

The Gut Microbiota Dysbiosis as a Trigger of Inflammation-Driving Pathogenesis of Alzheimer's Disease

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Abstract. Alzheimer's disease (AD) is a degenerative disease of the central nervous system, and its pathogenesis is very complex. Gut microbiota is an immense and complicated microbial community that is regarded as the “second brain” by scientists. These microorganisms exist in the ecosystem of the gastrointestinal tract which is in the human body and form a relatively stable environment within the gastrointestinal tract. As a large number of microorganisms that can survive and coexist harmoniously in the human body, intestinal flora is a very important environmental factor and plays a very important role in the mutual transformation of people's health and diseases. On this basis, the cerebral intestinal axis is a two-way information regulation system that connects the brain and gastrointestinal functions. This means that intestinal microorganisms can participate in the brain-intestinal axis. Recent studies have shown that disturbances (compositional changes and translocations) of the gut microbiota are associated with neurological disorders (AD), where the gastrointestinal tract communicates with the central nervous system via the gut-brain axis, including direct effects on nerves, endocrine pathways, and immune regulation. Animal models, fecal microbiota transplantation, and probiotic interventions provide evidence for the association of gut microbiota with AD. The leaked bacterial metabolites may directly damage neuronal function, and may also induce neuroinflammation and promote the pathogenesis of AD. Therefore, the main goal of this review is to summarize, study and discuss the nowadays research and results of intestinal microbiota in Alzheimer-related mechanisms and to understand the relevance, function, and impact between the mechanism and Alzheimer's disease.

Keywords: Alzheimer's disease (AD); Gut microbiota; inflammation; Therapeutic intervention.

1. Introduction

Alzheimer's disease (AD), which is a kind of progressive neurodegenerative disease, is one of the most catholic illnesses prevalent in modern society nowadays. Accounting, almost 60% to 70% of cognitive impairment in elderly patients and the patients usually have symptoms of memory loss, cognitive impairment and significantly reduced learning ability [1]. AD has many related etiologies, while the current researches mostly focus on the toxic aggregates of amyloid form extracellular amyloid plaques and hyperphosphorylated proteins form intracellular neurofibrillary tangles [1]. However, recent studies show that the role of inflammation occurs before the abnormal deposition of the amyloid during the process of AD. While this review aims at the disorder of gut microbiota which can cause inflammation in several methods.

The gastrointestinal (GI) tract of human-being is colonized by trillions of gut microbiotas, while they form a huge, complex, but the relatively stable community in our gut [2]. The gastrointestinal tract affects brain function and vice versa. The microbial-brain-gut axis is a two-way communication pathway that sends and receives signals from the gut to the brain. The intestinal microbiota is a mechanism that induces Alzheimer's and leads to inflammatory reactions in the body. Emergent

pieces of evidence show that the increase of gut probiotics is advantageous to the autoimmunity protection of the central nerve system (CNS). On the other hand, aging, unhealthy eating habits, and sleep habits may lead to the dysbiosis of the community of the micro-species before the emergence of the inflammation [2-4]. Although gut microbiota is not the initial reason for AD, the microbiota is strongly associated with inflammation, which leads to damage to the nerve system and even causes Alzheimer's disease, in the internal body of mammals.

Inflammation is the body's defensive response to injury. When the process begins, it follows a certain event process until the source of inflammation is eliminated and the healing process begins. However, if the cause of inflammation cannot be eliminated, the inflammation will continue to exist. gut microbiota is one of the causes of gastrointestinal inflammation. They are related to a certain extent, and because of the occurrence of inflammation, intestinal microorganisms are disordered, which eventually leads to AD. Therefore, the article will summarize, study and discuss the mechanism of bacteria-induced inflammation and hence AD induction.

Gut microbiota can influence our nervous systems through secreting molecule signals, which play an essential character in the gut-brain axis (GBA). There are several potential pathways that the gut microbiome can communicate with the brain, including the HPA axis, spinal mechanism, neurotransmitters, enteroendocrine signals, and nervous systems of autonomic, and intestinal [5]. However, when the microorganism in the gastrointestinal (GI) tract becomes a disorder, it may harm nervous systems including GBA, and, eventually, induces neurodegenerative disease. Here we will enteroendocrine some of the nervous systems and discuss it.

2. Gut Microbiota Leads To Alzheimer's Disease

In our intestinal system, the permeability of the epithelial barrier on the inner wall of the intestine will lead to the invasion of different bacteria, viruses and their neuroactive products, eventually contributing to inflammatory reactions in the brain. The inflammatory infection hypothesis of Alzheimer's disease is to emphasize the importance of intestinal microbial groups, mainly because it gradually replaced the amyloid cascade concept decades ago.

2.1. The destruction of gut barrier

The intestinal gut barrier has the ability to absorb nutrients and block harmful substances from entering the body environment, and protect the mucosal tissue and circulatory system from pro-inflammatory substances such as microorganisms, toxins, and antigens. However, when there is a big issue with the tight connection between cells, it may also cause to intestinal leakage, and lead to kinds of diseases. The permeability of the intestinal mucosal barrier and blood-brain barrier will also increase during ageing. Calprotectin levels in the cerebrospinal fluid and brain of Alzheimer's patients are drastically elevated, promoting amyloid aggregation and co-aggregation with amyloid protein. Increased fecal calprotectin levels were found in over 70% of AD patients in one study [6], leading to the hypothesis that it could translocate into the circulation and cause neuroinflammation. Similar changes in intestinal epithelial barrier integrity and intestinal immune system activation have been described in AD patients with higher fecal calprotectin expression. This calcium-binding protein from our intestines may play a role in the development of amyloid fibers in the intestine or directly in the brain. And the destruction of the intestinal barrier is related to intestinal inflammation and ecological disorders. Increased intestinal permeability ("intestinal leakage") may lead to neurodegeneration. Some researchers such as Leblhuber[7] and his partner found that the concentration of calcium reticin in the blood of AD patients increased significantly through high performance liquid chromatography, in their continuous research and attempt, it was found and shown that calcium-retin protein can enter the circulatory system from the intestinal tract through the damaged intestinal barrier, causing neuroinflammation. This is equivalent to harmful metabolites produced by intestinal flora that can pass through the blood-brain barrier, thus damaging the function of neurons.

2.2. Microbial invasion of blood activates immune response

Microbial invasion is composed of four steps, and simply identifying information related to microbial invasion and sorting them in stages reveals a general, step-by-step invasion process. Microbial invasion most closely follows a sequential process that requires an introduction, establishment of populations, subsequent growth and spread, and impact aspects. Chronic microglial activation (reactive microglia) supports neurotoxic processes, resulting in brain damage and neuronal death [8]. Reactive microglia also stimulate astrocytes, which aid neuronal activity. Neuroinflammatory load and blood-brain barrier (BBB) dysfunction are caused by reactive astrocytes and reactive microglia. [9] The BBB is an important protective barrier for the central nervous system that regulates the flow of chemicals into and out of the brain. This perfectly working machine will break down as you get older, permitting pathogens (viruses, bacteria, and fungus), immune cells, and their products to hybridize and infect the brain.

2.3. The effect of microbial metabolism on Alzheimer's disease

In the hippocampus, cytokines can increase the expression of APP and stimulate the production of A β . Bacterial amyloid is considered to be a recognition molecule of the pathogen-associated molecular pattern (PAMP), which can cause the activation of TLR2. Studies [10] have found that TLR2 induces the upregulation of Notch1 and the activation of microglia, and can promote the development of AD. By activating the host's innate immune system, the gut microbiota can exacerbate the inflammatory response to A in the brain, resulting in neuroinflammation. Peripheral inflammation can contribute to the onset and progression of chronic neuroinflammation. Peripheral inflammation can play a role in the occurrence and development of chronic neuroinflammation [11]. Villarán et al.[12] used dextran sulfate sodium (DSS) to induce the establishment of a rat model of ulcerative colitis (UC), and injected LPS into the substantia nigra to induce midbrain inflammatory response to verify whether peripheral inflammation was. Changes in midbrain inflammation. The researchers discovered that UC increased the inflammatory response to LPS, increased serum inflammatory markers (TNF, IL-1, IL-6, and acute-phase protein C-reactive protein), and increased the populations of inducible nitric oxide synthase, intercellular adhesion molecule-1, microglia, and astrocytes. A leaky gut leading to LPS leakage can cause peripheral inflammation, thereby affecting the occurrence of AD. As a result, the gut microbiota plays an essential role in the induction and cultivation of the immune system of the host, as well as the immune system in general. The symbiosis between the host and these highly diverse and evolving microbes is maintained. The microbiota is closely related to the normal functioning of the nervous system, but when homeostatic changes in the microbiota lead to increased intestinal permeability, it can promote the translocation of bacteria and endotoxins across the intestinal epithelial barrier, triggering pro-inflammatory Cytokines to generate relevant immune responses that lead to various neurological diseases.

There are large amounts of publications stating that the microbiota of the GI tract can induce AD whereas the mechanism of AD influencing microflora in the intestinal tract is lacking research. Some of the research using the animal pattern found that the nervous system and immune system have something unusual, but it cannot make a conclusion that the dysbiosis of the gut is made by a consequence of AD.

3. Gut-Brain-Microbiota Axis In AD Towards Gut Dysbiosis

Gut-brain-microbiota axis reflects the bidirectional, continuous connections between the brain and gastrointestinal (GI) tract. On the one side, CNS modulates the GI tract through the pathway of parallel neuroendocrine output efferent systems [13]. Besides, secreted by intestinal microbial populations, incoming signalling pathways and active molecules are able to regulate the mainly brain function [8]. Similarly, in addition to what the former said, changes in microbial diversity are described in the amyloid transgenic fruit fly model [14]. In this AD model, it is very obvious that damaged intestinal microbiota causes neuroinflammation and cerebrovascular degradation, which

means that there was a link between the microbiome and brain injury. AD can demonstrate gut dysbiosis and the main alterations in the constitution of the intestinal microbiome as compared to a healthy population [15]. Alzheimer's disease have lower amounts of bacteria from the Actinobacteria phylum (particularly, bacteria from the genus *Bifidobacterium*) and the Firmicutes phylum. It's worth noting that the microbiome of people with type 2 diabetes has been found to have lower amounts of Firmicutes (T2DM)[16] obesity. Diabetes and insulin resistance, by the way, are well-known risk factors for Alzheimer's disease. [17-18]. However, even though many studies have revealed that the gut-brain-microbiota axis might induce the clinical symptoms of AD, the information about that AD influences the dysbiosis of intestinal microbiota remains limited. Since the relative studies are not enough, more research is needed to be organized to find its mechanism of it.

3.1. patients' unusual action influencing the microfloras

Not only do people who have AD express the symptom of cognitive drawback, but also eating preferences or even habits will change as the illness gets worse, which means the structure of microflora may change as a result of diet. Initially, loss of short-term memory may influence AD sufferers' circadian clocks, which also includes eating regularly [19]. According to Seab et al [20], brain atrophy, especially the process in the hippocampus, can be detected in AD patients with the use of MRI and PET imaging. This proves that the function of memory is damaged since the hippocampus act in the role of memorizing [21]. Adequate shreds of evidence have supported that short-term memory can be influenced during the change of the hippocampus [22-24]. In Yukitoshi and Yoshio's research [22], they found that short-term memory can be influenced by the lesion of the right hippocampi in the experiment. Although they did not explain the specific mechanism in the process of lesion clearly, Yuan Jiao et al briefly explained the mechanism of hippocampus lesion via postsynaptic density-95 protein (PSD-95) and α -amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptors in synaptic density area [20]. With the loss of short-term memory, patients will forget what they have done a few days ago or even several minutes ago, including food intake. Therefore, the internal clock of intake will possibly be in chaos. Furthermore, appetite as well as the preference for food in the colony of individuals who have AD can change [25]. However, few experts doing research in this area, and the result of the relative research are unstable and conflicting [25,26]. Even though these articles could not reveal a specific mechanism that could explain how Alzheimer's Disease changes the habit of eating, they marked a pronounced phenomenon that Alzheimer's Disease can greatly influence patients' intake habits randomly.

What's more, the behaviour of eating may also change the constitution of groups of microorganisms. While emerging evidence is able to claim that changes in diet can influence the gut microbiome, a diet that is unhealthy or irregular will induce gut dysbiosis [24,25]. From Zhernakova et al, over a thousand volunteers from Dutch were asked to be analyzed with the method of metagenomic using deep sequencing while the data if it detects the factors including diet etc [27]. Total carbohydrate consumption and micro biodiversity decreased most significantly: Especially *Bifidobacterium* increased, and also the *Lactobacillus*, *Streptococcus* and *Rosebacter* decreased. The study illustrate that the Shannon diversity index of total carbohydrates is the lowest, and followed by sugared drinks, bread, beer, flavoured snacks, followed by total fat, pulses and legumes. The diversity of self-reported IBS patients has also decreased, and the use of antibiotics is associated with the reduction of two *Bifidobacterium*. On the contrary, the diversity of microorganisms would increase when the host intake coffee, fruit, vegetable, and even red wine and have a smaller extent during eating breakfast and drinking tea. Increased abundance of *F. prausnitzii* [24]. Red wine consumption was connected to an anti-inflammatory species seen in lean-type, high-richness microbiota. Polyphenols are substances that have prebiotic and bifidogenic properties., are abundant in coffee, tea, and red wine [27]. Through the research about AD's eating habits previously, patients' diets change obviously whereas the statistics were unstable. Namely, the changes in diet in some of the groups of the participants can theoretically benefit the improvement of the diversity among

microbiota in the GI tract, and some of the others are the opposite [24,25]. A deeper study is needed to be conducted or AD may get little influence on the dysbiosis among the gut microflora.

4. Several drugs and therapies for AD

Following the introduction of the core diagnostic criteria for Alzheimer's disease in 1984, Alzheimer's disease is defined by the progressive loss of memory and cognitive functioning [28]. After death, high-density plaques containing beta amyloid peptides and defective neurons were discovered, as well as the loss of neurons and synapses in the brain [28]. Serious degeneration of the base forebrain leads to the content of acetylcholine and the activity of acetyltransferase [28]. Although neurotransmitters are involved, acetylcholine loss occurs. In this regard, the symptomatic treatment of Alzheimer's disease focusses on enhancing cholinergic nerve transmission [28]. Alzheimer's disease is not without any drug treatment. The current medical level supports and has the ability to get some treatment for these people (most elderly people). The aim of Alzheimer's disease treatment has been to enhance or at least reduce memory and cognitive decline while maintaining independent function. Drugs are well-known and widely used to treat a variety of ailments [28]. Although this does not completely eliminate Alzheimer's disease, it will greatly improve the lives of the elderly. Here, according to the drugs now invented, there are several important drugs against Alzheimer's disease are summarized. [29]

4.1. Cholinergic augmentation therapy

The lecithin and choline of acetylcholine actually have no effect on Alzheimer's disease, which does not increase central cholinergic activity. However, the results of cholinesterase inhibitors (anticholinesterase) are completely opposite to acetylcholine. They improve cholinergic transmission by blocking acetylcholinesterase in synaptic intervals, lowering acetylcholine hydrolysis by presynaptic neurons, unlike acetylcholine. The drug treatment of cholinergic energy is the cognitive function that starts to recover after agonists for traumatic brain injury. The management of cognitive impairment is somewhat challenging, because traumatic brain damage of cognitive impairment can bring lasting and permanent damage. There is evidence that after our brain injury, the synthesis and transportation of acetylcholine are destroyed, which leads to cognitive impairment. Secondly, the cholinergic system will also have reaction disfunction. Therefore, cholinergic drug treatment can obviously help Alzheimer's disease achieve therapeutic effect, inhibit brain damage, and restore cognitive impairment [30] here have been studies that show physostigmine, a cholinergic agonist, can help people with TBI recover their verbal memory and attention [30]. In a double-blind, placebo-controlled research, Cardenas et al⁵ found that 44 percent of patients improved their memory. Levin et al⁶ completed a double-blind, placebo-controlled trial of oral physostigmine and lecithin in combination (a precursor to acetylcholine). In 16 individuals with moderate to severe TBI, sustained attention was found to be significantly better with physostigmine than with placebo [30].

4.2. Cholinesterase inhibitor drugs

Cholinesterase inhibitors are considered to be another functional drug for Alzheimer's disease. At present, there are three approved symptomatic treatments for Alzheimer's disease in the world: "Donepezil, Galantamine and Rivastigmine". These three drugs are classified as second-generation drug production products., and the first generation of drugs are no longer popular due to side effects. Here is a brief introduction to several drugs. Among these three drugs, Donepezil is one of the drugs. It is a reversible non-competitive acetylcholinesterase inhibitor based on piperidine, which is centrally active and highly selective [31]. In some studies, data show that Donepezil inhibits human erythrocyte acetylcholinesterase activity in vivo, increasing the cerebral cortex and extracellular acetylcholine levels in rats and hippocampus. In addition to Donepezil, Rivastigmine is also an inhibitor, which has excellent characteristics in terms of specificity and a low risk of side effects. There are many indications in clinical studies. Rivastigmine shows central nervous system selectivity over peripheral

inhibition, according to preclinical biochemical studies. It helped mice with forebrain injuries improve their memory. Besides, studies also indicated that Rivastigmine selectively inhibits a part of the place such as G1 isoenzyme of AChE, it usually stays in neurotic plaques the cortex and the hippocampus [31]. The first two symptomatic drugs that can treat Alzheimer's disease, Galantamine can achieve the same purpose. This Drug was first marketed in 2001 in USA. At first, it was separated from several plants, and daffodils were no exception. It can be said that Galantamine is a specific, reversible and competitive inhibitor, which can be regarded as acetylcholinesterase inhibitor. Early clinical trials have proved that this drug has a therapeutic effect on Alzheimer's disease [32].

4.3. Efficacy of Treatments to Delay Disease Progression

The main problem with Alzheimer's disease is cognitive function, which is affected by nutrients. For example, the brainstem part of the brain affects the cell membrane [34]. In particular, the formation and maintenance of neurons require adequate supply, most of which require dietary supply, that is, the nutrients in the food we need every day. Food contains fatty acids, and fatty acids must be obtained from food. Of course, a good eating habit can relieve Alzheimer's disease. Diet can provide sufficient precursors to release nerve mass. It is shown that the synthesis of acetylcholine is controlled by the intake of choline in the diet. Therefore, it can be seen that nutrients are one of the ways to delay and obtain control Alzheimer's disease [34].

5. Conclusion

In conclusion, the intestine can also indirectly affect Alzheimer's disease. The entry of encephalitis into the circulatory system leads to nerve inflammation, and harmful metabolites produced by intestinal flora can pass the blood to brain barrier, thus damaging the function of neurons. In addition, the intestinal-brain-microbial axis reflects bidirectional and continuous communication between the brain and the gastrointestinal tract, which further proves that Alzheimer's disease is related to the intestinal flora and is transmitted through the intestinal-brain-axis. Whether encephalitis is related to Alzheimer's disease has aroused people all over the world thinking. Scientists may perform more in-depth research on encephalitis in the future, and a more accurate description of encephalitis and Alzheimer's disease are inextricably linked. Furthermore, treating Alzheimer's disease as a result of encephalitis will be of enormous benefit to the majority of Alzheimer's patients in the future. The beta-amyloid protein deposition of plaque reduces the load of myeloid protein is a symptom of Alzheimer's Disease. In the study, it was found that Alzheimer's disease has relevant information about encephalitis. A small number of patients have neurological complications due to inflammatory reactions to encephalitis. Neuro-pathological examination did not find meningitis and a small number of atypical diffuse and neuroinflammatory plaques, but no vascular amyloid protein, neurogenic fibre entangles mentation and nerve fibre filaments did not show tau pathological deposition. In the study, the researchers found that inflammatory infiltration consisted of CD8+, CD3+, CD5+ and rare CD7+ lymphocytes [35]. Therefore, Alzheimer's disease is still waiting for the research and treatment plan of scientists and medical scientists, which is expected to make progress in the future.

References

- [1] Jiang, C., et al. "The Gut Microbiota and Alzheimer's Disease.", 2017. *J Alzheimers Dis* 58(1): 1-15.
- [2] Pickard, J. M., et al. "Gut microbiota: Role in pathogen colonization, immune responses, and inflammatory disease.", 2017. *Immunol Rev* 279(1): 70-89.
- [3] Sengoku, R. "Aging and Alzheimer's disease pathology.", 2020. *Neuropathology* 40(1): 22-29.
- [4] Kim, C. S., et al. (2021). "Probiotic Supplementation Improves Cognitive Function and Mood with Changes in Gut Microbiota in Community-Dwelling Older Adults: A Randomized, Double-Blind, Placebo-Controlled, Multicenter Trial." *J Gerontol A Biol Sci Med Sci* 76(1): 32-40.

- [5] Wang Hong, Niu Chen, Wand huijing. Zhaochao. "Understanding the underlying pathogenesis of Alzheimer's disease from the perspective of gutmicrobiota.", 2019. Journal of microbes and infections 14(5): 310-316. DOI: 10.3969/j.issn.1673-6184.2019.05.008
- [6] Kowalski, K. and A. Mulak "Brain-gut-microbiota axis in Alzheimer's disease.", 2019. Journal of neurogastroenterology and motility 25(1): 48. DOI: 10.5056/jnm18087
- [7] Leblhuber, F., et al. "Elevated fecal calprotectin in patients with Alzheimer's dementia indicates leaky gut.", 2015. Journal of neural transmission 122(9): 1319-1322.
- [8] Sochocka, M., et al. "Inflammatory response in the CNS: friend or foe?", 2017. Molecular neurobiology 54(10): 8071-8089. DOI: <https://doi.org/10.1007/s12035-016-0297-1>
- [9] Heneka, M. T., et al. "Neuroinflammation in Alzheimer's disease.", 2015. The Lancet Neurology 14(4): 388-405. DOI: [https://doi.org/10.1016/S1474-4422\(15\)70016-5](https://doi.org/10.1016/S1474-4422(15)70016-5)
- [10] Ghosh, S., et al. "Sustained interleukin-1 β overexpression exacerbates tau pathology despite reduced amyloid burden in an Alzheimer's mouse model.", 2013. Journal of Neuroscience 33(11): 5053-5064.
- [11] Pistollato, F., et al. "Role of gut microbiota and nutrients in amyloid formation and pathogenesis of Alzheimer disease.", 2016. Nutrition reviews 74(10): 624-634.
- [12] Villarán, R. F., et al. "Ulcerative colitis exacerbates lipopolysaccharide-induced damage to the nigral dopaminergic system: potential risk factor in Parkinsons disease.", 2010. Journal of neurochemistry 114(6): 1687-1700.
- [13] Vogt, N. M., et al. "Gut microbiome alterations in Alzheimer's disease.", 2017. Scientific reports 7(1): 1-11
- [14] Janeiro, M. H., et al. "Dysbiosis and alzheimer's disease: cause or treatment opportunity?", 2021. Cellular and molecular neurobiology: 1-11.
- [15] Wu, S.-C., et al. "Intestinal microbial dysbiosis aggravates the progression of Alzheimer's disease in Drosophila.", 2017. Nature Communications 8(1): 24.
- [16] Bostanciklioğlu, M. "The role of gut microbiota in pathogenesis of Alzheimer's disease.", 2019. Journal of applied microbiology 127(4): 954-967.
- [17] Larsen, N., et al. "Gut microbiota in human adults with type 2 diabetes differs from non-diabetic adults.", 2010. PloS one 5(2): e9085. DOI: <https://doi.org/10.1371/journal.pone.0009085>
- [18] Ott, A., et al. "Diabetes mellitus and the risk of dementia: The Rotterdam Study.", 1999. Neurology 53(9): 1937-1937. DOI: <https://doi.org/10.1212/WNL.53.9.1937>
- [19] de la Monte, S. M. and J. R. Wands "Review of insulin and insulin-like growth factor expression, signaling, and malfunction in the central nervous system: relevance to Alzheimer's disease.", 2005. Journal of Alzheimer's Disease 7(1): 45-61. DOI: 10.3233/JAD-2005-7106
- [20] Rawlings, A. M., et al. "Diabetes in midlife and cognitive change over 20 years: a cohort study.", 2014. Annals of internal medicine 161(11): 785-793. DOI: <https://doi.org/10.7326/M14-0737>
- [21] Seab, J., et al. (1988). "Quantitative NMR measurements of hippocampal atrophy in Alzheimer's disease." Magnetic resonance in medicine 8(2): 200-208. DOI: <https://doi.org/10.1002/mrm.1910080210>
- [22] Opitz, B. "Memory function and the hippocampus." , 2014. Front Neurol Neurosci 34: 51-59. DOI: <https://doi.org/10.1159/000356422>
- [23] Sakaguchi, Y. and Y. Sakurai "Left-right functional difference of the rat dorsal hippocampus for short-term memory and long-term memory.", 2020. Behav Brain Res 382: 112478. DOI: <https://doi.org/10.1016/j.bbr.2020.112478>
- [24] Jiao, Y., et al. "Sevoflurane Impairs Short-Term Memory by Affecting PSD-95 and AMPA Receptor in the Hippocampus of a Mouse Model.", 2019. Behav Neurol 2019: 1068260. DOI: <https://doi.org/10.1155/2019/1068260>
- [25] Grady, C. L., et al. "Altered brain functional connectivity and impaired short-term memory in Alzheimer's disease.", 2001. Brain 124(4): 739-756. DOI: <https://doi.org/10.1093/brain/124.4.739>
- [26] Ikeda, M., et al. "Changes in appetite, food preference, and eating habits in frontotemporal dementia and Alzheimer's disease.", 2002. Journal of Neurology, Neurosurgery & Psychiatry 73(4): 371-376. DOI: <http://dx.doi.org/10.1136/jnnp.73.4.371>

- [27] Cullen, P., et al. "Eating disorders in dementia.", 1997. International journal of geriatric psychiatry 12(5): 559-562.
- [28] Le Chatelier, E., et al. "Richness of human gut microbiome correlates with metabolic markers.", 2013. Nature 500(7464): 541-546.
- [29] Hills, R. D., et al.. "Gut microbiome: profound implications for diet and disease.",2019. Nutrients 11(7): 1613.
- [30] Rosas-Ballina, M. and K. J. Tracey. "Cholinergic control of inflammation.", 2009. J Intern Med 265(6): 663-679.
- [31] Olin, J. and L. Schneider. "Galantamine for dementia due to Alzheimer's disease (Cochrane Review).", 2004. The Cochrane Library (2)
- [32] Birks, J. S. and J. G. Evans. "Rivastigmine for Alzheimer's disease.", 2015. Cochrane Database of systematic reviews (4).
- [33] Burns, A., et al. "The Effects of Donepezil in Alzheimer's Disease—Results from a Multinational Trial1.", 1999. Dementia and geriatric cognitive disorders 10(3): 237-244.
- [34] Seltzer, B. "Donepezil: a review.", 2005. Expert opinion on drug metabolism & toxicology 1(3): 527-536.
- [35] Thompson, S., et al. "The benefits and risks associated with cholinesterase inhibitor therapy in Alzheimer's disease.", 2004. Expert opinion on drug safety 3(5): 425-440.