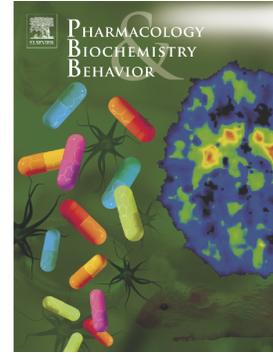


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Katarzyna Szczechowiak, Breno S. Diniz, Jerzy Leszek



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Diet and Alzheimer's Dementia – Nutritional Approach to Modulate Inflammation

Katarzyna Szczechowiak<sup>a</sup>, Breno S. Diniz<sup>b</sup>, Jerzy Leszek<sup>c</sup>

- a) Wrocław Alzheimer's Research Center, Wrocław, Poland;
- b) Department of Psychiatry, Faculty of medicine, University of Toronto, Toronto, ON, Canada; and Centre for Addiction and Mental Health, Toronto, ON, Canada.
- c) Department and Clinic of Psychiatry, Wrocław Medical University, Wrocław, Poland

**Abstract**

**Background:** Alzheimer's disease (AD) is the most common neurodegenerative disease causing dementia in the elderly population. Due to the fact that there is still no cure for Alzheimer's dementia and available treatment strategies bring only symptomatic benefits, there is a pressing demand for other effective strategies such as diet. Since the inflammation hypothesis gained considerable significance in the AD pathogenesis, elucidating the modulatory role of dietary factors on inflammation may help to prevent, delay the onset and slow the progression of AD. Current evidence clearly shows that synergistic action of combined supplementation and complex dietary patterns provides stronger benefits than any single component considered separately. Recent studies reveal the growing importance of novel factors such as dietary advanced glycation end products (d-AGE), gut microbiota, butyrate and vitamin D<sub>3</sub> on inflammatory processes in AD. **Conclusion:** This paper summarizes the available evidence of pro- and anti-inflammatory activity of some dietary components including fatty acids, vitamins, flavonoids, polyphenols, probiotics and d-AGE, and their potential for AD prevention and treatment.

**Keywords:** Alzheimer's disease, inflammation, diet, omega-3, probiotics, advanced glycation end-products

## 1. Introduction

Due to worldwide elderly population growth and lifespan extension, the number of patients with dementia, most often caused by Alzheimer disease (AD), will probably increase exponentially. According to the demographic data published in 2009, it is highly possible that most children born since the year 2000 in countries with high life expectancies will reach the age of 100 in the twenty-second century (Christiansen et al., 2009). However, there is still no cure for dementia, and the available treatment strategies bring only symptomatic benefits. A recently published systematic review of 51 trials also showed that there is no evidence of the use of pharmacological treatments for cognitive protection in people with normal cognition or mild cognitive impairment (MCI) to prevent the progression to AD (Fink et al., 2018). In this scenario, other strategies to prevent, delay the onset and slow the rate of cognitive decline in AD should be considered.

The major neuropathological hallmarks of AD include the accumulation of extracellular senile plaques made up of aggregates of beta-amyloid ( $A\beta$ ) protein, intraneuronal neurofibrillary tangles built up of tau protein and neuronal and synaptic loss (Serrano-Pozo et al., 2011; Venigalla et al., 2016). In addition to these neuropathological hallmarks, there is a large body of evidence highlighting the role of neuroinflammation in the pathophysiology of AD (Gąsiorowski et al., 2018). These findings have spurred huge interest in elucidating whether interventions that modulate inflammation, including diet, can be alternative therapeutic option in AD. In this paper, we review the impact, mechanisms, and evidence for the effect of various dietary components and nutritional approaches on inflammatory processes in AD and MCI due to AD.

## 2. Inflammation and its impaired resolution in AD and MCI

A large body of evidence explains AD as a multifactorial disorder. Accordingly, several hypotheses have been formulated, including the  $A\beta$  hypothesis, the tau hypothesis, the

cholinergic hypothesis, and the inflammation hypothesis (Rashid et al., 2015). Thereby, the inflammation hypothesis has gained considerable significance and provided more information about the connection between the peripheral and central nervous system (CNS) immune systems. Inflammation plays a crucial role in the pathogenesis and progression of the AD. The accumulation of A $\beta$  causes microglia activation, recruitment of astrocytes, and increased generation of pro-inflammatory cytokines (Sastre et al., 2006) such as interferon gamma (IFN- $\gamma$ ), interleukin (IL-1 $\beta$ ) and tumor necrosis factor alpha (TNF- $\alpha$ ) (Tan et al., 2013). Other studies show that the activation of endothelial cells of the neurovascular unit, oligodendrocytes, or neurons itself could be involved in this processes. The acute inflammatory response is a self-defense mechanism which restores tissue integrity and eliminates detrimental stimuli. However, the inflammatory processes in the CNS (neuroinflammation) become harmful when they turn chronic. In this context, the unresolved pro-inflammatory activation stimulates the production of greater amounts A $\beta$ 42 oligomers by astrocyte-neuron (Venigalla et al., 2016). These events lead to a vicious cycle in which the neurons become damaged, stimulate more microglia-activating factors, greater production of A $\beta$  that in turn leads to additional neuronal damage.

Neuroinflammation in AD starts in patients with MCI and increases at the later stages of the disease (Arends et al., 2000). A key aspect of the inflammatory response is its proper resolution. The failure of inflammatory resolution can lead to a chronic inflammatory response, such as seen in AD (Whittington et al., 2017). Resolution is propagated by the production of specialized pro-resolving mediators (SPMs) derived from the omega-3 polyunsaturated fatty acids (PUFA): docosahexaenoic acid (DHA) – resolvin D series, protectins, and maresins, and eicosapentaenoic acid (EPA) – resolvin E series, and omega – 6 PUFA arachidonic acid – lipoxins (via LOX), and aspirin-triggered lipoxins (via-COX-2) (Whittington et al., 2017).

### 3. Pro-inflammatory aspects of the diet

First of all, the discussion about the anti-inflammatory potential of the diet should be preceded by pro-inflammatory factors identification because mutual interactions between them can be crucial to AD diet efficiency. Further, dietary patterns and multidomain interventions are more important and more effective than single nutrients action.

Obesity, as one of the AD risk factors, is doubtless related to low-grade chronic inflammation (Hotamisligil et al., 2006, Ułamek-Kozioł et al., 2016)). Furthermore, a systematic review of 28 longitudinal studies conducted between 2003 and 2013 with long-term follow-up revealed that midlife overweight and obesity increase the risk of late-onset dementia (Emmerzaal et al., 2015). Monocyte-derived macrophages and adipocytes in adipose tissue produce pro-inflammatory cytokines, such as IL-6, IL-1 $\beta$ , TNF- $\alpha$  and induce secretion of acute-phase protein, such as CRP (Grant et al., 2015; Hotamisligil et al., 2006). Moreover, some findings suggest high levels of plasma amyloid proteins in obese persons (Jahangiri et al., 2013) and higher blood-brain barrier (BBB) permeability in elderly who were obese or overweight in midlife (Gustafson et al., 2007). Another noteworthy aspect of obesity and overweight is a clear connection between them and hypertension, dyslipidemia, atherosclerosis, type II diabetes mellitus (T2DM), and insulin resistance (IR). All are well-known risk factors for dementia (de la Torre et al., 2013).

Overconsumption of foods rich in simple carbohydrates and saturated fatty acids causes increased insulin secretion and has a major influence on cerebral glucose metabolism. Accordingly, regular physical activity, adherence to a fat and carbohydrate controlled diet (Bharadwaj et al., 2017), high dietary fiber intake (Tucker et al., 2018; Weickert et al., 2018) and low consumption of processed food can have a more positive effect of insulin secretion patterns.

Dietary lipids can influence the CNS inflammatory processes. Saturated fatty acids induce inflammatory responses on microglia, with the secretion of pro-inflammatory cytokines (Morris et al., 2004; Velloso et al., 2015). Cross-sectional studies suggest that a lower ratio of omega-6 to omega-3 FA intake can improve inflammatory response and predict more accurate hippocampus-dependent spatial memory and faster learning on virtual navigation tasks, as well as higher cognitive status overall (Andruchow et al., 2017). Other studies suggest that some diets, like the Mediterranean diet, which has a low omega-6:3 FA ratio, can significantly reduce the risk of AD and cognitive decline (Andruchow et al., 2017).

On the other hand, it is worth to highlighted that arachidonic acid (AA) is a precursor of pro-resolution eicosanoids lipoxins (LXA) and n-6 PUFA can have also positive impact on CVD and T2DM (Farvid et al., 2014; Harris et al., 2017; Wu et al., 2017)). Therefore, recent critical findings (Harris et al., 2018) suggests that use of PUFA ratio (n-6/n-3) is based on invalid/false assumptions, such as adverse effects of omega-6 FAs on cardiovascular health or only pro-inflammatory activity of omega-6 FAs, pointing the “Omega-3 Index” based on red blood cells (RBC) EPA + DHA content as the successor of the pro-/ anti-inflammatory PUFA ratio. Author suggests providing more EPA and DHA PUFA instead of n-6 PUFA restriction (Harris et al., 2017). Growing number of articles emphasize use of EPA + DHA PUFA in RBC membranes as an effective biomarker of “omega” status (Harris et al., 2018; Hooper et al., 2018) correlated with cognitive decline and AD (Hooper et al., 2018).

#### **4. Anti-inflammatory properties of the diet**

Compelling evidence shows that higher adherence to a Mediterranean diet (MedDiet, MeDi) is associated with decreased cognitive decline (Panza, 2018) and a reduced incidence of AD in the elderly (Sofi et al., 2010). A prospective study which examined associations between cognitive changes and MeDiet and DASH (Dietary Approaches to Stop Hypertension) diet reveals that greater adherence to DASH and MeDiet and higher

consumption of vegetables, fruits, nuts, legumes, and whole grains were significantly associated with higher MMSE scores in 3831 elderly participants. Data from large systematic review and meta-analysis suggest that higher adherence to the MeDi is associated not only with the reduced risk of developing MCI and AD but also reduced risk of progression from MCI to AD (Singh et al., 2014). Likewise, a combined dietary approach of MeDiet and DASH called MIND diet (enriched with neuroprotective berries and green leafy vegetables) was also positively correlated with slower cognitive decline (Morris et al., 2015a, 2015b) and reduction in the incident AD (Morris et al., 2015b).

#### **4.1. Omega-3 LC-PUFAs**

The PUFAs (polyunsaturated fatty acids) are crucial components of neuronal cell membranes, maintaining membrane fluidity for synaptic signaling process. The n-3 long-chain PUFA (n-3 LC-PUFAs) which include omega-3, docosahexaenoic acid (DHA), and eicosapentaenoic acid (EPA) improve neuronal transmission and regulate neuronal membrane excitability, improving memory and learning in healthy persons (Vauzour et al., 2015). There are different mechanisms for the anti-inflammatory properties of n-3 LC-PUFA. They regulate cytokines and chemokines expression and the production of EPA and DHA-derived specialized pro-resolving mediators (SPMs) (Whittington et al., 2017; Fiala et al., 2017). They also decrease the pro-inflammatory prostaglandins and eicosanoids (Fiala et al., 2017). Furthermore, recent studies suggest that n-3 PUFA can modulate innate immunity in MCI patients by inducing the polarization of macrophages to an intermediate M1-M2 phenotype enhancing A $\beta$  phagocytosis (Fiala et al., 2017). Other roles of n-3 PUFA are the reduction of neuroinflammation, oxidative damage, and A $\beta$  production (Tab. 1) (Tan et al., 2012).

Observational studies suggest that the dietary intake of oily fish and EPA and DHA is associated with lower risk of AD (Barberger-Gateau et al., 2011; Gillette-Guyonnet et al., 2013). A meta-analysis of 21-cohort studies demonstrated that fish products are correlated

with a lower risk of cognitive impairment and the marine-derived DHA is associated with decreased risk of dementia and AD (Zhang et al., 2015). On the other hand, it should be noted that there was no statistically significant evidence for n-3 LC-PUFA intake and risk of dementia and AD (Wu et al., 2015). Finally, a recent clinical trial (MAPT) showed that multi-domain intervention and polyunsaturated fatty acids, either alone or in combination, had no significant impact on cognitive decline over three years in elderly with memory complaints (Andrieu et al., 2017).

It is important to highlight possible reasons why association between n-3 PUFAs and omega-3 and AD remain elusive. First, omega-3 fatty acids seem to be more effective at the earliest stages of AD (preclinical, MCI). Other factors include varied time of supplementation, differences genetic (APOE  $\epsilon$ 4 vs non-APOE  $\epsilon$ 4 allele carriers), differences in the amount of omega-3 (from 200 mg to over 2 g/day), use of different sources of omega-3 (plant oils enriched only with EPA and DHA precursors such as ALA or fish/algae oils containing EPA and DHA) (Calder, 2013; Fonteh, 2018), age differences among samples (Gillette-Guyonnet et al., 2013), the omega-6 and omega-3 ratio, and no measurement of n-3 PUFA levels in plasma/serum or more accurate red blood cells (RBC) (Calder, 2013; Fonteh, 2018; Gillette-Guyonnet et al., 2013).

#### ***4.2. Single and combined anti-inflammatory interventions***

Growing body of evidence points to multi-ingredient supplementation and combined dietary interventions as a more efficient way to counteract inflammation in MCI and AD than single nutrient use. Currently published data shows that following components of the diet such as n-3 LC-PUFA, vitamin B complex (folic acid, vitamins B6 and B12), vitamin D3, resveratrol and curcumin, can prevent AD and MCI progression via enhanced A $\beta$  clearance and have anti-inflammatory properties (Tab. 1) (Fiala et al., 2017).

#### 4.2.1. Vitamin B complex

Meta-analysis of RCT (Clarke et al., 2013) on 22,000 individuals reveals no significant effect of homocysteine-lowering vitamin B (mainly folic acid) use on individual cognitive domains, global cognitive function and cognitive aging. Furthermore, van Dijk *et al.* (2016) show no influence on endothelial function or low-grade systemic inflammation of vitamin B12 and folic acid in elderly with hyperhomocysteinemia. On the other hand, it has to be stress that an RCT VITACOG (2012) in elderly with MCI found B vitamin treatment to lower homocysteine level, slowed brain atrophy and cognitive decline (de Jager et al., 2012). Moreover, RCT conducted by Chen *et al.* (2016) reveals benefits of folic acid supplementation in AD patients such as significantly higher MMSE score, and lower A $\beta$ <sub>40</sub>, PS1-mRNA, and TNF $\alpha$ -mRNA levels in the intervention group than in controls. The authors suggested that inflammation may play a crucial role in this association. Recent results may help elucidate unclear relationships between MCI/AD and vitamin B supplementation. Smith *et al.* (2016) reported that B vitamins slowed brain atrophy and cognitive decline only in patients with a good baseline omega-3 fatty acid status and suggest that combination of EPA and DHA and vitamin B supplementation can improve synaptic function and be beneficial for MCI patients.

#### 4.2.2. Curcumin

Tumeric-derived biophenolic curcumin is a potent inhibitor of the NF- $\kappa$ B signaling, the expression of cyclooxygenase 2 (COX-2), and of pro-inflammatory cytokines such as IL-1 $\beta$  and IL-6 (Gardener et al., 2016; Kuszewski et al., 2018). It is also involved to decrease the level of oxidative stress and reduce the concentrations of oxidized proteins. RCT show that curcumin can affect A $\beta$  protein plaques what can also influence chronic inflammatory processes in the brain (Panahi et al., 2015). However, RCTs conducted by Baum et al. and

Ringman et al. reveal no significant difference between placebo and intervention (treated with curcumin) groups of AD patients in cognitive functioning (Goozee et al., 2016). Scientific data shows that curcumin may be more beneficial in the early stages of the disease (MCI) (Goozee et al., 2016), but the results remain unclear. Nonetheless, it is worth noting that higher curry intake (which contains turmeric and pepper) in cognitively intact elderly Asian population (n=1010) was correlated with better MMSE scores compared with those who ate curry very rarely or never (Ng et al., 2006). Furthermore, Kuszewski et al. point that combination of omega-3 LC-PUFA and curcumin may mitigate inflammation more efficiently and affect inflammatory processes by pro-resolving properties, which can be more beneficial for cognitive functioning (Kuszewski et al., 2018).

#### 4.2.3. *Vitamin D<sub>3</sub>*

Numerous observational studies have highlighted that low vitamin D concentration is inversely correlated with AD risk (Grant, 2016). Authors of international recommendations of vitamin D intake in adults point to its antioxidant and anti-inflammatory properties which can protect the brain (Annweiler et al., 2015). Vitamin D has also been found to stimulate phagocytosis of A $\beta$  and enhance brain-to-blood A $\beta$  efflux in animal models (Ito et al., 2011). The vitamin D receptor (VDR) may play an important role in regulating microglial activation as one of the anti-inflammatory systems (Lue et al., 2010). However, one human study did not show a significant association between circulating 25(OH)D and cerebral A $\beta$  in older adults (Nourhashemi et al., 2018).

On the other hand, recent results reveal a higher likelihood of cognitive decline in elderly with subjective memory complaints and vitamin D deficiency than in those with its higher level (Chhetri et al., 2018). A recent RCT high dose of vitamin D (4000IU/d) improves nonverbal (visual) memory after 18 weeks (Pettersen et al., 2017). The authors suggest that in

patients with plasma 25(OH)D levels  $< 75$  nmol/L at baseline supplementation could be even more beneficial [59]. Additionally, data from Lemire *et al.* (2018) cohort study show that vitamin D hypovitaminosis was accompanied by faster cognitive decline in AD patients and memantine has protective properties against hypovitaminosis D-related cognitive decline. Therefore, a combination of memantine and vitamin D in AD therapy gained considerable significance (Lemire *et al.*, 2018). Accordingly, there is a large ongoing RCT (VITAL) of vitamin D<sub>3</sub> (cholecalciferol), 2000 IU/d) and marine omega-3 fatty acids (Omacor<sup>®</sup> fish oil, a 1 g/d) in the primary prevention of cancer and CVD among 25,875 subjects which results may shed new light also on AD (Manson *et al.*, 2012).

#### **4.2.4. Resveratrol**

Resveratrol is a stilbene produced by grapes, apples, raspberries, blueberries, plums, peanuts and present also in grape-derived wine (Weiskirchen, Weiskirchen, 2016). Scientific reports point to neuroprotective properties of this polyphenol by free radicals elimination, suppression of glial activation, mitigation of lipopolysaccharide (LPS)-induced production of inflammatory cytokines (IL-1 $\beta$  and TNF- $\alpha$ ) induced by LPS or A $\beta$  in microglia and enhancement of production of anti-inflammatory IL-10 [63]. Resveratrol can also reduce damage to neuronal cells through activation of NAD<sup>+</sup>-dependent histone deacetylases enzymes, termed sirtuins (Braidy *et al.*, 2016). A recent RCTs demonstrated that resveratrol could affect neuroinflammation and A $\beta$  accumulation in mild and moderate AD patients (Martin, 2017), and also improve innate immunity and cognitive capacity in patients with ApoE  $\epsilon 3/\epsilon 3$  in comparison to those with ApoE  $\epsilon 3/\epsilon 4$  (Famenini *et al.*, 2017). Another RCT showed significant differences at week 52 at in CSF A $\beta$ 40 and plasma A $\beta$ 40 levels between resveratrol-treated group and placebo (Turner, 2015). Surprisingly, brain volume loss increase in the resveratrol-treated group compared to placebo in this study. Another study indicated that resveratrol modulates neuroinflammation, and induces adaptive immunity (Moussa,

2017). Finally, a recent meta-analysis suggest that resveratrol supplementation can improve select measures of cognitive performance such as delayed recognition (Marx, 2018).

Nevertheless, it is worth mentioning that in a small RCT (n=37), with multi-ingredient approach comprising of daily consumption of Smartfish® juice (3g omega-3 PUFAs - DHA and EPA, 10µg vitamin D3, 150mg resveratrol and 8g whey protein isolate) for 6 months, Moran et al. have found no significant differences in overall cognitive function or composite cognitive domains between elderly groups (Moran et al., 2018).

#### 4.2.5. *Coffee and caffeine*

Coffee is a rich source of polyphenols. Current evidences suggest that coffee and caffeine consumption is associated with decrease in cognitive decline in healthy elderly and AD patients (Arab et al., 2013; Johnson-Kozlow et al., 2002). A meta-analysis of prospective studies, involving 34,282 participants, showed a inverse association between coffee consumption and the occurrence of cognitive disorders (Alzheimer's disease, dementia, cognitive decline, and cognitive impairment). The lowest risk was observed at the daily intake level of 1–2 cups of coffee (Wu et al., 2017). These findings support Santos *et al.* (2010) meta-analysis which found a trend towards a protective effect of caffeine in dementia and Quintana's *et al.* (2007) quantitative review which points that coffee consumption is inversely associated with the risk of AD.

Epidemiologic studies have suggested caffeine and coffee consumption as an effective therapeutic against AD (Panza et al., 2015). Nonetheless, in a Mendelian randomization study (17,008 AD and 37,154 controls), coffee consumption was not beneficial to prevent AD, and there is no evidence for long-term causal effects of habitual coffee consumption on global cognition or memory (Kwok et al., 2016; Zhou et al., 2018). Despite the negative finding of these studies, caffeine has well-established anti-inflammatory properties, including the inhibition of microglia reactivity, attenuation of pro-inflammatory mediators and reduction in

infiltration of immune cells from the periphery. Higher plasma caffeine levels were correlated with decreased inflammatory cytokines amount in the hippocampus (Madeira et al., 2017). Animal models suggest critical role of caffeine content - coffee with caffeine, unlike caffeine-free coffee, reduce plasma A $\beta$  levels (Arendash, Cao, 2010). Finally recent findings also describe coffee extract (CSE) to be a natural source of specific inhibitors of in vitro formation of advanced glycation end products (AGE) acting by different pathways (Fernandez-Gomez et al., 2018).

#### **4.3. Dietary-Advanced Glycation End Products (d-AGEs)**

Growing body of evidence points to advanced glycation end-products (AGEs) as a factor involved in AD pathogenesis (Abate et al., 2017). AGEs are produced in nonenzymatic chemical reactions between reduced sugars and proteins and accumulate during aging. They are increased in hyperglycemic and oxidative stress conditions such as T2DM (Abate et al., 2017). Recent studies reveal that an elevated serum level of AGEs is correlated with increased cognitive decline (Spauwen et al., 2015). RAGE, the main AGE receptor expressed in monocyte/macrophage membranes, microglia, and astrocytes have also been also implicated in AD pathogenesis (Abate et al., 2017). The interaction of RAGE receptors with AGEs involves the activation of pro-inflammatory pathway NF- $\kappa$ B and release of inflammatory mediators like TNF- $\alpha$ , IL-6, and CRP (Abate et al., 2017). Furthermore, Spauwen *et al.* (2015) in a cohort Maastricht Study (n=215) found an inverse associations of SAF (a noninvasive marker for tissue AGEs) with cognitive performance (delayed word recall and response inhibition).

Current evidence shows that AGEs derived from the diet (d-AGEs) contribute pool of AGEs in the organism and constitute a large percent of the total AGE serum content. Interestingly, Cai *et al.* (2014) indicate that half-life of AGEs is about double the average of a

cell's life which is crucial for its detrimental impact on brain cells. Di Pino *et al.* (2017) suggest that chronic high dietary AGE could lead to vascular dysfunction and inflammatory activation in T2DM. They also found that patients with high d-AGEs intake had high arterial stiffness, inflammatory markers, and increased cardiovascular risk.

Dietary products contain low AGEs content are fresh, stewed or boiled, *e.g.*, starches, legumes, fruits, and vegetables (Uribarri *et al.*, 2010). Abate *et al.* points out that meat and meat-derived products processed by broiling, grilling, frying, and roasting are main sources of d-AGEs. Change in the method of thermal treatment (into boiling or stewing) can decrease AGEs intake by up to 50%. Overcooking can also be the reason for higher AGEs content (*e.g.*, in pasta, rice). Currently, following substances such as quercetin, genistein, tannic acid, gallic acid, curcumin, cinnamon, parsley, thyme, and clove have a potential to inhibit glycoxidation and to prevent cooking-induced AGE production (Abate *et al.*, 2017; Rajan, 2018). Also, authors suggest that pretreating meat with an acidic solution like vinegar or lemon juice can also reduce AGE formation (Abate *et al.*, 2017). In conclusion, meta-analyses of RCT reveals that consumption of low AGE diets increases adiponectin and sirtuin-1 levels, and decreases TNF- $\alpha$ , leptin, circulating AGE and RAGE amounts and have significant anti-inflammatory effect (Baye *et al.*, 2017).

#### **4.4. Microbiota and butyrate**

On the basis of a number of publications and scientific reports, specific function of gut microbiota in neuro-immune modulation may have considerable significance in the neurodegeneration process in AD. It is well known that commensal gut microbiota synthesize neuroactive compounds, such as serotonin, dopamine,  $\gamma$ -aminobutyric acid (GABA), melatonin, kynurenine, catecholamines, histamine, acetylcholine and enhance their

bioavailability to the CNS (Barret et al., 2012; de JR De-Paula et al., 2018). On the other hand, some microbial-related factors can be also detrimental. Mechanisms underlying this influence are compound. It is noteworthy that some gut bacteria species can produce amyloid peptides and lipopolysaccharides (LPS) endotoxins which can influence inflammation in AD (Lyte, 2011). It is also well known that some of the compounds produced by gut bacteria can enhance intestinal permeability which enables the contact of microbiota with submucosal lymphoid tissue and results in the promotion of neuroinflammation which can lead to neurodegeneration (Jiang et al., 2017). This is one of the reasons why the microbiota dysbiosis may reduce tightness of the gut barrier and increase BBB permeability which can also affect AD pathogenesis and increase inflammatory response leading to the release of more pro-inflammatory factors in the CNS (Giau et al., 2018; Lyte, 2011). Most notably, many studies suggest that microbiota-gut-brain axis can be associated a with AD and imbalances in the gut microbiota can induce inflammatory processes (Giau et al., 2018). Data published recently by Cattaneo *et al.* (2017) shows that increase of a pro-inflammatory taxon *Escherichia/Shigella*, and a reduction of an anti-inflammatory taxon, *Eubacterium rectale*, could be associated with a peripheral inflammation in subjects with cognitive decline and brain amyloidosis. Interestingly, recent research has suggested a connection between infectious diseases and dementia, and points to the antimicrobial activity of A $\beta$  and its enhanced production as a response to bacteria and bacterial endotoxins in the brain (Aguayo et al., 2018). In particular, recent scientific reports consider various spirochetal infections as a causative factor of AD (Kumari et al., 2017).

Furthermore, recent findings show that there is a causative link between oral pathogens and changes in the intestinal microbiota composition as well as inflammatory changes in various tissues and organs including brain tissue. Moreover, varied microbes and their products such as LPS, amyloids, can infect and infiltrate into the brain from periphery,

initiates the cascade of chronic neuroinflammatory reactions and neurodegenerative changes that can cause AD. The microbiome-derived secretory products are strong proinflammatory component which can activate innate immunity as well. Animal model studies revealed that oral bacteriotherapy and modification of gut microbiota have a positive impact on neural functions due to changes in genes involved in inflammatory and neural plasticity processes (Sochocka et al., 2019). Some authors point also at connection between dysbiosis, *Helicobacter pylori* infection and AD. *H. pylori* infection has been shown to alter gastric pH, thus influencing both gastric and GUT microbiota composition and promoting dysbiosis – a key point for AD occurrence and development. Authors suggest that *H. pylori* eradication may be as well a possible risk factor of dysbiosis caused by antibiotics, showing importance of probiotics use during the treatment (Franceschi et al., 2019).

Recent scientific reports show that aging is correlated with reduced microbial biodiversity, with a lower number of *Bifidobacteria* species, higher abundance of *Proteobacteria* and diminish SCFAs production (Kumari et al., 2017; Quigley, 2017). Therefore, cumulating evidence suggests that properly composed diet (prebiotics, plant-derived nutrients, and phytochemicals) and probiotic supplementation can play an anti-inflammatory role in AD (Pistollato, 2016). More specifically, dietary patterns with high intake of vegetables and fruits, and low consumption of meat are correlated with the greater amount of *Prevotella* than *Bacteroides* species, which can be beneficial for the brain (Pistollato, 2016). Further, review of Pistollato *et al.* point to anti-inflammatory properties of probiotics which not only decrease levels of pro-inflammatory cytokines including IL-5, IL-6, IL-1 $\beta$ , IL-8, and TNF- $\alpha$  (accelerated in the elderly), but also increase the level of NK cells, activate lymphocytes and phagocytosis and improve adaptive immune response (Pistollato, 2016). Recent meta-analysis (2018) targeting the impact of probiotic on low-grade inflammation in middle-aged adults and elderly, reveals that probiotic significantly reduce IL-

6 and CRP levels (Custodero et al., 2018). However, the results of RCTs seem to be ambiguous. Agahi *et al.* (n=23) report that patients with severe AD were insensitive to the probiotic supplementation (Agahi, 2018).

Akbari *et al.* (2016) found no significant effect of probiotics in AD patients on biomarkers of oxidative stress and inflammation, fasting plasma glucose, and other lipid profiles but there was considerable improvement in MMSE in the probiotic-treated group compared to control. It is worth to mention the number and species of probiotic bacteria used in each RCT –  $3 \times 10^9$  CFU of the first group *L. fermentum*, *L. plantarum*, and *B. lactis* or *L. acidophilus*, *B. bifidum*, and *B. longum* (Agahi et al., 2018) and  $2 \times 10^9$  CFU of *L. acidophilus*, *L. casei*, *B. bifidum*, and *L. fermentum* (Akbari et al., 2016). A third RCT, conducted in healthy elderly, shows that addition probiotics ( $1,12 \times 10^{11}$  CFU) to the diet (*B. infantis*, *B. longum*, *B. breve*, *L. acidophilus*, *L. delbrückii ssp. bulgaricus*, *L. paracasei*, *L. plantarum*, and *S. thermophiles*) resulted in increased *Bifidobacteria* species, decreased homocysteine, and improved folate and vitamin B12 concentrations in subjects with low-grade inflammation but there was no significant influence on inflammatory markers (Valentini, 2015).

It is well known that response on probiotics supplementation depends on multiple factors (*e.g.*, disease occurred, the age of a subject, bacteria strains, its number and amount-CFU) and RCTs show big diversity in doses. Thus, the potential anti-inflammatory activity and effective dose of probiotics in AD patients deserve further investigation. There are some studies where higher amount of probiotics proved to be more efficient. For example, meta-analysis of human studies shows that for the blood pressure higher doses (greater than  $10^{11}$  CFU) were more effective than lower doses (Ouwehand, 2017). Moreover, Cecarelli et al. (2017) reveal that multi-strain probiotic supplementation (2 sachets, each containing  $4,5 \times 10^{11}$ , twice a day) seems to exert a positive effect on neuroinflammation and neurocognitive

impairment in HIV-1 infected subjects. Interestingly, a growing body of evidence shows that also fecal microflora transplantation could be an important factor slowing down the progression of AD. In ex-germ free mice fecal transplantation influence brain chemistry and behaviour (Rogers et al., 2016). However, the impact of fecal transplantation requires further investigation in human studies.

In recent years also high fiber and butyrate-synthetizing diet gained considerable importance as a potential anti-inflammatory factor in AD. There are few components affecting gut health including probiotics, prebiotic (*e.g.*, fructooligosaccharides – derived from bananas, onions, garlic and asparagus), and butyrate – primary energy source of colonocytes. Butyrate is a short chain fatty acid (SCFA) produced via fermentation of nondigestible fiber, mostly resistant starches (whole grains, cereals, legumes) by bacteria in the colon or consumed with milk products (especially in butter) (Bourassa et al., 2016). SCFAs play a significant role in food intake reduction by increasing leptin level and decreasing proinflammatory cytokine production which can affect CNS (Proctor, 2011). Furthermore, butyrate has a beneficial impact on host metabolism by regulating immune response, promoting glucose and energy homeostasis (Bourassa et al., 2016) and may have anti-inflammatory potential as reported in microglial cells model (Bienenstock, 2015). Moreover, human studies show that butyrate intensifies effects of colonic functions such as inhibition of inflammation and carcinogenesis, decreasing the risk of gut permeability and decreasing oxidative stress (Hamer et al., 2008). It could be one of the reasons why legumes consumption was inversely correlated with serum levels of hs-CRP, TNF $\alpha$ , and IL-6 in Esmailzadeh's *et al.* (2011) study. It is noteworthy that the resistant starch content in products increases due to multiple heating/cooling processes (Yadav et al., 2009). On the other hand, it should be taken into account that butyrate has also the ketogenic potential and can be converted to ketones. Growing number of publications highlights the dietary-induced ketosis (mostly by adding medium chains triacylglycerols-

MCT) as an effective method to bypass deteriorating brain glucose in AD and deliver ketones as an alternative energy source for the brain (Huuskonen et al., 2004). Many scientific data suggests that high fiber diet increase blood levels of butyrate (Bourassa et al., 2016). A recent human study conducted by St-Pierre *et al.* (2017) revealed that butyrate seems to be more ketogenic than MCT and has a great ketogenic potential as a component of diet in AD.

Table 1. Summary of the protective action of dietary factors on inflammatory processes in Alzheimer's disease.

Dietary factor	Protective/anti-inflammatory action	References
n-3 LC-PUFA (EPA and DHA)	Production of specialized pro-resolving mediators (SPMs) <u>The decrease</u> of the pro-inflammatory prostaglandins and eicosanoids Modulation of innate immunity in MCI patients, enhancing A $\beta$ phagocytosis Reduction of neuroinflammation, oxidative damage, and A $\beta$ production	(Whittington et al., 2017; Fiala et al., 2017) (Fiala et al., 2017) (Tan et al., 2012)
Curcumin	Anti-amyloid, anti-tau protein hyperphosphorylation, anti-hyperhomocysteinemia, anti-oxidant, anti-inflammatory, and anti-apoptotic effects Combined with omega-3 reduce inflammation more efficiently,	(Mukherjee et al., 2019; Pluta et al., 2018) (Kuszewski et al., 2018)
Vitamin D <sub>3</sub>	Regulating role in microglial activation of vitamin D receptor (VDR)	(Lue et al., 2010)
Resveratrol	Affect neuroinflammation and A $\beta$ accumulation in mild and moderate AD patients Modulation of neuroinflammation, and induction of adaptive immunity Improving in cognitive performance (delayed recognition)	(Martin, 2017) (Moussa, 2017) (Marx, 2018).
Coffee and caffeine	Inhibition of microglia reactivity, attenuation of pro-inflammatory mediators and reduction in infiltration of immune cells from the periphery. Higher plasma caffeine levels - decreased inflammatory cytokines in the hippocampus	(Madeira et al., 2017).
Dietary-Advanced Glycation End Products (d-AGEs)	RAGE and AGEs interaction involves the activation of pro-inflammatory pathway NF- $\kappa$ B and release of inflammatory mediators (TNF- $\alpha$ , IL-6, and CRP) High dietary AGE may lead to inflammatory activation (high level of inflammatory markers)	(Abate et al., 2017) (di Pino et al., 2017)
Microbiota and butyrate	Imbalances in the gut microbiota can induce inflammatory processes Probiotics decrease levels of pro-inflammatory cytokines including IL-5, IL-6, IL-1 $\beta$ , IL-8, TNF- $\alpha$ and increase the level of NK cells, activate lymphocytes and phagocytosis, and improve adaptive immune response Probiotics significantly reduce IL-6 and CRP levels in elderly Positive effect of probiotic on neuroinflammation and	(Cattaneo, 2017, Giau et al., 2019) (Pistollato, 2016, Sochocka et al., 2019) (Custodero et al., 2018)

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## 5. Conclusion

Since the inflammation hypothesis of AD gained considerable significance, there is a pressing demand in finding dietary factors which can modulate inflammation and prevent, delay the onset and slow the progression of AD. Specification of both pro-inflammatory and anti-inflammatory dietary constituents seems to be crucial for AD diet efficiency. Overconsumption of foods rich in d-AGEs, simple carbohydrates, saturated and trans fatty acids, and unprocessed red meat, processed meat, organ meats, chips, have a pro-inflammatory influence on AD patients brains. Inflammatory processes may also be accelerated due to midlife obesity, especially related to hypertension, dyslipidemia, atherosclerosis, T2DM, and IR.

On the other hand, growing body of evidence highlights that multi-component supplementation, complex dietary patterns (e.g. Mediterranean, DASH and MIND diets) and combined dietary interventions, are more effective as anti-inflammatory agents than any single component considered separately. On the basis of a number of human studies including RCTs, we found a large compendium of anti-inflammatory nutritional substances and products such as omega-3 LC-PUFAs (EPA and DHA) especially when combined with vitamins (B complex, D<sub>3</sub>), flavonoids (e.g., resveratrol), polyphenols (e.g., curcumin); alkaloids (e.g., caffeine), low-d-AGEs products, probiotics and butyrate which can counteract inflammation in many different ways including production of specialized pro-resolving mediators (SPMs) or decreasing pro-inflammatory prostaglandins and eicosanoids (EPA and

DHA). Nevertheless, further research is needed to clarify benefits and help elucidate possible modulatory effects on inflammatory processes in AD.

#### **6. Conflict of interest**

The authors declare that there are no competing financial or non-financial interest in relation to the present paper.

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### Highlights

- We found a large compendium of anti-inflammatory nutritional substances and products such as omega-3 LC-PUFAs (EPA and DHA) especially when combined with vitamins (B complex, D<sub>3</sub>), flavonoids (*e.g.*, resveratrol), polyphenols (*e.g.*, curcumin); alkaloids (*e.g.*, caffeine), low-d-AGEs products, probiotics and butyrate which can counteract inflammation in Alzheimer's disease
- Current evidence clearly shows that synergistic action of combined supplementation and complex dietary patterns provides stronger anti-inflammatory benefits than any single component considered separately
- Overconsumption of foods rich in d-AGEs, simple carbohydrates, saturated and trans fatty acids, and unprocessed red meat, processed meat, organ meats, chips, have a pro-inflammatory influence on AD patients brains