progressive cognitive decline caused by degeneration of specific cholinergic neuronal populations ultimately leading to profound dementia. One of

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1871-5273/14 $58.00+.00

the crucial pathological features of AD are the so-called senile plaques, which constitute abnormally aggregated amyloid beta (Aβ) fibrils, and are likely to develop before the onset of neuronal abnormalities. Although the initial cause of sporadic AD is still debated, the "amyloid cascade hypothesis" proposes that the aberrant production, aggregation and extracellular deposition of Aβ are the key factor in the pathogenesis of both the familial and sporadic form of AD [14, 15]. The other key pathological hallmark, neurofibrillary tangles (NFTs), are formed as a result of abnormal hyperphosphorylation of tau protein, one of the microtubule-associated proteins that bind and stabilize neuronal microtubules for their role in the development of cell processes, establishment of cell polarity and intracellular (axonal) transport [4, 6, 7]. During AD, they occur intracellularly in cerebral pyramidal neurons and consist predominantly of "paired helical filaments", comprising abnormally phosphorylated tau and a small amount of ubiquitin [4].

The neurodegenerative processes in AD include synaptic damage, extensive neuronal loss accompanied by astrogliosis and microglial cell proliferation ultimately leading to marked atrophy in susceptible regions of the brain, such as hippocampus, amygdala and basal forebrain [16, 17]. Taken it all together, senile neuritic Aβ plaques, NFTs, and disruption of cholinergic transmission including reduced acetylcholine (ACh) levels in the basal forebrain have been well-established neuropathological hallmarks of AD for decades [17].

While the underlying molecular mechanisms in AD are still not completely understood, a potential initiating factor is thought to be hypoxia caused by reduced cerebral perfusion due to head injuries or vascular abnormalities [13, 18, 19]. Abnormally increased oxidative stress is also known to contribute to neuronal loss [20, 21]. More possible causes and risk factors of AD have been discussed in detail elsewhere and will not be the focus of this review [22, 23]. However, accumulating evidence suggests a pivotal role of chronic neuroinflammation in the aetiopathology of AD [24]. In this review, we will therefore give an overview over the components and mechanisms involved in chronic neuroinflammation of AD pathology as well as over contributing (peripheral) factors and potential preventive or disease modifying anti-inflammatory treatment strategies.

INFLAMMATION IN ALZHEIMER'S DISEASE

During the last two decades, accumulating evidence suggests a pivotal role for neuroinflammatory processes in the development of AD [24-26]. Various studies have shown that AD is associated with a number of innate immune system components, including activation of the complement system, increased levels of cyclooxygenase (COX) 1 and 2 associated with increased levels of prostaglandins (PGs), cytokine and chemokine release, acute phase reaction, microgliosis and astrocytosis [27-29]. Additionally, ACh has been shown to exert anti-inflammatory actions by inhibition of pro-inflammatory cytokine production and suppression of nuclear factor κB (NF-κB) expression [30]. AChE and butyrylcholinesterase are increased in brains of patients suffering from AD, and their activity seems to correlate positively with AD pathologies, including elevated levels of Aβ plaques and NFTs. The increase in AChE and butyrylcholinesterase activities and the degeneration of cholinergic neurons typical for AD imply a depletion of ACh. Therefore, an enhanced local inflammatory state occurs due to the lack of anti-inflammatory actions mediated by ACh [30]. What is not clear is whether inflammation is a consequence of other, already existing pathologies of AD, such as Aβ plaques, NFTs, ACh depletion, and/or debris of degenerated neurons, or inflammation plays a more etiological role. But regardless of the order of events, it appears that AD hallmarks are necessary, yet not sufficient to cause neurodegeneration and dementia on their own unless advanced neuroinflammatory reactions are present [26].

In the AD brain, there is a profound increase in activated microglia that can execute both beneficial and detrimental functions such as the expression of pro-inflammatory mediators [28, 31]. Accordingly, virtually all the cytokines and chemokines that have been studied with reference to AD, including interleukin (IL) -1β, IL-6, IL-8, tumour necrosis factor-α (TNF-α), tumour growth factor-β, macrophage inflammatory protein-1α, and inducible nitric oxide synthase (iNOS) are up-regulated in *in vitro* and *in vivo* models of AD, brain samples of AD patients post-mortem, and individuals with AD when compared to levels in controls [24, 32-35]. IL-1β has also been reported in the cortex, hypothalamus, thalamus, and hippocampus post-mortem, whereas IL-1α was found in up to 30 times as many glial cells (mostly microglia) in AD brain tissue compared to controls [36, 37]. Furthermore, strong immunoreactivity in AD cortices and hippocampi indicates an association of IL-6, α-2-macroglobulin, and C-reactive protein with senile plaques in these brain regions [32, 38]. An association between AD and pro-inflammatory genes polymorphisms has also been described, including those that code for IL-1, IL-6, TNF-α, and α1-antichymotrypsin, an acute phase protein [39-43]. Animal models of the familial forms of AD, such as Tg2567 mice carrying the Swedish mutation and over-expressing APP, also show enhanced levels of TNF-α, IL-1α, IL-1β, chemo-attractant protein-1, COX-2, and complement C1q [44-46]. In addition, it has been reported that mice over-expressing the mutant human P301 tau protein have an increased immunoreactivity to IL-1 and COX-2 [47]. It therefore seems plausible, that Aβ activates microglia and astrocytes, which provokes cytokine production; in turn increasing Aβ levels by facilitating amyloid precursor protein (APP) cleavage. Similarly, tissue damage arising from primary events in AD provokes inflammatory responses, which in turn cause further tissue damage [26]. Finally, PG production is elevated in response to cytokines *in vitro*, and the expression of cytokines and other inflammatory mediators changes in response to certain PGs [29]. As a consequence, neuroinflammation and classic AD pathology events are intertwined in a vicious cycle. The two major types of cells that participate in the brain immune/inflammatory response in AD are the resident glial cells, namely astrocytes and microglia. While both cell types are capable of clearing or degrading Aβ deposits under certain circumstances, a more detrimental role is associated with their activation in AD [48]. Like microglia and astrocytes, neurons have also been found to produce inflammatory mediators that are increased during AD

including COX, molecules of the complement pathways and cytokines. Perivascular macrophages seem to be involved in cerebral amyloid angiopathy by clearing Aβ deposits from cortical blood vessels [49, 50]. Since the larger portion of the already published research has focused on the role of microglia and astrocytes we will concentrate on their involvement in inflammatory processes during AD pathogenesis.

THE LINK OF OXIDATIVE STRESS AND THE REACTIVE OXYGEN SPECIES TO ALZHEIMER'S DISEASE

In general, oxidative stress describes a state of imbalance between generation and elimination of reactive oxygen species (ROS) and nitrogen species [51]. The main source of endogenous ROS production is the electron transport chain in the membranes of mitochondria, especially when these are damaged [52-55]. The most important ROS generated by aerobic cells are superoxide anion, hydrogen peroxide, hydroxyl radical, and perhydroxyl radical. Under hypoxic conditions, the respiratory chain in mitochondria also produces nitric oxide (NO), which generates other reactive nitrogen species like peroxynitrite [56, 57]. Free radicals are a by-product of normal metabolism and ROS act as specific signalling molecules in cell cycle and intercellular transduction pathways [58, 59]. Therefore, ROS play a key role in the modulation of critical cellular functions such as ion transport, calcium mobilisation and apoptosis, and are essential to maintain homeostasis [51, 55]. Under normal conditions, they are scavenged by antioxidants such as vitamin C and E, coenzyme Q10, and glutathione or neutralised by antioxidant enzymes including superoxide dismutase, glutathione peroxidise and catalase [60]. Nevertheless, if these antioxidant defences are incapable of counteracting the oxidative stress burden, overproduction of ROS leads to pathogenic mechanisms including oxidative damage to DNA, lipids and proteins, excitotoxicity caused by excessive calcium influx, and apoptosis [51, 55, 58].

The brain has a high metabolic rate using around 20% of basal oxygen consumption [51]. It is also rich in polyunsaturated fatty acids, which are particularly prone to oxidative modification [61]. Furthermore, antioxidant levels and the capacity for regeneration are lower in the brain compared to the rest of the body. Hence, the CNS is thought to be particularly vulnerable to oxidative stress, which may explain its susceptibility to neurodegenerative diseases involving oxidative damage [60, 62]. In fact, many of the risk factors for AD including normal aging are associated with increased levels of ROS [63]. Furthermore, oxidative stress is also associated with various key features of AD such as metabolic, mitochondrial, metal, and cell cycle abnormalities [64]. It is therefore not surprising that direct evidence for free-radical oxidative damage is evident in brains of patients with AD. More specific, increased levels of iron, aluminium, and mercury, able to stimulate free radical formation, as well as increased lipid peroxidation and decreased polyunsaturated fatty acids have been found in AD brains [65]. Accordingly, levels of highly reactive by-products of lipid peroxidation, such as 4-hydroxynonenal and F_2-isoprostanes are higher in the cerebrospinal fluid and plasma of AD patients [66]. Similarly, DNA and protein oxidation is also elevated in the AD brain [65]. Advanced glycation endproducts (AGEs), a product of accelerated oxidation of glycated proteins, are present in NFTs and Aβ plaques [67, 68]. Furthermore, oxidative stress is evidenced by lipid peroxidation end products, formation of toxic peroxides, alcohols, aldehydes, free carbonyls, ketones, cholestenone and oxidative modifications in nuclear and mitochondrial DNA [68]. A sensitive marker for oxidative stress, heme-oxygenase-1, has also been shown to be upregulated in astroglia of post-mortem brains from patients with mild cognitive impairment [64]. Supporting evidence also comes from a study by Pappolla *et al.* (1992) where tissue sections from five brains of AD patients were immunostained against superoxide dismutase and catalase and compared to brains from healthy subjects. They found that a subgroup of NFTs and senile plaques showed immunoreactivity for both enzymes as well as occasional elements with features consistent with reactive microglia [69]. Similarly, Good *et al.* (1996) demonstrated the presence of nitrotyrosine, the result of nitration of tyrosine residues in proteins during oxidative damage, in NFTs of AD compared to controls without NFTs. These findings link oxidative stress to a key pathological lesion of AD [70].

ANTI-INFLAMMATORY AND NEUROPROTECTIVE EFFECTS OF NON-STEROIDAL ANTI-INFLAMMATORY DRUGS IN AD MODELS

The list of drugs that are under investigation for their potential use against AD is long and covers diverse approaches ranging from the improvement of cholinergic function through AChE inhibitors, muscarinic receptor agonists, anti-Aβ drugs such as active and passive vaccines, and furthermore, calcium antagonists, antioxidants and metal chelators [8]. Here, we focus on the strategies addressing the containment and abatement of the inflammatory processes occurring in AD.

Non-steroidal anti-inflammatory drugs (NSAIDs) represent a class of therapeutics that temper inflammation by inhibition of cyclooxygenase (COX) (as competitive enzyme inhibitors) and thus lower prostaglandin production [71-73]. *In vitro* and *in vivo* studies showed that NSAIDs are able to diminish microglial activation and reduce Aβ formation by affecting APP processing [49, 74]. Accordingly, indomethacin, dexamethasone, and colchicines were all able to inhibit neurotoxicity displayed by peripheral blood monocytes co-cultured with brain tissue when exposed to aggregated Aβ [75]. Most traditional NSAIDs inhibit both COX isoforms, COX-1 and COX-2 [27, 76]. Another target of NSAIDs is the peroxisome proliferator-activated receptor-γ (PPAR-γ), a member of the nuclear hormone receptor superfamily of transcription factors which is, among other cells, expressed by macrophages where it regulates genes involved in the inflammatory response and modulates macrophage differentiation [77]. It has been shown that PPAR-γ is up-regulated in activated macrophages and inhibits the Aβ-induced expression of various inflammatory mediators like IL-6, TNF-α, iNOS or COX-2 by mechanisms including the inhibition of STAT (signal transducer and activator of transcription) activity [78, 79]. Furthermore, PPAR-γ is likely to be involved in Aβ processing/metabolism. The activation of PPAR-γ decreased Aβ levels in cell cultures of

non-neuronal and primary murine-mixed glia and cortical neuronal cells indicating a role in the induction of an Aβ-clearing mechanism [80]. In another study Sastre *et al.* (2003) showed that, like indomethacin and ibuprofen, PPAR-γ was also able to reverse cytokine-induced Aβ secretion in neuroblastoma cells. Here, the inhibitory actions exhibited by NSAIDs could be suppressed by PPAR-γ antagonists suggesting that the effects of these drugs are mediated, at least partly, by PPAR-γ activation [81]. A more recent study by the same group showed that depletion of PPAR-γ increased levels of BACE1 (β-site APP cleaving enzyme 1) mRNA alongside γ-secretase, the main enzyme responsible for the unfavourable cleavage of APP, *in vitro*. On the contrary, PPAR-γ over-expression, PPAR-γ agonists or NSAIDs decrease BACE1 gene promoter activity and Aβ levels while increasing PPAR-γ mRNA *in vivo* [82]. This suggests that the potential effect of NSAIDs could be through regulation of BACE1 promoter activity.

Intracerebroventricular (icv) or subcutaneous injections of indomethacin and oral administration of flurbiprofen significantly attenuated microglial proliferation in response to Aβ infusion into the lateral ventricle or nucleus basalis in rats [83, 84]. Ibuprofen has been shown to directly and selectively affect APP processing *in vitro*, leading to a reduced production of the toxic $A\beta_{42}$ in favour of $A\beta_{38}$ and not affecting $A\beta_{40}$ [85]. A study by Lim *et al.* (2000), agreed that Tg2576 mice fed with 46mg/kg/day ibuprofen for six months showed a significant reduction in activated microglia, IL-1β, glial fibrillary acidic protein, Aβ deposits and dystrophic neurites [86]. Yan *et al.* (2003) confirmed these *in vitro* results with ibuprofen treatment, and also showed a 60% reduction of plaque load in cortex of Tg2576 mice *in vivo* [87]. Furthermore, COX-2 has been associated with Aβ accumulation and cognitive decline in mice treated with lipopolysaccharide (LPS) [88]. Indeed, a three-week oral pre-treatment with 3.75mg/kg and 7.5mg/kg of the selective COX-2 inhibitor sulindac sulphide suppressed LPS-induced memory impairments, neuron death and amyloidogenesis in rats and ICR mice *in vivo*. LPS-induced amyloidogenesis was also suppressed in cultured astrocytes and neurons *in vitro* [88]. Another study showed that selective inhibition of COX-2 but not COX-1 inhibited Aβ-induced suppression of hippocampal long-term plasticity. Furthermore, alongside the non-selective NSAIDs ibuprofen and naproxen, a selective COX-2 inhibitor, MF-tricyclic, restored memory function in Tg2576 mice [89]. Nevertheless, the picture of the efficacy of COX-inhibition in the treatment of AD is far from being complete. Many studies focusing on COX-2 inhibition failed to deliver promising results. For example, COX-2-selective drugs were ineffective in reducing Aβ-load in APP+PS1 mice and even increased $A\beta_{42}$ in Tg2578 mice and cell cultures [90, 91].

A large body of epidemiological studies have shown that NSAIDs are protective against AD. They have been found to delay the onset of AD in a co-twin study [92, 93]. Further evidence was provided by several population-based cohorts and case-control studies that revealed a decreased risk for AD when comparing (long-term) NSAID-users to non-users [94-99]. However, when examined in humans based on medical records or self-reports of NSAID use, NSAID-based γ-secretase modulators (Aβ-lowering drugs) such as ibuprofen, indomethacin or sulindac sulphide were not shown to be advantageous over normal NSAIDs [100, 101].

Together, these studies strongly suggest that NSAIDs do reduce the risk of AD or delay its onset in presymptomatic patients, but they do not slow down cognitive decline in already diagnosed AD patients.

CLINICAL TRIALS OF NSAIDs IN AD PATIENTS

Interest in the use of NSAIDs for AD prevention was sparked by a study indicating that indomethacin, in doses of 100-150mg/day, appeared to protect mild to moderately impaired AD patients from the degree of cognitive decline compared to placebo-treated controls [102]. A further encouraging double-blind placebo-controlled clinical pilot study with 50mg diclofenac/200mg misoprostyl was conducted in subjects with mild to moderate AD. However, this study, like that by Rogers *et al.*, suffered from low power and a high dropout rate [103]. Larger studies could not confirm these positive pilot trials. In a randomized controlled trial in patients with mild to moderate AD twice-daily treatment with 220mg naproxen for one year failed to show any benefits in slowing or preventing further cognitive decline when compared to placebo while causing severe side effects [104].

Studies in humans were similarly disappointing. Neither of the COX-2-selective NSAIDs rofecoxib, celecoxib, and nimesulide was able to show beneficial effects on cognitive decline, clinical status or activities of daily living compared to placebo in patients with AD of different severity [104-107]. Therefore, it is likely that selective COX-2 NSAIDs are either unfeasible drugs to treat AD, or have to be applied earlier in the disease progression, before an actual cognitive impairment is apparent.

While epidemiological and animal studies show a clear trend towards effectiveness of NSAIDs, results from clinical trials indicate that NSAIDs are only effective before the onset of AD, presumably interfering with peripheral inflammation, which can intensify CNS damage. Based on the clinical trials alone, NSAIDs in clinically diagnosed AD patients have failed to prove the efficacy of NSAIDs in the treatment of AD.

ANTI-INFLAMMATORY COMPOUNDS IN PLANT BASED FOODS

In recent years studies have focused on different nutritional approaches to benefit AD patients, many of them involving compounds or foods known to decrease inflammation. Deficiencies of specific dietary nutrients, such as ω-3 fatty acids and certain vitamins, have been associated with loss of memory and other cognitive impairments in the elderly and are thought to aggravate pathological processes in the AD brain [108, 109]. Observational studies examining different dietary patterns with regard to the risk of developing AD revealed that diets rich in red meat, high-fat dairy products, butter, and refined sugar were associated with a higher AD risk, whereas diets rich in grains, vegetables, fruit, poultry, fish, and nuts decreased the risk [110-112]. More specifically, foods rich in ω-3 fatty acids, vitamins, and diverse groups of polyphenolic plant

secondary metabolites have been shown to be effective against several AD pathologies, including abnormal Aβ processing, synaptic degeneration, oxidative stress, and inflammation, and slowed the progression of cognitive decline [109, 113-115]. Extensive research has accumulated data over the last few decades on the efficacy in AD treatment utilising anti-amyloidogenic, anti-oxidative, and anti-inflammatory properties of naturally occurring substances like curcumin, catechins (from green tea), several fatty acids, and polyphenols (anthocyanins) for example found in blueberries [2, 114, 116]. Naturally occurring compounds from dietary sources are sustainable, provide diverse, yet unexplored phytochemical scuffolds, and are relatively safe to consume without major side effects in most cases. In the following sections, we will focus on the progress made with some of the most promising plant secondary metabolites.

Curcumin from Turmeric: A Multi-Target Treatment Strategy in AD

Curcumin, a diarylheptanoid polyphenol isolated from the rhizomes of *Curcuma longa* L. (Zingiberaceae, common name: turmeric) is a food additive in Indian cuisine and is used in Ayurvedic medicine [117]. Curcumin has an excellent safety profile and is known to exhibit various pleiotropic properties, including antioxidant, anti-inflammatory, anti-amyloidogenic, lipophilic and cognition/memory enhancing actions, which suggests a potential neuroprotective nature of this compound [118, 119].

Curcumin has been shown to decrease Aβ plaques, delay neurodegeneration, metal-chelation, and decrease microglia activation *in vitro* [119]. Curcumin has the capacity to inhibit COX-2, and therefore also PGE_2 synthesis, lipoxygenase (LOX), and iNOS, which are all important components in AD-correlated inflammation processes [120, 121]. Cho *et al.* (2007) found an inhibitory effect of curcumin on TNF-α-induced IL-1, IL-6 and TNF-α expression in an immortal human keratinocyte cell line (HaCaT), and that this effect is most likely mediated through inhibition of nuclear NF-κB and MAPK (mitogen-activated protein kinase) pathways [122]. Another study showed that curcumin was able to block NO, TNF-α, IL-1α, and IL-6 production by microglia activated by Aβ or LPS *in vitro* [123]. Similarly, in a rat model of diabetes, which is known to be a risk factor for AD, 100mg/kg of curcumin administered orally for seven days reversed the diabetes-induced increase in blood IL-6, MCP-1 (monocyte chemotactic protein-1), TNF-α, and oxidative stress levels [124]. Yang *et al.* (2005) showed that curcumin inhibits $Aβ_{40}$ aggregation more effectively than ibuprofen or naproxen, and prevents $Aβ_{42}$ oligomer formation and toxicity at low doses *in vitro* [125]. In addition to decreased levels of IL-1β and oxidised proteins, another study found suppression of microgliosis and reduced levels of the astrocyte marker glial fibrillary acidic protein (GFAP), insoluble and soluble Aβ, and plaque burden in APPsw mice treated with different doses of dietary curcumin [126]. In a more recent study in APPsw/PS1dE9 mice, curcumin was able to cross the blood brain barrier, clear and reduce existing Aβ plaques, and reverse structural changes in dystrophic dendrites after one week of treatment [127]. The mechanisms by which curcumin exerts the effects on the different AD pathologies is still to be clarified. However, there are indications that curcumin might act through the activation of PPAR-γ [128]. Numerous studies suggest that curcumin might exert its beneficial effects through interaction with PPAR-γ which is supported by the finding that curcumin blocks COX-2, LOX and iNOS, all known to be inhibited by PPAR-γ activation [78, 79, 120]. However, Narala *et al.* (2009) found curcumin to be inactive in various reporter and DNA binding assays as well as PPAR-γ ligand binding and antagonising experiments examining the interaction between PPAR-γ and curcumin. They therefore concluded that curcumin was not a ligand for PPAR-γ [129]. Thus, curcumin could act indirectly on PPAR-γ receptors.

The bioavailability and EC_{50} values of curcumin for various effects have been established in rodents. Oral administration of 500ppm and 2000ppm curcumin in chow for four months resulted in 1.276μM and 1.428μM concentrations, respectively, in the brain [130]. It has been shown that curcumin is metabolised (glucuronidated) to a higher extent in humans compared to rodent intestine, leaving the bioavailability in humans critically low [131, 132]. However, optimised formulations of lipidated curcumin reached brain concentrations of 5.79μM in mice after two weeks of oral administration of 500ppm in chow [130]. This will hopefully transfer to human studies in order to produce significant beneficial effects due to increased bioavailability.

Curcumin has well-established anti-inflammatory effects in various pathologic conditions in humans including rheumathoid arthritis, gastrointestinal conditions and several forms of cancer [133]. However, despite these promising findings *in vivo* and *in vitro*, in a 24-week randomised, double-blind, placebo-controlled pilot study no differences between groups in cognitive performance or Aβ and tau measures could be found in patients with mild to moderate AD. The authors state that this might have been due to poor bioavailability of the compound [134]. On the contrary, frequent consumption of curry was associated with better Mini Mental State Examination scores compared to rare curry consumption in a population-based study with healthy Asian subjects between the age of 60 and 93 years [135]. Furthermore, the prevalence for AD appeared to be lower in a sample of Indians 55 years of age or older compared to a sample of elderly people being 70 years of age or older from the U.S. in a cross-national epidemiological study [136]. Nevertheless, a randomised, placebo-controlled, double-blind pilot clinical trial of curcumin in AD patients failed to show beneficial effects of curcumin on cognition, while Aβ aggregation was prevented [137]. Further investigation with regards to its mode of action, involved components and mechanisms, the best curcumin dosing regimen and the best pharmaceutical form is therefore urgently needed.

Bacosides – Dammarane Triterpenoid Saponins - from Brahmi: Anti-Inflammatory Cognition-Enhancers

Brahmi (*Bacopa monnieri* L.; Pennell, Syn. *Baciopa monnieri* L. Wettestein, placed both in Scrophulariaceae and Plantaginaceae by some authors) is also known as water hyssop. Brahmi is used in Ayurvedic medicine to enhance memory, concentration, and learning, and thought to have anti-anxiety, anti-depression, anti-inflammatory, analgesic,

anti-pyretic, sedative and antiepileptic properties [138, 139]. The active fractions of this medicinal herb contain bacosides, dammarane triterpene saponins, more specifically bacosides A and B fractions. The basic aglycones of bacosides are jujubogenin and pseudojujubogenin [140, 141]. Bacoside A is found to facilitate mental retention in avoidance response in rats and reverse amnesic effects of various stressful stimuli [142, 143]. In more recent years, modern science rediscovered the beneficial effects of this plant and numerous studies now investigate its applicability in chronic diseases.

Brahmi extract is also able to inhibit LOX, COX-2 and decrease TNF-α levels in rat monocytes *in vivo* and in a human whole blood assay *in vitro* [144]. Williams *et al.* (2014) investigated the effect of incubation with Brahmi extract on stimulated murine RAW 264.7 macrophage cells with LPS and interferon-γ as well as whole human blood cells with LPS and phytohemeagglutinin. They found a down-regulation of NO and TNF-α in stimulated RAW 246.7 macrophages and of interferon-γ in stimulated human blood cells, providing evidence for an anti-inflammatory effect of Brahmi extract on cells of the immune system *in vitro* [145]. Another group showed Brahmi's ability to reduce ROS and inhibit NO-induced cellular alterations in cultured rat astrocytes [146]. In an acute inflammatory rodent model of paw oedema, Brahmi extract was able to selectively inhibit PGE_2-induced inflammation [147]. An *in vitro* study examining the viability of neuronal cells following Aβ and glutamate exposure with and without Brahmi extract showed that it was able to prevent Aβ-induced cell death but not glutamate-induced excitotoxicity. The authors further found increased viability and reduced levels of oxidative stress in cells cultured in medium containing the extract [148]. Holcomb *et al.* (2006) found that in PSAPP mice, a mouse model of AD, 40 or 160mg/kg/day Brahmi extract for two or eight months could not only lower $A\beta_{40}$ and $A\beta_{42}$ levels in cortex, but also restore Y-maze performance and open field behaviour in these mice [149]. In line with these findings, 50mg/kg of Brahmi extract were able to reverse colchicine-induced memory impairments in the elevated plus maze in rats. Another animal model of AD similarly showed that different doses of an alcoholic extract of Brahmi administered for three weeks improved spatial memory in the Morris water maze and attenuated reductions in cholinergic neurons in rats that received icv administration of ethycholine aziridinium ion [150].

While its anti-inflammatory effects have been established in various animal models and its potency is comparable to that of indomethacin, human trials regarding the anti-inflammatory properties of Brahmi are few in numbers [147, 151]. More focus has been put on research regarding its cognition enhancing effects. In a double-blind, placebo-controlled study in healthy human subjects, oral administration of 300mg of Brahmi extract for twelve weeks significantly improved visual information processing, learning rate, memory consolidation and anxiety levels [142]. The same treatment regimen also led to reduced depression and heart rate compared to placebo controls [140]. Another double-blind placebo-controlled independent group design study by Stough *et al.* (2001) used a different treatment pattern, 150mg of extract twice daily for 90 days, in healthy subjects. Again, the active treatment group showed significant improvements in spatial working memory and visual information processing [143]. These are promising findings; however, further clinical studies examining the effects of Brahmi extract in AD patients are needed to confirm its efficacy against the actual disease.

Polyphenols from Green Tea: Multi-Target Neuroprotectants

Green tea (*Camellia sinensis* L. Kuntze, Theaceae) is prepared by drying the tea leaves either by steaming or pan-frying. Tea polyphenols account for ~30-40% of water soluble solids in brewed green tea and the four major tea polyphenols are (-)epicatechin, (-)epicatechin gallate, (-)epigallocatechin, and (-)epigallocatechin-3-gallate (EGCG). Green tea also contains other antioxidant oligomeric procyanidins, gallic acid, galloyquinic acids, minerals and vitamins [152, 153]. A variety of health benefits have been associated with the consumption of tea for millennia. Their antioxidant effects have been demonstrated in numerous *in vitro* and *in vivo* studies, while the polyphenols are also thought to exhibit anti-inflammatory, anti-diabetic, antibacterial, anti-viral, anti-carcinogenic and, neuroprotective properties [154, 155]. In addition, several studies suggest an anti-amyloidogenic effect of EGCG [156, 157]. Because of their broad spectrum of cellular targets and diverse pharmacological activities, green tea polyphenols may be considered powerful neuroprotective drugs acting on several disease mechanisms [153].

Cell culture studies using different models of induced toxicity (for example neurotoxin- or Aβ-induced) and apoptotic damage confirmed a positive effect of EGCG on cell survival [153]. In human chondrocytes stimulated with IL-1β EGCG was able to decrease levels of NO and PGE_2 correlating with the inhibition of iNOS and COX-2 activities [158]. Choi and colleagues (2001) exposed hippocampal neurons to Aβ for 48 hours and showed increased cell viability and a reduction in markers of oxidative stress with concordant EGCG treatment [156]. In another study, cultured rat PC12 cells treated with Aβ showed elevated levels of ROS and underwent apoptosis, whereas those co-treated with green tea extract were found to have reduced ROS levels and higher survival rate. In addition, the extract inhibited the Aβ-induced activation of the NF-κB and ERK/MAPK pathways [159]. As mentioned earlier, the effects of green tea polyphenols including EGCG are diverse and not fully understood to date. Nevertheless, being phenolic compounds, they possess the ability to chelate transition metal ions thereby preventing iron-induced lipid peroxidation and the formation of iron-induced free radicals. Hence, polyphenols act as radical scavengers of ROS and reactive nitrogen species [153]. The promotion of the non-amyloidogenic pathway and a corresponding reduction in Aβ levels and plaques could also be demonstrated in APPsw mice treated with EGCG [156]. Similarly, pre-treatment with 1.5 or 3mg/kg EGCG in mice for three weeks lead to the inhibition of Aβ-induced increases in β- and γ-secretase activities as well as ERK (extracellular signal-regulated kinases) and NF-κB pathways [157]. The anti-amyloidogenic effect of EGCG is likely to be due to an early interference in the Aβ cascade. Inhibition of the formation and elongation of nascent Aβ fibrils and a destabilisation of Aβ assemblies

have been shown with green tea polyphenols [153]. In addition to lower plasma concentrations of lipid peroxides, an improvement in spatial cognition learning ability was shown in young rats after an oral 26-week treatment with green tea catechins [160].

There is a lack of well-controlled clinical trials examining the capacity of green tea polyphenols in the human brain and AD case-control studies did not report any significant outcome when comparing tea consumption of patients and controls. However, epidemiological data show a reduced risk of Parkinson's disease, a neurodegenerative disease whose chemical pathology is similar to that of AD, with consumption of two or more cups per day [152]. A study by Katiyar *et al.* (1999) showed that EGCG reduced UVB (ultraviolet B) -induced inflammatory responses in human skin including PGE_2 levels [161]. Another study showed an association between higher consumption of green tea and lower prevalence of cognitive impairment in a cross-sectional community-based assessment of the elderly in Japan [162]. The progress of studies investigating the effects of green tea in humans is still in its fledging stages and results from epidemiological and clinical studies about the potential health benefit of green tea are inconclusive [155]. The poor bioavailability of EGCG has to be overcome in order to diminish variations in experimental outcome and to gain more reliable and stronger results in clinical studies [163]. In a next step, well-designed clinical studies are needed to undermine the positive findings of epidemiological data and to establish the full potential of green tea polyphenols in treating chronic diseases like AD.

Ginkgo Flavone Glycosides: Versatile Cognition-Enhancers

Ginkgo biloba L. (Ginkgoaceae), also known the maidenhair tree, is the sole survivor species of an ancient group of Gymnosperms [164]. *G. biloba* is a native Chinese tree whose leaves are rich in antioxidant flavone glycosides derived primarily from quercetin, kaempferol and isorhamnetin flavone aglycones [165]. The first commercial standardised *Ginkgo* leaf extract EGb 761 was first marketed in Europe about 40 years ago as food supplement and drug against various conditions including vascular, cerebral, and neurosensory deficits. EGb 761 is a leaf extract standardised to 24% *Ginkgo* flavonol glycosides and 6% terpene lactones (ginkgolides A, B, C, J and bilobalide) [166]. Recent evidence on *Ginkgo* flavone glycosides suggests a potential role in the prevention or treatment of neurodegenerative disorders [167].

Pre-treatment with EGb 761 suppresses LPS-induced production of NO in RAW 264.7 macrophages and C57BL/6 mice by inhibiting LPS-induced rises in iNOS levels [168]. It has also been shown to significantly reduce PGE_2 and TNF-α levels in RAW 264.7 macrophages [169]. Kwak *et al.* (2002) investigated the mechanisms underlying PGE_2 inhibition after administration of *Gingko* extract in LPS-stimulated RAW 264.7 macrophages. They found that down-regulation of COX-2 expression rather than direct inhibition of COX-1 or COX-2 was involved in this effect [170]. In a neuroblastoma cell line as well as transgenic nematodes both expressing Aβ, a rise in hydrogen peroxide (H_2O_2) levels was found when compared with wild type controls. However, treatment with EGb 761 significantly reduced baseline and Aβ-induced levels of H_2O_2-related ROS production suggesting a potential beneficial antioxidant role in AD [171]. A study investigating the effects of EGb 761 against Aβ- and H_2O_2-induced toxicity in hippocampal primary cultured cells showed that co-administration of EGb 761 dose-dependently and effectively protected and rescued cells from Aβ- and H_2O_2-derived toxicity. Furthermore, it was able to block aversive events caused by Aβ including apoptosis, and ROS accumulation [172].

In line with these findings, a study using Tg2576 mice investigated the effects of dietary EGb 761 supplementation (300mg/kg/day) for one to 16 months. It showed that long-term treatment with the extract significantly lowered APP levels by more than half in cortex but not hippocampus when compared to controls. APP levels, however, were not affected in young mice treated for one month [173]. While the soluble Aβ load and plaque burden were not changed, Tg2576 mice receiving six months of oral treatment with 70mg/kg of EGb 761 daily were able to retain spatial memory to a similar level as wild type mice whereas untreated Tg2576 mice showed spatial learning impairments [174].

Human trials concerning the anti-inflammatory effects of *Ginkgo* leaf extracts are scarce. Nevertheless, a study examining the effects of *Ginkgo* extract on IL-6 levels in patients of neurologic disorders showed decreased IL-6 serum levels in those patients treated with the extract [175]. In line with this, scores of attention, memory, and activities of daily life were significantly better for those outpatients with pre-senile and senile AD receiving a daily oral dose of 240mg EGb 761 compared to the placebo group in a 24-week prospective, randomised, double-blind, placebo-controlled, multi-centre study [176]. In a three-month double-blind, randomised, placebo-controlled, parallel-group design study by Maurer *et al.* (1997) using the same dose in 20 outpatients with mild to moderate AD, the active treatment group obtained improved scores for attention and memory when compared to the placebo group [177]. Similarly, in a 52-week randomised, double-blind, placebo-controlled, parallel-group, multi-centre study in mildly to severely demented AD outpatients, daily treatment with 120mg EGb 761 lead to better results in all cognitive and daily life tests assessed when compared to placebo [178]. These studies suggest a stabilising or improving effect of EGb 761 on cognition and social functioning as well as a good tolerability with negligible side effects. Nevertheless, not all studies lead to such positive results. For example, in a randomised, double-blind, placebo-controlled trial, Schneider *et al.* (2005) were unable to show convincing differences in cognitive test scores between treatment groups, while a rather marginal cognitive decline in the placebo group might have compromised any possible positive outcomes for EGb 761 [179]. Larger scale clinical trials are therefore needed to shed further light on the potential of this extract towards preventative treatment of AD.

Polyphenols from Blueberries: Potent Anti-Oxidants and Anti-Inflammatories

Numerous epidemiological studies confirm the beneficial effects of the polyphenols found in blueberries and other

fruit and vegetables on various aspects of health [180]. Blueberries, especially highbush blueberries (*Vaccinium corymbosum* L., Ericaceae) are rich in anthocyanins and are reported to contain ~25-495mg/100g. Anthocyanins are polyphenols and are glycosidic and acyloglycosidic forms of anthocyanidin aglycones. Anthocyanidins are polyhydroxy and polymethoxy derivatives of 2-phenylbenzopyrilium (flavilium salts). Anthocyanins possess $C_6C_3C_6$ skeletal structure, a common feature of all flavonoids [181]. Blueberry anthocyanins have strong antioxidant properties and interfere with the cell metabolism on different levels, exerting a great potential for anti-aging, anti-inflammatory, anti-excitotoxic, and therefore neuroprotective and cognition-enhancing effects [182].

An *in vitro* study by Lau *et al.* (2007) showed that blueberry extract inhibited the production of NO, IL-1β, and TNF-α and reduced protein and mRNA levels of iNOS and COX-2 in LPS-stimulated BV2 microglia [183]. A later study by the same group revealed reduced iNOS and COX-2 promoter activities as well as inhibited NF-κB nuclear translocation in LPS-activated BV2 cells treated with polyphenol-enriched blueberry extract. The authors therefore suggested that the beneficial effects of blueberries might be mediated through modulation of oxidative stress and inflammation pathways [184]. This was confirmed by Han *et al.* (2005), showing that 100μg/mL of blueberry extract inhibited the increase of PGE_2 production upon LPS stimulation in human endothelial cells [185]. Another group found that blueberry extract significantly increased Aβ clearance of primary mouse microglia in culture, inhibited its aggregation and suppressed microglial activation *via* inhibition of a MAPK pathway [186]. Similar results were found in animal studies. TNF-α and IL-6 serum levels as well as protein and mRNA expression in peritoneal macrophages were lower in $ApoE^{-/-}$ mice fed with a diet containing 1% blueberry for five weeks when compared to animals fed with a regular diet. A subsequent treatment of macrophages with polyphenol-enriched extracts gained from the mice's sera containing either none or 10% blueberries showed an attenuation of LPS-induced TNF-α and IL-6 mRNA and protein expression as well as inhibition of NF-κB and MAPK phosphorylation [187]. In another study, a diet containing 2% blueberry supplement was fed to a group of aged rats, while another group of the same age and a group of young rats received a control diet for four months. The performance in object recognition memory and visual paired comparison tasks of aged rats receiving the blueberry diet was restored to a level comparable with that of young controls and significantly better than that of old control diet rats. Levels of NF-κB were also found to be significantly lower in several brain regions of blueberry-fed aged rats compared to aged control diet rats [188].

Despite promising epidemiological data on polyphenols, similar to *Ginkgo* and Brahmi, studies concerning anti-inflammatory effects of blueberry extract in humans are rare, although well established in animal models [189]. Nevertheless, in older adults with early stages of age-related mild cognitive impairment, daily consumption of wild blueberry juice for twelve weeks was associated with improvements in different aspects of memory and reduced symptoms of depression and glucose levels [190]. These findings, together with epidemiological, *in vitro* and animal data provide a strong basis to further establish the beneficial effects of blueberries as a potential treatment against AD in more elaborated human trials and clinical studies.

Omega-3 Fatty Acids: Potent Neuroprotective Anti-Inflammatories

Omega-3 polyunsaturated fatty acids (ω-3 PUFAs), in form of oily fish such as salmon, herring, mackerel, sardines, or trout, have been shown to be beneficial for skeletal health and function as well as in various chronic diseases; therefore, they are an essential part of a healthy diet [191-194]. By modulating neuronal function and controlling oxidative stress, they are also crucial for brain development. Docosahexanoic acid (DHA), the primary ω-3 fatty acid found in neurons, has caught particular interest of researchers investigating its role in the development of psychiatric and neurological disorders [195]. Accordingly, there are a vast number of studies regarding the potential of ω-3 fatty acids in the prevention or treatment of AD.

In a study conducted with CaCo-2 colon cancer cells treated with DHA, a down-regulation of PGs as well as COX-2 and iNOS expression was found [196]. In human kidney-2 (HK2) cells, DHA and eicosapentaenoic acid (EPA) both exerted anti-inflammatory effects, evidenced by decreased LPS-induced NF-κB activation and MCP-1 expression. The authors found increased levels of PPAR-γ mRNA and protein levels upon DHA or EPA administration. In addition, a PPAR-γ antagonist inhibited the DHA- and EPA-induced reductions in LPS-induced NF-κB and MCP-1, which suggests that the anti-inflammatory effects of these fatty acids involve PPAR-γ pathways [197]. In line with that, Dyall *et al.* (2010) found that the age-related decreases in PPAR-γ in the forebrain of old rats could be prevented by supplementation with 270mg/kg/day DHA and EPA for twelve weeks. They also reported potential positive effects on neurogenesis in the hippocampus [198]. Animal studies were also able to provide promising results. Aged TG2576 mice fed with a diet high in DHA (0.6%) for approximately five months had significantly lower overall levels of Aβ, $Aβ_{42}$, and plaque burden, especially in hippocampus and parietal cortex, when compared to those fed with low-DHA (0%) or control (0.09%) diets [199]. In a study by Hashimoto *et al.* (2002), pre-administration of DHA in rats seemed to attenuate the decline in avoidance learning ability caused by icv injections of Aβ when compared to animals without DHA treatment. Furthermore, they could show a reduction in apoptotic products and a prevention of Aβ-induced increases of lipid peroxide and ROS in cortex and hippocampus, suggesting a neuroprotective and antioxidant effect [200].

The anti-inflammatory properties of ω-3 PUFAs have been extensively investigated in epidemiological studies and in several clinical trials, showing strong efficacy in rheumatoid arthritis or psoriasis, and weaker efficacy in asthma and inflammatory bowel disorders [201, 202]. Accordingly, a study investigating the effects of 2.4g/day ω-3 PUFA supplementation in young and older women for three months showed reduced levels of IL-1, IL-6 and TNF-α, especially in older subjects indicating beneficial anti-inflammatory effects [203]. Epidemiological or clinical studies focusing on beneficial effects in AD pathogenesis, however, failed to deliver clear results. In a prospective

study examining the development of AD in initially healthy subjects between 65 and 94 years of age over a period of about four years, the analysis of dietary questionnaires regarding the consumption of fish and ω-3 PUFAs revealed that those participants consuming fish once or more per week had a remarkably reduced risk of developing AD. Total consumption of ω-3 PUFAs as well as DHA was also associated with a decreased AD risk, whereas EPA failed to show such an effect [204]. Investigating plasma levels of ω-3 PUFAs in patients with cognitive impairment or dementia and controls aged 65 years or older revealed that while there was no difference between overall ω-3 PUFAs concentrations between controls and both patient groups, cognitively impaired subjects had higher levels of EPA than controls, whereas demented subjects exhibited higher DHA and overall ω-3 PUFA levels than controls [205]. This finding either challenges the hypothesis that ω-3 PUFAs have beneficial effects in AD and other forms of dementia, or the elevated levels in patients represent a compensatory mechanism occurring during AD pathogenesis for protective reasons. In contrast, the Framingham Heart Study, a prospective nine-year follow-up study in initially healthy subjects with a median age of 76 years, Schaefer *et al.* (2006) found those subjects in the highest quartile of baseline phosphatidylcholine DHA levels to have a significantly lower risk of developing all-cause dementia and a lower risk of developing AD when compared to subjects in the lower three quartiles [206]. In a randomized, double-blind, placebo-controlled clinical trial, patients diagnosed with AD received daily DHA (1.7g) and EPA (0.6g) or placebo for six months, after which both groups received the ω-3 PUFA treatment for another six months. After the first six months, only a subgroup in the ω-3 PUFA-treated group with very mild cognitive dysfunction showed a significant reduction in Mini Mental State Examination score decline rate when compared to the placebo group. Similar results could also be shown for the placebo group after receiving six months of ω-3 PUFAs [207]. Another clinical trial by the same group using the same treatment regimen in AD patients on AChE inhibitor medication investigated the effects of ω-3 PUFA supplementation on neuropsychiatric symptoms and was unable to find any overall treatment effects. However, potential positive effects were observed for depressive symptoms in non-carriers of the ApoE ε4 allele, and for agitation symptoms in patients with this allele [208]. Finally, a systemic review of literature addressing the effects of fish consumption or ω-3 PUFA supplementation on AD risk and cognitive decline found that in patients without AD ω-3 PUFAs may yield positive effects on cognitive decline, whereas they did not seem to prevent or treat AD, reflected by the results of studies reporting cognitive decline or AD incidence as primary outcome [209]. Hence, outcome measures, dosing regimens, stage and severity of pathological status as well as genetic predisposition all have to be taken into account when planning studies and interpreting data.

SUMMARY OF THE EFFECTS AND MECHANISM OF SECONDARY PLANT METABOLITES

Taken the findings above together about the actions of secondary plant metabolites, including curcumin, bacosides, EGCG, EGb 761, anthocyanins and ω-3 PUFAs, we can conclude that all of these compounds reach the intracellular space of the mammalian cells, and exhibit mostly inhibitory effects (Fig. **1**).

Curcumin decreases Aβ-plaque deposition, inhibits $A\beta_{40}$ aggregation and prevents $A\beta_{42}$ oligomer formation and toxicity. It also inhibits LOX, COX-2 and iNOS expression leading to decreased levels of PGE_2 and NO. It has an inhibitory effect on TNF-α-induced IL-1, and IL-6 that is most likely mediated through inhibition of NF-κB and MAPK pathways. Curcumin also reduces levels of the astrocyte marker GFAP in the brain as well as protein oxidation and reversed increases in blood MCP-1.

Bacosides increase cell viability while lowering $A\beta_{40}$ and $A\beta_{42}$ levels and Aβ-induced cell death. They also inhibit COX-2 expression, thereby inhibiting PGE_2-induced inflammation. TNF-α and ROS levels are reduced upon bacoside treatment. Lipid peroxidation levels are decreased and NO-induced cellular alterations are inhibited.

The extract from tea leaves, (2)-epigallocatechin-3-gallate (EGCG) decreases Aβ levels and –plaque deposition by promoting the non-amyloidogenic pathway, thereby reducing Aβ-induced activation of the NF-κB, ERK, and MAPK pathways as well as β- and γ-secretase activity. Cells treated with EGCG show increased viability upon Aβ-exposure. iNOS and COX-2 are inhibited, leading to decreased levels of NO and PGE_2. A reduction of markers of oxidative stress, lower ROS levels and reduced lipid peroxidation are also noticed.

Ginkgo-flavonol glycoside, the main active component of the *Ginkgo biloba* extract is called EGb 761. Cells treated with EGb 761 show decreased levels of APP and are rescued from Aβ-derived toxicity and adverse events including apoptosis and ROS accumulation. The production of NO is suppressed by inhibition of iNOS expression. Similarly, COX-2 is down-regulated, leading to reduced levels of PGE_2. TNF-α and IL-6 levels are also significantly reduced by EGb 761.

Blueberry extract decreases microglial activation by inhibiting the MAPK pathway. Increased Aβ-clearance and lower levels of aggregated Aβ have also been reported. Levels of NF-κB are significantly lower in certain brain regions upon treatment with blueberry extract and its nuclear translocation is inhibited. Phosphorylation of NF-κB and MAPK is also inhibited. Blueberry extract inhibits the production of TNF-α, IL-1β, and IL-6 and reduces iNOS as well as COX-2 levels thereby preventing increases in PGE_2 and NO.

ω-3 PUFAs include DHA and EPA. DHA lowers overall levels of Aβ and Aβ-plaques, while both DHA and EPA have potential positive effects on neurogenesis. COX-2 and iNOS expression are down-regulated, accompanied by reduced levels of PGs. Reductions of NF-κB activation as well as MCP-1 expression have also been found upon DHA and EPA treatment whereas PPAR-γ levels are increased. DHA treatment prevents lipid peroxidation and lowers ROS levels and apoptotic products. ω-3 PUFAs were also able to lower levels of TNF-α, IL-1, and IL-6.

Taken all these together, as shown in Fig. (**1**), we found that all plant secondary metabolites ω-3 PUFAs influence Aβ by either promoting its clearance or inhibiting its aggregation

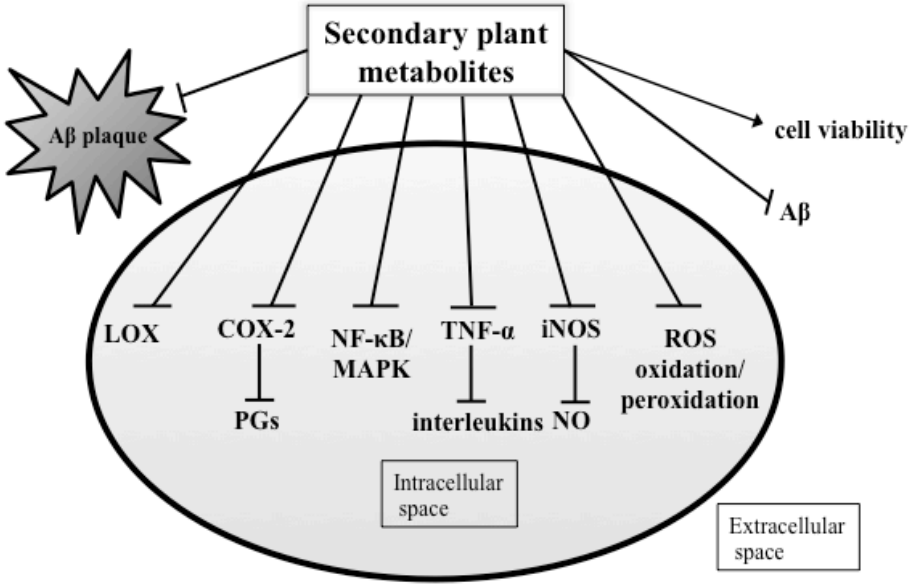

Fig. (1). Simplified schematic illustration of the different actions of secondary plant metabolites and ω-3 PUFAs in and outside of the neuron. Curcumin, bacosides, EGCG, EGb 761, anthocyanins and ω-3 PUFAs all inhibit iNOS and COX-2, and therefore block the production of NO as well as PGs. All plant secondary metabolites also influence Aβ by either promoting its clearance or inhibiting its aggregation and oligomer formation. Curcumin, EGCG and ω-3 PUFAs also reduce Aβ plaques. All metabolites introduced here except ECGC block IL production by inhibiting TNF-α, and all metabolites except anthocyanins block ROS production and therefore lipid peroxidation/protein oxidation. EGb 761 is the only plant secondary metabolite that has not yet been shown to block NF-κB or the MAPK pathway. Bacosides, EGCG and ω-3 PUFAs promote neurogenesis or cell viability. Finally, curcumin and bacosides block LOX.

and oligomer formation. Curcumin, EGCG and ω-3 PUFAs also reduce Aβ plaques. All metabolites introduced here except ECGC block interleukin production by inhibiting TNF-α, and all metabolites except anthocyanins block ROS production and therefore lipid peroxidation/protein oxidation. EGb 761 is the only plant secondary metabolite that has not yet been shown to block NF-κB or the MAPK pathway. Bacosides, EGCG and ω-3 PUFAs promote neurogenesis or cell viability.

CONCLUSION

This review aimed to provide a comprehensive overview of the contribution of central and peripheral inflammation in AD pathology and the development exploring the traditional and newer anti-inflammatory treatment strategies. It is still not confirmed to date, whether inflammatory processes that accompany normal aging are a primary trigger for the formation of Aβ plaques, NFTs, or neurodegeneration, or whether inflammatory mediators are employed secondarily as a protective mechanism in order to fight AD pathologies. Nevertheless, it is undeniable that inflammation, central as well as systemic, contributes to and aggravates the condition of AD patients in a vicious cycle. Pre-clinical studies with traditional NSAIDs targeting COX-1, COX-2, or PPAR-γ showed promising results but so far these drugs failed to provide convincing evidence in clinical trials. Furthermore, strong adverse side effects occurring with these drugs often hinder the employment of higher, more effective doses. As a consequence, during the last decades, more and more attention was paid to herbal or natural compounds. Many of these substances have been known to have beneficial effects in human health and disease for centuries, and are known to be safe either from their use in traditional/ancient medicines, or from their use as an actual food. However, modern medicine and research has only discovered their potential in the last few decades.

Here, we reviewed the antioxidant, anti-inflammatory, anti-amyloidogenic, neuroprotective, and cognition-enhancing effects of curcumin, bacosides, green tea, *Ginkgo biloba*, blueberries and omega-3 fatty acids. These compounds were examined in numerous *in vitro* and *in vivo* animal studies and were supported by a large body of epidemiological data. In conclusion substances like curcumin, polyphenols, and ω-3 PUFAs counteract various pathopysiological aspects of AD, such as Aβ plaques, ROS, or inflammation, and are able to ameliorate several of these pathologies. The fact that these properties are not limited to the brain but also occur systemically, for example regarding inflammation, are likely to be advantageous as there is supporting evidence for a connection between immune systems in the periphery and brain.

Results so far from clinical trials have not provided a clear indication about their beneficial effects, which might be due to the many different conditions, such as time of onset and progress of the disease, dose, frequency, and duration of treatment, bioavailability of the compounds, combination of substances, primary study outcome and measurements applied, genetic predisposition of the patient as well as environmental factors and individual variety. These factors strongly influence the results of the clinical studies and have

Table 1. Clinical trials using anti-inflammatory substances for the treatment of AD.

Drug	Dose	Duration	Participants	Outcome	Author	Year
NSAIDs						
Indomethacin	150-1100mg/d	6 months	patients with mild-to-moderate AD	improvements in cognition	Rogers *et al.*	1993
Diclofenac + Misoprostol	N/A	25 weeks	patients with mild-to-moderate AD	no changes in cognition	Scharf *et al.*	1999
Prednisone	20 then 10mg/d	4 weeks then 1 year	patients with AD	no beneficial changes in cognitive tests	Aisen *et al.*	2000
Hydrochloroquine	200 or 400mg/d	18 months	patients with early AD	no cognitive/behavioural improvements	van Gool *et al.*	2001
Nimesilude	100mg twice daily	24 weeks	patients with probable AD	no effect on cognition, clinical status or behaviour	Aisen *et al.*	2002
Rofecoxib	25mg/d	12 months	patients with mild-to-moderate AD	no delay in cognitive decline	Aisen *et al.*	2003
Naproxen	220mg twice daily	12 months	patients with mild-to-moderate AD	no delay in cognitive decline	Aisen *et al.*	2003
Rofecoxib	25mg/d	12 months	patients with mild-to-moderate AD	no improvements in cognition and behaviour	Reines *et al.*	2004
Rofecoxib	25mg/d	up to 4 years	patients with MCI	no improvements in cognition	Thal *et al.*	2005
Celecoxib	200mg twice daily	up to 7 years	people 70 years or older with family history of AD	no improvements in cognitive functions	Martin *et al.*	2008
Naproxen	220mg twice daily	up to 7 years	people 70 years or older with family history of AD	no improvements in cognitive functions	Martin *et al.*	2008
Corticosteroids						
Estradiol	2mg/d	6 weeks	women with senile dementia AD type	improvements in cognition and mood in 3/7 women	Fillit *et al.*	1986
Estrogen	1.25mg/d	16 weeks	women with mild-to-moderate AD	no improvements in cognition or mood	Henderson *et al.*	2000
Curcumin						
Curcumin	1 or 4g/d	6 months	patients with probable AD	probable slower decline in cognition	Baum *et al.*	2008
Curcumin C3 Complex	2 or 4g/d	24 weeks	patients with mild-to-moderate AD	no difference in clinical or biomarker efficacy measures	Ringman *et al.*	2012
Ginkgo biloba						
EGb 761	240mg/d	24 weeks	outpatients with presenile and senile AD	better cognition and activities of daily living	Kanowski *et al.*	1997
EGb 761	240mg/d	3 months	patients wit mild-to-moderate AD	better attention and memory	Maurer *et al.*	1997
EGb 761	120mg/d	52 weeks	outpatients with mild to severe AD	better cognition and daily living	Le Bars *et al.*	1997
EGb 761	120 or 240mg/d	26 weeks	patients with AD	no convincing differences in cognition	Schneider *et al.*	2005
Fish Oil/ω-3 fatty acids						
fish oil	1.7g/d DHA + 0.6g/d EPA	12 months	in patients with AD	did not slow cognitive decline	Freund-Levi *et al.*	2006
alpha-lipoic acid	600mg/d	48 months	patients with mild dementia/mild-to-moderate AD	stabilisation of cognitive function	Hager *et al.*	2007
omega-3 fatty acids	1.8g/d	24 weeks	patients with mild mild-to-moderate AD or MCI	improvements in Clinician's Interviews-Based Impression of Change scale, improvements in cognition for MCI patients	Chin *et al.*	2008
omega-3 fatty acids	675mg/d DHA + 975mg/d EPA	12 months	patients with probable AD	less decline in activities of daily living scores (fatty acids only)	Shinto *et al.*	2013
lipoic acid	600mg/d	12 months	patients with probable AD	less decline in cognitive and daily activities scores (fatty acids + lipoic acid)	Shinto *et al.*	2013
Anthocyanins						
Blueberry juice	6-9mL/kg/d	12 weeks	elderly with age-related MCI	improvements in memory and reduction of depression	Krikorian *et al.*	2010

to be taken into account. As with many other diseases, however, the earlier during disease development the intervention starts, the better are the chances for improvement. Therefore, in addition to an overall healthy lifestyle, the increased consumption of the above mentioned compounds might be a safe strategy to prevent or delay the onset of AD. The continuing investigation of the potential of these compounds and comprehensive clinical study designs are necessary for future investigations, which in turn might offer a promising potential remedy to fight or delay Alzeimer's disease.

LIST OF ABBREVIATIONS

ω-3 PUFAs	=	ω-3polyunsaturated fatty acids
Aβ	=	Amyloid beta protein
ACh	=	Acetylcholine
AChE	=	Acetylcholineesterase
AD	=	Alzheimer's disease
ApoE	=	Apolipoprotein E
APP	=	Amyloid precursor protein
BACE1	=	β-site APP cleaving enzyme 1
CNS	=	Central nervous system
COX	=	Cyclooxygenase
DHA	=	Docosahexanoic acid
DNA	=	Deoxyribonucleic acid
EGb 761	=	Standardised *gingko biloba* extract
EGCG	=	(2)-epigallocatechin-3-gallate
EPA	=	Eicosapentaenoic acid
ERK	=	Extracellular signal-regulated kinases
HIV	=	Human immunodeficiency virus
icv	=	Intracerebroventricular
IL	=	Interleukin
iNOS	=	Inducible nitric oxide synthase
H_2O_2	=	Hydrogen peroxide
LOX	=	Lipoxygenase
LPS	=	Lipopolysaccharide
MAPK	=	Mitogen-activated protein kinase
MCP-1	=	Monocyte chemotactic protein-1
NFT	=	Neurofibrillary tangle
NF-κB	=	Nuclear factor κB
NMDA	=	N-methyl-d-aspartate
NO	=	Nitric oxide
NSAID	=	Non-steroidal anti-inflammatory drug
PG	=	Prostaglandin
PPARγ	=	Peroxisome proliferator-activated receptor-γ
ROS	=	Reactive oxygen species
STAT	=	Signal transducer and activator of transcription
TNF-α	=	Tumour necrosis factor-α
UVB	=	Ultraviolet B

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

The authors would like to thank the Commonwealth Government and the University of Western Sydney for granting an Australian Postgraduate Award and scholarship to Nadine Apetz. The authors thank Mrs. Margaret Clarke for the final editing of the manuscript.

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Received: November 6, 2013 **Revised: March 19, 2014** **Accepted: March 19, 2014**