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Modulation of Gut Microbiota through Mediterranean Diet as a New Insight for the Alzheimer's Disease Therapy

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Abstract

Despite the fact that Alzheimer's disease (AD) is the most common form of dementia, its underlying pathogenesis has not yet fully known. As an intricate and multifactorial disease, finding a potential therapy intercepting its pathological process is still out of reach. With an increase in evidence of the success of gut microbiota modulation as a therapy to other diseases, one should consider the same possibility in AD. Therefore, this literature review focuses on exploring the possibility of dietary intervention as an innovative therapy for AD by modulating the gut microbiota composition based on recent researches. The method used to assemble this literature review is by performing a comprehensive literature search with corresponding keywords. The result shows that Mediterranean dietary intervention, characterized by the high intake of omega-3 polyunsaturated fatty acids, antioxidant nutrients, and vitamins, has shown to be beneficial for brain functions development which targets the gut-brain axis. However, a higher level of evidence-based research is still needed to confirm further the findings in hope for a future implementation of this new insight as a therapy for AD and to unfold the gut microbiota role in it.

Keywords: *'Alzheimer Disease', 'Gut Microbiota', 'Gut-brain axis' and 'Mediterranean Diet'.*

Introduction

Alzheimer's disease (AD) prevalence accounts for 50-75% of all forms of dementia, making it the most common form worldwide.[1] In April 2016, the World Health Organization (WHO) reported that there were 47.5 million people suffering from dementia, in which the older age group had a greater proportion and an impaired normal day-to-day activity.[2] In Indonesia, with a rising number of elderly population; 7.6% in 2010 to 8.03% in 2014 of the total population; the estimation of people living with AD will be double by the year 2030, and reach the sum of 4 million people in 2050.[3]

Unfortunately, with this alarming rate of increase in prevalence, the cause of the disease itself has yet to be fully

elucidated, let alone its therapy. The beta-amyloid (Aβ) plaque which represents one of the hallmarks of AD is believed to be a marker of upstream process instead of the cause. On the contrary, in cases of AD caused by amyloid precursor protein (APP) gene mutation, the Aβ plaque buildup is considered to be a primary process.[4] With this long-standing debate and the fact that AD is a multifactorial disease,[5] a potential therapy for it is still far from being reached. However, in the light of other proven therapeutic approaches addressing the role of gut microbiota in irritable bowel syndrome patients, such as fecal microbiota transplantation and probiotics, gut microbiota modulation could hold promising insights to other diseases.[6] Recent studies suggest that gut microbiota could play a role in the onset of AD through the gut-brain axis.[7] Aging process characterized by chronic pro-inflammatory response disrupts the balance and composition of gut microbiota.[7] This decreased of gut microbiota diversity can lead to changes in brain function and in host behavior.[8] Intriguingly, one study has proven that antibiotic-induced changes of gut microbiota diversity in a murine model of AD decreases its Aβ plaque deposition.[9]

Thus, the focus of this literature review is to highlight the intricate relationship between gut microbiota and AD pathogenesis as well as the possibility of gut microbiota composition alteration as a potential therapy of AD.

Materials and Methods

A comprehensive literature search was performed in January 2017 using Google Scholar. This database was searched with combinations of the terms 'Alzheimer Disease', 'Gut Microbiota', 'Gut-brain axis' and 'Diet'.

Result and Discussion

AD Pathogenesis Hypothesis

AD becomes manifested when genetic, lifestyle, and environmental factors play their role together, such as smoking, obesity, lack of physical activity, and certain genes including PS1, PS2, and APP genes. That is why until now scientists have not fully understood the real cause of AD since the pathogenesis itself is a complex "cascade" which takes place in the brain over a long course of time.[9]

According to the amyloid cascade hypothesis (see Figure 1), the increase of Aβ peptide, which is produced via altered processing of APP, gives rise to a series of events which results in the formation of plaques, neurofibrillary tangles of hyperphosphorylated tau, and neuronal death. Formation of Aβ peptide requires β- and γ-secretases, in which presenilin proteins (PS1 and PS2) play role in catabolizing APP.[11] This neuronal death then causes the typical AD clinical dementia syndrome.[4] Nonetheless, although this Aβ plaque buildup is considered as the main hallmark of AD, it does not always apply to all cases. This was already proven through failures of most clinical trials which target the elimination of Aβ levels.[11] One study even suggests a shift of perspective, to see Aβ plaque buildup as a physiological response of the body, since in healthy brain, it is needed for synaptic plasticity and memory. In this new vision, therapy targeting Aβ plaque elimination might worsen the side effects, making the need of finding the true pathogenesis of AD become more imperative than ever.[12]

Correlation of Gut Microbiota with Hypothalamic-pituitary Axis, Neurotransmitters, and AD

The gut is home to most of the symbiotic microbes. These microbes can be divided into three dominant genus, which are *Bacteroides*, *Prevotella*, and *Ruminococcus*. Each genus has its own metabolism properties. *Bacteroides* are good at fermenting carbohydrates and protein. *Prevotella* can degrade plant polysaccharides and mucin glycoprotein in the gut mucosal layer as well as interact with immune system. *Ruminococcus* are great in degrading mucins and help epithelial cells in sugar uptake.[13,14]

Various animal studies have discovered that gut microbiota have effects on animal's behavior, including anxiety-like behavior and spontaneous motor activity. Moreover, it can also affect biochemical composition in the brain.[15] Responsiveness to stress and many physiologic activities are regulated by hypothalamic-pituitary-adrenal (HPA) axis, an important part in the neuroendocrine system. In the germ free mice, there is abnormal HPA. However, that abnormalities could be reversed by colonization of germ free mice with microbiota from specific probiotic *Bifidobacterium infantis*. Therefore, gut microbiota has influence in regulating the activity of HPA and nervous system development.[16]

Disruption of rapid gut microbiota colonization during childhood and adolescence can affect the gut-brain axis signals and the health in the whole life. This condition occurs because childhood and adolescence are critical periods for brain development. Alteration of gut microbiota in the adulthood period may also affect the brain function and behavior.[17]

In addition, disruption in the gut barrier can cause disturbance in the brain blood barrier. The epithelial lining of the mucosal layer of the gut are connected through tight junction which limits the permeability of the gut.[18] Disturbance in this structure can be caused by inflammation, such as those triggered by lipopolysaccharide (LPS).[19,20] LPS can only enter the circulation when there is alteration of the tight junction.[19] Studies also found that LPS can cause prolonged elevation of Aβ and hippocampal deficits.[20] Thus, LPS plays a role in Aβ accumulation in the brain and AD progression.[21,22]

Gut microbiota also perform key roles in the production of neurotransmitters. Some of the neurochemicals we know can be synthesized in the gut. For example, *Lactobacillus brevis* and *Bifidobacterium dentium* can produce GABA by metabolizing glutamate.[23] The increase of GABA in gastrointestinal tract is correlated with the increase of GABA in CNS.[24,25] NMDA, a receptor for glutamate, are expressed significantly less in germ free mice. This indicates that disturbance in the gut microbiota can decrease the expression of NMDA receptor in hippocampus.[26] The other example is serotonin which is synthesized mostly in the gut. The gut microbiota plays an important role in synthesizing serotonin. Animals and human clinical trials suggest that selective serotonin reuptake inhibitors could reduce the Aβ protein production in the brain, indicating that the increase of extracellular serotonin levels can effectively reduce Aβ plaque formation and thereby reduce the risk of AD.[27]

Gut microbiota also plays role in controlling the gut-brain axis by modulating signaling and preserving normal gut physiology. The gut-brain axis itself has effects on amyloid-enhancing factors, such as serum amyloid A and misfolded Aβ, which might be implicated in the onset of AD. Therefore, disturbance of gut microbiota can increase amyloid formation and thus worsen the progression of AD.[28]

The Normalization of Gut Microbiota through the Adherence Towards the Mediterranean Diet

Current available treatments of AD are symptomatic and are not used for the curative or preventive purposes in the progression of AD.[29] Moreover, these treatments are not universally beneficial and some are not considered clinically significant.[30,31] Given the lack of pharmaceutical treatment for AD, research invested in the modification of lifestyle is currently growing.[32] It is obvious that diet has an important influence on the diversity of gut microbiota as the diversity of gut microbiota in the host highly depends on the food consumed.[33,34] Studies have shown that the alterations of gut microbiota have clear effects on intestinal homeostasis, gut microbiome, immune system, physiology, and host metabolic pathways.[35]

Among various pattern of diets, one dietary intervention that has gained a fair amount of interest in Alzheimer's research is the Mediterranean diet (MD).[36] This diet is characterized by the daily intake of lots of plant food including vegetables, fruits, cereals, nuts and beans, moderate intake of dairy products, with intake of fatty fish and olive oil as the source of fat.[37] Human intervention studies have shown that high intake of vegetables, fruits, and cereals correlates with the significant increase of short chain fatty acids, which are very important in the regulation of several physiological processes.[4]

Research shows that MD is beneficial in the reduction of inflammation biomarkers and in the normalization of gut microbiota.[38,39] This anti-inflammatory effects of MD are often linked with the changes in the composition of gut microbiota, including the increase of *Bacteroides* genus and the decrease of *Bacillaceae* genus.[36]

The consumption of MD, reflected as high intake of omega-3 polyunsaturated fatty acids which are found mainly in the fish and olive oil, polyphenols contents in the fruits and cereals, antioxidant nutrients, as well as vitamins, has been proven vital for neuronal and brain functions development and are able to enhance healthy gut microbiota.[40-42]

Several studies also suggest that MD may delay cognitive decline.[42,43] Although these lines of studies mostly are resting exclusively on epidemiological studies which link nutritional factors with AD, the biomarker findings provide biological evidence which further support those studies. Lower adherence to the MD was related to the increased atrophy of the key brain regions for AD among cognitively normal individuals, as depicted in the study of Mosconi L, *et al*[45] through the results of MRI scans of the subject representative of the lower versus higher adherence to the

MD.

Conclusion

In spite of the increasing rate of the prevalence of AD, the cause of the disease itself remains a mystery, and so does its therapy. Recent studies suggest that gut microbiota might play a role in the onset of AD through the gut-brain axis. Mediterranean Diet has been shown to delay cognitive decline among AD patients. Both of these findings further suggest the potential approach for the treatment of AD through the modulation of gut microbiota which can be achieved through the adherence to Mediterranean Diet.

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Conflict of Interest

The authors do not have any conflict of interests

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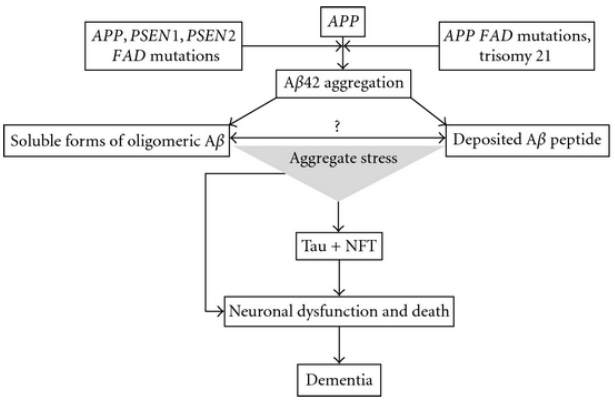

Figure 1. Amyloid cascade hypothesis.[46]