Animal Health Prod and Hyg (2023) 12 (2) : 56 - 62

Animal Health, Production and Hygiene

www.dergipark.or.tr/tr/pub/aduveterinary

Review

The Relationship Between Microbiota and Alzheimer's Disease

Elif Nurcan EMRE[1], Ümit Yasin ÇOBAN[1], Beyza SUVARIKLI ALAN[1*], Zafer BULUT[1,2]

[1]*Department of Biochemistry, Faculty of Veterinary Medicine, Selçuk University, Konya, TÜRKİYE*

[2]*Faculty of Veterinary Medicine, Dokuz Eylül University, İzmir, TÜRKİYE*

ABSTRACT

The term microbiota refers to the micro-organisms that interact with the host from birth to death. These interactions can reach the brain via the bloodstream or the gut-brain nervous system. The microbiota performs important beneficial functions, such as contributing to digestive processes, breaking down toxins and creating defense mechanisms against pathogenic bacteria. However, this positive situation only takes place when the microbiota is also positive, i.e. when the probiotics, known as eubiosis, are dominant. Factors such as nutritional habits, age and the use of antibiotics can impair the balance of the microbiota and lead to a situation where harmful microorganisms, known as dysbiosis, are dominant in the gut. In this case, the production of many microbial products that are normally beneficial to the body, such as neurotransmitters and some short-chain fatty acids, reduces and pathogenic metabolites are produced. In the case of dysbiosis, intestinal permeability increases, allowing harmful pathogenic metabolites to enter the bloodstream and even reach the brain via the bloodstream. For these reasons, prolonged dysbiosis is known to pave the way for many diseases such as depression, anxiety, schizophrenia, autism, diabetes, and Alzheimer's disease. Alzheimer's disease is characterized by the death of nerve cells in the brain and loss of cognitive abilities. The disease is associated with amyloid plaques and tau protein. It has been argued that disruption of the intestinal microbiota may contribute to the pathology of Alzheimer's disease and may also have therapeutic potential. Amyloid production may be triggered by the intestinal microbiome, causing a way for the studies on Alzheimer's disease. This review examines the relationship between the intestinal microbiota and Alzheimer's disease.

Keywords: *Alzheimer's, microbiota, probiotics.*

Mikrobiyata ve Alzheimer İlişkisi

ÖZET

Mikrobiyota, doğumdan ölüme kadar konakçı ile etkileşimde bulunan mikroorganizmaları ifade etmektedir. Bu etkileşimler kan dolaşımı veya bağırsak-beyin sinir sistemi yoluyla beyine kadar gidebilmektedir. Mikrobiyota, sindirim süreçlerine katkı sağlama, toksinleri parçalama ve patojen bakterilere karşı savunma mekanizmaları oluşturma gibi önemli faydalı işlevleri yerine getirir. Ancak bu olumlu durum mikrobiyotanın da olumlu yani ösbiyozis adı verilen probiyotiklerin baskın olduğu durum ile gerçekleşmektedir. Beslenme alışkanlıkları, yaş, antibiyotik kullanımı gibi faktörler mikrobiyotanın dengesini bozabilir ve disbiyözis adı verilen olumsuz ve zararlı mikroorganizmaların bağırsaklarda baskın olduğu duruma yol açabilmektedir. Bu durumda normalde vücut için yararlı olan nörotransmitterler, bazı kısa zincirli yağ asitleri gibi birçok mikrobiyal ürünün üretimi azalacak ve patojen metabolitler üretilemeye başlanacaktır. Disbiyozis durumunda bağırsak geçirgenliği artmakta, bu da zararlı patojen metabolitlerin kana karışmasına ve hatta kan dolaşımı yoluyla beyne ulaşmasına yol açmaktadır. Bu sebeplerden dolayı disbiyözis durumunun uzun sürmesi sonucunda, depresyon, anksiyete, şizofreni, otizm, diyabet, Alzheimer gibi birçok hastalığın önü açıldığı bilinmektedir. Alzheimer hastalığı, beyinde bulunan sinir hücrelerinin ölümü ve bilişsel yeteneklerin kaybıyla karakterizedir. Bu hastalığın amiloid plakları ve tau proteini ile ilişkilendirildiği belirtilmektedir. Bağırsak mikrobiyotasının bozulmasının Alzheimer hastalığının patolojisine katkıda bulunabileceği ve aynı zamanda bu konuda tedavi potansiyelinde olabileceği tartışılmaktadır. Özellikle amiloid üretimi bağırsak mikrobiyomu tarafından tetiklenebilmekte ve bu da Alzheimer hastalığıyla ilgili çalışmalar için yeni bir yol açmaktadır. Bu derleme de bağırsak mikrobiyotası ile Alzheimer arasındaki ilişki incelenecektir.

Anahtar Kelimeler: *Alzheimer, mikrobiyota, probiyotikler.*

[(*)] **Corresponding author:** Beyza SUVARIKLI ALAN, Department of Biochemistry, Faculty of Veterinary Medicine, Selçuk University, Konya, TÜRKİYE.
beyza.alan@selcuk.edu.tr

Received Date: 16.10.2023 – Accepted Date: 04.12.2023
DOI: 10.53913/aduveterinary.1376464

Introduction

The word 'microbiota', which was defined in the early 1900s, refers to the community of microorganisms that live in different parts of the human body. These microorganisms have 150 times more genetic information than the human genome and are referred to as "hidden organs". While the term 'microbiota' refers to the living microorganisms, the term "microbiome" includes the genomes, structural elements, and metabolites of these organisms. The concept of microbiome therefore describes a wider scope than microbiota (Hou et al., 2022).

The fact that the microbiota has 10 times the number of cells in the body, and the microbiome has 100 times the number of genes, is a clear indication of how effective these organisms are for the living beings (Dinan and Cryan, 2015). In the past, it was thought that the number of microorganisms comprising the microbiota was quite small, but today it has been reported that research in this field is gaining momentum as more microorganism species are being discovered using cheaper and more efficient culture-independent methods and new-generation sequencing methods, such as 16S rRNA sequencing (Koçak and Şanlıer, 2017). The formation of the microbiota is influenced by many factors, such as race, mode of birth, age, gender, diet, previous diseases, and antibiotic use. While a healthy balance, or eubiosis, is associated with positive microbiota, unhealthy imbalance, or dysbiosis, is associated with negative microbiota (Yılmaz and Altındiş, 2017). There is a symbiotic, pathogenic, and commensal relationship between the microbiota and the human body. Metabolites produced by microbiota can affect brain through gut-brain relations, suggesting important connections and interactions between brain and intestinal microbiota. The Human Microbiome Project was undertaken to better understand this relationship, to find treatments for disease and to maintain human health, and at the end of the project it was reported that the human body is a super-organism (Çetinbaş et al., 2017).

Alzheimer's disease is the primary one of the world's major health problems, especially among the elderly population. Current treatments for the disease are aimed at slowing the progression of the disease or reducing symptoms. In addition to these treatments, exercise programs that can be applied at every stage are used. Exercise can prevent or delay the decline of cognitive signals in the aging brain, because exercise increases the formation of new neurons (Keleş and Özalevli, 2018). Regarding the relationship between the microbiota and Alzheimer's disease, it has been reported that an imbalance in the intestinal microbiota may increase the risk of Alzheimer's disease by causing microbial amyloids to enter the bloodstream and neuroinflammatory processes. Probiotics, made up of bacteria that benefit the health of the host, have been found to have the capacity to stabilize the pH of the digestive system, reduce inflammation and increase levels of neuroprotective molecules, while prebiotics are substances that provide nutrients to the bacteria that make up probiotics (Angelucci et al., 2019). This leads researchers to believe that probiotic and prebiotic supplements could be a potential treatment for Alzheimer's patients today. Therefore, understanding the intestinal microbiota and its relationship with the human body could shed light on the development of treatment methods in the future.

Relationship between Microbiota and Brain

The human body has interacted with microorganisms since its existence. Beneficial, harmless, or harmful microorganisms are found in many tissues of the body, such as the skin, throat, mouth, mucous membranes of organs and the gastrointestinal tract. These microorganisms are called the "microbiota" and the genes they carry are called the "microbiome" (Çetinbaş et al., 2017). Gastrointestinal system is the system that contains the most microbiota due to its large surface area. The community formed by all microorganisms in or passing through this system is called "intestinal microbiota" (Gerritsen et al., 2011). The intestinal microbiota has many important functions and benefits. These include facilitating the absorption of hard-to-digest or indigestible foods by breaking them down, preventing the proliferation of harmful microorganisms by creating an acidic environment, and playing a role in the immune system. In addition, the intestinal microbiome and its metabolites are involved in fundamental neurogenerative processes such as neuroinflammation, formation of blood-brain barrier, myelination, neurogenesis, and microglial maturation (Nazlıkul and Acarkan 2014; Li et al., 2018). The microbiota includes many eukaryotic organisms such as viruses, bacteria, archaea, and fungi, but is predominantly composed of bacteria, which have a significant effect on human health and diseases. The microbiome generally contains two essential bacterial phylotypes: *Bacteriodetes* and *Firmicutes*. In addition, other bacteria such as *Proteobacteria, Actinobacteria, Fusobacteria* and *Verrucomicrobia* are found in smaller rates. The microbiota of older people differs from that of younger people. These age-related changes in the microbiota have been associated with adverse health effects, and in particular, the number of probiotic bifidobacteria has been found to decrease with increasing age (Dinan and Cryan, 2015; Yılmaz and Altındiş, 2017). The intestinal microbiota has an important place in producing neurotransmitters and short-chain fatty acids. *Lactobacillus* and *Bifidobacterium* can produce 70% of the inhibitory neurotransmitter GABA, which contributes to the development of the nervous system and formation of synapse. The 90% of serotonin produced by the microbiota regulates cognitive functions, mood, sleep and appetite. In addition, species such as *Escherichia*, *Bacillus* and *Saccharomyces* produce dopamine and norepinephrine. Short-chain fatty acids produced in the intestine include butyrate, acetate, propionate, and lactic acid. Butyrate is noted for its health benefits and is produced by *Butyricicoccus* and *Clostridium* species, providing a source of energy and increasing ATP production (Li et al., 2018). The microbiota of adult individuals can be divided into permanent and transient microbiota. The permanent microbiota is usually unchanging and can regenerate rapidly; whereas, the transient microbiota consists of microorganisms that

are constantly changing and are usually harmless, but can also be pathogenic (Çetinbaş et al., 2017).

The microbiota that emerges in late pregnancy is the first microbiota to affect infancy and begins in the womb. The type of birth is known to affect the structure of the microbiota: vaginal delivery is dominated by the vaginal microbiota, and caesarean section is dominated by the maternal skin microbiota. Vaginally delivered babies have higher concentrations of *Bacteroides*, *Bifidobacterium* and *Lactobacillus* in the first days of their life and greater microbial change in the following weeks. Caesarean-born babies have been reported to have *Staphylococcus*, *Streptococcus,* and *Clostridium*, with less diversity, except for a microbiota similar to the mother's skin and the hospital setting (Coelho et al., 2021). The initial microbiota is a determinant for the individual in later periods of life and tends to return to a similar structure with age. Breast milk plays a critical role in shaping the microbiota of infants (Dinan and Cryan, 2015). From the prenatal period to old age, the intestinal microbiome and metabolites are involved in neurogenerative conditions such as formation of blood-brain barrier and neuroinflammation (Li et al., 2018). In newborns aged 4 weeks and older, Bifidobacteria were reported to be the most abundant species in both breastfed and formula-fed infants, and in most cases no significant numerical differences were found between breastfed and formula-fed infants (Guaraldi and Salvatori, 2012). In another study, Bezirtzoglou et al. (2011) reported that breastfed infants had higher bacterial cell counts than formula-fed infants.

Nutritional habits and diets, which are an important factor, can change the structure of the microbiota. The studies have reported that diets can change the intestinal microbiota in 3 weeks (Kalip and Nazlı, 2018). Some nutrients, especially diets containing substances such as carbazoles and tryptophan, prevent the formation of some diseases, while diets containing phosphatidylcholine and some fatty acids may increase the risk of disease (Çetinbaş et al., 2017). Imbalance in the intestine can increase the permeability of the intestinal barrier, which leads to the entry of pathogenic substances into the body (Kalip and Nazlı, 2018). Drugs such as antibiotics can cause disturbances in the microbiome (Çetinbaş et al., 2017).

Communication between the brain and intestine is established through the central nervous system, enteric nervous system, and hypothalamic pituitary adrenal axis. This interaction starts in the womb and intestinal microbiota has an important role in this relationship (Nazlıkul and Acarkan, 2014). The central nervous system (CNS) communicates with the enteric nervous system, intestinal muscles, and mucosa via afferent and efferent pathways. Through this communication, intestinal permeability, mucus secretion, motility and immunity are regulated (Pistollato et al., 2016). Gut-brain communication also occurs through the circulatory system. Neurotransmitters and short-chain fatty acids produced by the intestinal microbiota are transmitted to the brain by mixing into the blood (Özer et al., 2019). Immune system modulation, hypothalamic pituitary adrenal (HPA) axis, tryptophan metabolism and bacterial metabolite production can also be added to the mechanisms by which intestinal microbiota affect behavior (Kelly et al., 2016).

Effects of Probiotics, Prebiotics and Diets on Microbiota

Probiotics involve the direct delivery of live bacteria to the host in the form of artificial encapsulation or fermented foods (Green et al., 2020). A microorganism accepted as a probiotic should be non-pathogenic, tolerate gastric acid, be able to secrete antimicrobials, be able to attach to intestinal cells, adapt to the natural intestinal microbiota, and have a positive effect on the health of the individual (Taşdemir, 2017). Probiotics strengthen immunity by interacting with the immune system, support the intestinal barrier, prevent the proliferation of pathogens, and have protective and therapeutic effects in allergic diseases (Çetinbaş et al., 2017). Probiotics can directly affect the gastrointestinal tract. By interacting with the intestinal mucus and epithelium, they can modulate the intestinal barrier and mucosal immune system and affect the systemic immune system and organs such as the liver and brain (Gerritsen et al., 2011).

Prebiotics include nutrients that are utilized by microorganisms living in the intestine and promote their growth (Green et al., 2020). Some prebiotics are found naturally (e.g. in breast milk) (Orel and Trop, 2014), while others are added to foods. Examples of prebiotics include fructooligosaccharides (FOS), inulin, galacto-oligosaccharides (Orel and Trop, 2014; Özer et al., 2019) and soy oligosaccharides (Orel and Trop, 2014). Prebiotics and probiotics can inhibit the growth of potentially pathogenic microorganisms by increasing the production of short-chain fatty acids and lowering colonic pH. These compounds have antimicrobial secretory properties and inhibit bacterial adhesion (Gerritsen et al., 2011; Orel and Trop, 2014).

Diet is effective on mental and physical health; in this sense, stress and obesity play an important role. The Mediterranean diet, for example, is known for its health benefits; it includes healthy ingredients such as vegetables, fruit, nuts, and olive oil, and limits red wine and saturated fats. This diet is associated with longer life and lower rates of cardiovascular disease. On the other hand, a high-fat diet can lead to obesity, anxiety, and cognitive dysfunction. Stress can lead to obesity by triggering overeating behavior, which is associated with changes in neurotransmitters, neuropeptides, and inflammatory factors (Bremner et al., 2020).

Conditions Causing Dysbiosis and Their Effects

The gastrointestinal system forms a complex intestinal barrier to limit the exposure of the host's immune system to the microbiota. This barrier has physical, biochemical, and immunological components. However, an imbalance in the microbiota can weaken the function of this barrier (Thursby and Juge, 2017). The intestinal microbiota has an important role in bidirectional interactions between the intestine and the nervous system and may interact with the CNS by affecting neuroendocrine

systems involved in stress response, anxiety, and memory function (Carabotti et al., 2015). It has been reported that individuals with autism are unable to digest casein and gluten, and this deficiency leads to the formation of peptides that produce opioid effects in the brain. It is also known that a casein- and gluten-free diet reduces the symptoms of autism. In addition, people with autism have more intestinal problems than healthy people, strengthening the possibility that autism may be associated with intestinal health (Doenyas, 2018). Intestinal disorders may also play a role in other neuropsychological disorders. Psychological stress can cause intestinal problems, and antidepressants can make this condition worse. Therefore, in some cases, probiotic supplementation may be a more effective treatment option than antidepressants (Nazlıkul and Acarkan, 2014). Studies in Alzheimer's disease have reported that the intestinal microbiota can produce neurotransmitters and neuromodulators. These neurotransmitters include compounds such as GABA, serotonin, and dopamine. GABA in particular plays an inhibitory role in the brain and when this signaling is disrupted, problems such as anxiety, depression and cognitive impairment can occur (Akbari et al., 2016).

Intestinal Microbiota in Veterinary Medicine

The dominant bacterial phyla in the human intestinal microbiota, such as *Firmicutes* and *Bacteroidetes,* have also been evaluated for suitability in various animal species (Nguyen et al., 2015). The dominant intestinal bacterial phyla in humans are *Firmicutes* and *Bacteroidetes.* Various animal species have also been evaluated for microbiota suitability (Turner, 2018). It has been reported that the microbiota of rats and mice are most like each other, but the microbiota profile of rats is more similar to that of humans than that of mice (Flemer et al., 2017).

Both mini-pigs and traditional pig models contain *Firmicutes* and *Bacteroidetes* species that are present in the human intestinal microbiota. They are also considered as useful models for human gastrointestinal health (Lamendella et al., 2011; Pedersen et al., 2013). The intestinal microbiome of non-human primates, such as macaques, shows significant differences when compared to mice and humans (McKenna et al., 2008).

Although the mouse intestinal microbiome shows similarities to the human intestinal microbiome, it has been reported that human-specific bacterial genera are missing from detailed analyses. While this situation leads to thoughts about how effectively mouse models reflect human intestinal health and diseases, it is also part of the information that the mouse is the commonly used model for general mechanisms of intestinal microbiome and microbiota transfers, as it is more appropriate to genetic manipulation (Turner, 2018). Garcia-Mazcorro et al. (2011) reported that probiotic and prebiotic intake in cats and dogs did not alter the bacterial phylum found in feces, while symbiotic supplementation led to an increase in probiotic bacteria in the feces of healthy cats and dogs.

Alzheimer's Disease

Alzheimer's disease is a progressive, irreversible neurodegenerative disorder that affects cognition, function, and behavior (Porsteinsson et al., 2021). Symptoms of the disease result from a progressive loss of cholinergic function due to neuronal cell death in the hippocampus and cerebral cortex, as well as other regions of the brain that regulate thought and memory processes (Ton et al., 2018). Alzheimer's disease is a progressive condition that can be treated with medication and exercise, but it cannot be stopped completely, only slowed down. Between 2012 and 2017, the prevalence rate of Alzheimer's disease in the elderly population in Turkey increased by 17.1%. In addition to mental and behavioral differences and memory-related symptoms, sleep problems, dependence on daily tasks and depression are observed in people with Alzheimer's disease (Keleş and Özalevli, 2018). Alzheimer's disease is known to progress over a long period of time, usually such as 15-25 years. During this time, patients may not manifest any symptoms, including mild cognitive impairment, until the symptoms of dementia are clear. The onset of dementia may be a consequence of the long persistence of pathology of Alzheimer's disease. However, it is known that this process is not the same for every patient (Scheltens et al., 2021). The main pathological manifestations of Alzheimer's disease are amyloid plaques, tau protein and loss of neurons and synapses (Li et al., 2018). The ApoE gene used as a marker is recognized by three different allelic polymorphisms: ApoE2 is considered as protective, ApoE3 as neutral and ApoE4 as high risk (Ton et al., 2018). Amyloid β, the culprit in Alzheimer's disease, also normally forms in healthy individuals, due to proteolysis of APP. The disruption of the healthy system is the beginning of the pathology of Alzheimer's disease. The enzymes α-secretase, β-secretase and γ-secretase are involved in this process; α-secretase and β-secretase cleave APP at different sites to form α-APP and β-APP, respectively. Then, cleavage by γ-secretase produces p3 and Aβ fragments. This normal Aβ formation is a pathological precursor of the Aβ plaques that are the onset of Alzheimer's disease. The tau protein is involved in the organization of microtubules and is a gene located on chromosome 17. Hyperphosphorylation of tau causes the pathology of Alzheimer's disease. Hyperphosphorylated tau cannot bind to microtubules and forms structures that are the main pathological features of Alzheimer's disease (Saka, 2010).

Alzheimer's Disease and Intestinal Microbiota

Alzheimer's disease is a complex neurodegenerative disorder and the most common form of dementia. Its main pathological symptoms are amyloid plaques and neurofibrils. It is also recognized that the disease may be associated with intestinal dysbiosis. This theory is strengthened by the connection of the intestinal microbiota with the brain via the vagus nerve. The vagus nerve is an important interface between the intestine and the central nervous system. It connects to nuclei in the brainstem and exchanges signals via afferent (sensory) and efferent (motor) fibers. This allows the brainstem to control in-

testinal functions and communicate with other brain regions (thalamus, cortical areas, etc.). This multidirectional communication between the intestinal microbiota and the central nervous system occurs through many different mechanisms and pathways (Angelucci et al., 2019). Microbial amyloids fulfil many functions in the gut. For example, some bacteria, such as *Escherichia coli,* can increase the formation of amyloid protein fibrils, which has been accepted to be effective in Alzheimer's disease (Pistollato et al., 2016). Neuroinflammation is a long-term inflammatory process associated with some neurodegenerative diseases, including AD. Neuroinflammation describes the inflammation of neurons and the secretion of substances that trigger the immune response. The microbiota influences neuroinflammation, contributing to the modulation of microglia and astrocytes (Li et al., 2018). Microglial activation is considered to be an important factor in the pathogenesis of Alzheimer's disease. It can be activated in response to the accumulation of amyloid beta (Angelucci et al., 2019). Increased intestinal permeability caused by altered intestinal microbiome leads to the leakage of harmful bacterial metabolites into the bloodstream. These metabolites interact with the brain and influence signaling that contributes to Alzheimer's pathogenesis and neurodegeneration. Furthermore, the intestinal microbiota can enhance the inflammatory response that triggers amyloid beta deposition (Ton et al., 2018). Escherichia coli in the microbiome is the source of curli protein, a bacterial amyloid (Kowalski and Mulak, 2019). Chen et al. (2016) reported increased neuronal alpha-synuclein accumulation, increased microgliosis and astrogliosis, and increased expression of TLR2, IL-6 and TNF, which play a role in neuroinflammation, in rats exposed to *Escherichia coli* producing curli protein. High levels of bacterial lipopolysaccharides have been observed in the brains of patients with Alzheimer's diseases, particularly in the hippocampal and temporal lobe regions. In addition, in blood analyses in patients with amyloid deposition in the brain and cognitive impairment, the number of proinflammatory *Escherichia/Shigella* increased, anti-inflammatory *Escherichia rectale* decreased and proinflammatory cytokine levels increased (Angelucci et al., 2019). It has been reported that the number of Firmicutes and Actinobacteria decreased in the microbiota of patients of with Alzheimer's disease, the number of Bacteroidetes increased, and Ruminococcaceae, Turicibacteraceae, Clostridiaceae and Clostridium sensu stricto families in Firmicutes were at lower levels (Li et al., 2018). Based on all this information, impaired intestinal barrier in patients with Alzheimer's disease has led to new approaches to the formation and treatment of the disease. However, it is still a matter of curiosity whether the impaired intestinal microbiota is the culprit or consequence of the disease.

While antibiotics are used to treat bacterial infections, they can also have a negative effect on the intestinal microbiota. This effect varies depending on whether or not the antibiotic is broad-band spectrum or narrow-band spectrum. Because broad-spectrum antibiotics are effective against many types of bacteria, they can also reduce the number of beneficial bacteria in the gut. The use of such antibiotics can reduce the diversity of the microbiota, and this imbalance persists for a long time after use. While this imbalance can be corrected over time with short-term use of antibiotics, long-term and frequent use of antibiotics can lead to permanent imbalances. Antibiotic use may adversely affect the course of Alzheimer's disease by increasing neuroinflammatory responses. Antibiotics thought to trigger Alzheimer's disease include streptozotocin and ampicillin. In addition to causing an imbalance in the intestinal microbiota, streptozotocin has been used to induce cognitive impairment that mimics Alzheimer's disease in animal models (Angelucci et al., 2019).

It has been noted that diet has an important role to play in the treatment and prevention of Alzheimer's disease. Tully et al. (2003) found that levels of docosahexaenoic acid, an omega-3 fatty acid important for brain function, were low in the serum of patients with Alzheimer's disease. In the "Cardiovascular Risk Factors, Ageing and Dementia" study conducted at the University of Eastern Finland, 1409 randomly selected people aged 65-79 were followed for an average of 21 years. They were examined under 3 groups: 0-2 cups (low), 3-5 cups (medium) and >5 cups (high) daily coffee drinkers. It was reported that the risk of dementia was lower at the rate of 65-70% and the risk of Alzheimer's disease was lower at the rate of 62-64% in moderate coffee drinkers compared to low coffee drinkers (Eskelinen et al., 2009). In the Chicago Health and Aging Project, it was reported that 815 people aged 65 years and older without a history of heart attack, stroke or diabetes were followed for 6 years and there was a positive correlation between saturated and trans-fat intake and the risk of developing Alzheimer's disease (Morris et al., 2004). These findings suggest that saturated and trans fats may increase the risk of Alzheimer's disease (Barnard et al., 2014). In particular, diets containing antioxidant compounds may reduce the risk of Alzheimer's disease, while high-fat diets may increase the risk. It has been found that people who eat a low-fat diet have a lower risk of Alzheimer's disease (Ton et al., 2018). The study on rats reported that amyloid beta-induced learning difficulties could be treated with probiotics. Probiotic supplements containing Lactobacillus and Bifidobacterium were found to have positive effects on learning and memory. Although probiotics are known to be effective in the treatment of Alzheimer's disease, antibiotic treatment remains the preferred treatment for many patients due to its low cost and prevalence (Rezaeiasl et al., 2019).

Conclusion

Consequently, it is understood that the intestinal microbiota is closely related to the body's health and disease states. Healthy lifestyles support eubiosis, while negative factors lead to dysbiosis. Dysbiosis can be the cause of many diseases, and Alzheimer's in particular. Evidence has been found that Alzheimer's disease may be associated with the intestinal microbiota, with reduced neurotransmitter production in the intestine and microbial amyloid production. This association has led to the idea that probiotics may have a potential role in the treat-

ment of Alzheimer's disease. Due to the negative effects of antibiotics on the microbiota, probiotic-based therapies are attracting increasing attention. Interest in this area is growing by the day. It is thought that probiotic supplements may reduce inflammation, strengthen the intestinal barrier and even have neuroprotective effects. However, further studies are needed to understand exactly the functionality of these effects and their clinical effectiveness.

Conflict of Interest

The authors declare no conflict of interests.

References

Akbari, E., Asemi, Z., Daneshvar Kakhaki, R., Bahmani, F., Kouchaki, E., Tamtaji, O.R., Hamidi, G.A., & Salami, M. (2016). Effect of probiotic supplementation on cognitive function and metabolic status in Alzheimer's disease: a randomized, double-blind and controlled trial. *Frontiers in Aging Neuroscience,* 8, 256. https://doi.org/10.3389/fnagi.2016.00256.

Angelucci, F., Cechova, K., Amlerova, J., & Hort, J. (2019). Antibiotics, gut microbiota, and Alzheimer's disease. *Journal of Neuroinflammation,* 16(1), 108. https://doi.org/10.1186/s12974-019-1494-4.

Barnard, N.D., Bunner, A.E., & Agarwal, U. (2014). Saturated and trans fats and dementia: a systematic revew. *Neurobiology of Aging,* 35(2), 65-73. https://doi.org/10.1016/j.neurobiolaging.2014.02.030.

Bezirtzoglou, E., Tsiotsias, A., & Welling, G.W. (2011). Microbiota profile in feces of breast- and formula-fed newborns by using fluorescence in situ hybridization (FISH). *Anaerobe,* 17(6), 478–482. https://doi.org/10.1016/j.anaerobe.2011.03.009.

Bremner, J.D., Moazzami, K., Wittbrodt, M.T., Nye, J.A., Lima, B.B., Gillespie, C.F., Rapaport, M.H., Pearce, B., Shah, A.J., & Vaccarino, V. (2020). Diet, stress and mental health. *Nutrients,* 12(8), 2428. https://doi.org/10.3390/nu12082428.

Carabotti, M., Scirocco, A., Maselli, M.A., & Severi, C. (2015). The gut-brain axis: interactions between enteric microbiota, central and enteric nervous systems. *Annals of Gastroenterology,* 28(2), 203-209.

Chen, S.G., Stribinskis, V., Rane, M.J., Demuth, D.R., Gozal, E., Roberts., A.M., Jagadapillai, R., Liu, R., Choe, K., Shivakumar, B., Son, F., Jin, S., Kerber, R., Adame, A., Masliah, E., & Friedland R.P. (2016). Exposure to the functional bacterial amyloid protein curli enhances alpha-synuclein aggregation in aged fischer 344 rats and caenorhabditis elegans. *Scientific Reports,* 6, 34477. https://doi.org/10.1038/srep34477.

Coelho, G.D.P., Ayres, L.F.A., Barreto, D.S., Henriques, B.D., Prado, M.R.M.C., & Passos, C.M.D. (2021). Acquisition of microbiota according to the type of birth: An integrative review. *Revista Latino-americana de Enfermagem,* 29, e3446. https://doi.org/10.1590/1518.8345.4466.3446.

Çetinbaş, S., Kemeriz, F., Göker, G., Biçer, İ., & Velioğlu, Y.S. (2017). İnsan mikrobiyomu: beslenme ve sağlık üzerindeki etkileri. *Akademik Gıda,* 15(4), 409-415.

Doenyas, C. (2018). Mikrobiyota ve otizm. *Türkiye Sağlık Bilimleri ve Araştırmaları Dergisi,* 1(2), 43-48.

Eskelinen, M.H., Ngandu, T., Tuomilehto, J., Soininen, H., & Kivipelto, M. (2009). Midlife coffee and tea drinking and the risk of late-life dementia: a population-based CAIDE study. *Journal of Alzheimers Disease,* 16(1), 85-91. https://doi.org/10.3233/JAD-2009-0920.

Flemer, B., Gaci, N., Borrel, G., Sanderson, I.R., Chaudhary, P.P., Tottey, W., O'Toole, P.W., & Brugère, J.F. (2017). Fecal microbiota variation across the lifespan of the healthy laboratory rat. *Gut Microbes,* 8(5), 428-439. https://doi.org/10.1080/19490976.2017.1334033.

Garcia-Mazcorro, J.F., Lanerie, D.J., Dowd, S.E., Paddock, C.G., Grützner, N., Steiner, J.M., Ivanek, R., & Suchodolski, J.S. (2011). Effect of a multi-species synbiotic formulation on fecal bacterial microbiota of healthy cats and dogs as evaluated by pyrosequencing. *FEMS Microbiology Ecology*, 78(3), 542-554. https://doi.org/10.1111/j.1574-6941.2011.01185.x.

Gerritsen, J., Smidt, H., Rijkers, G.T., & de Vos, W.M. (2011). Intestinal microbiota in human health and disease: the impact of probiotics. *Genes & Nutrition,* 6(3), 209-240. https://doi.org/10.1007/s12263-011-0229-7.

Green, M., Arora, K., & Prakash, S. (2020). Microbial medicine: prebiotic and probiotic functional foods to target obesity and metabolic syndrome. *International Journal of Molecular Sciences*, 21(8), 2890.

Guaraldi, F., & Salvatori, G. (2012). Effect of breast and formula feeding on gut microbiota shaping in newborns. *Frontiers in Cellular and Infection Microbiology,* 2, 94. https://doi.org/ 10.3389/fcimb.2012.00094.

Hou, K., Wu. Z-X., Chen, X-Y., Wang, J-Q., Zhang, D., Xiao, C., Zhu, D., Koya, J.B., Wei, L., Li, J., & Chen, Z-S. (2022). Microbiota in health and diseases. *Signal Transduction and Targeted Therapy,* 7(1), 135. https://doi.org/10.1038/s41392-022-00974-4.

Kalip, K., & Nazlı, A. (2018). Bağırsak mikrobiyotası ve sağlık. *Turkish Journal of Public Health,* 16(1), 58-73.

Keleş, E., & Özalevli, S. (2018). Alzheimer hastalığı ve tedavi yaklaşımları. İzmir Kâtip Çelebi Üniversitesi Sağlık Bilimleri Fakültesi Dergisi, 3(2), 39-42.

Kelly, J.R., Clarke, G., Cryan, J.F., & Dinan, T.G. (2016). Brain-gut-microbiota axis: challenges for translation in psychiatry. *Annals of Epidemiology,* 26(5), 366-372. https://doi.org/ 10.1016/j.annepidem.2016.02.008.

Koçak, T., & Şanlıer, N. (2017). Mikrobesin öğeleri ve mikrobiyota etkileşimi. *Gümüşhane Üniversitesi Sağlık Bilimleri Dergisi,* 6(4), 290-302.

Kowalski, K., & Mulak, A. (2019). Brain-gut-microbiota axis in Alzheimer's disease. *Journal of Neurogastroenterology and Motility,* 25(1), 48-60. https://doi.org/10.5056/jnm18087.

Lamendella, R., Domingo, J.W., Ghosh, S., Martinson, J., & Oerther, D.B. (2011). Comparative fecal metagenomics unveils unique functional capacity of the swine gut. *BMC Microbiology,* 11, 103. https://doi.org/10.1186/1471-2180-11-103.

Li, Z., Zhu, H., Zhang, L., & Qin, C. (2018). The intestinal microbiome and Alzheimer's disease: A review. *Animal Models and Experimental Medicine,* 1(3), 180-188. https://doi.org/10.1002/ame2.12033.

McKenna, P., Hoffmann, C., Minkah, N., Aye, P.P., Lackner, A., Liu, Z., Lozupone, C..A, Hamady, M., Knight, R., & Bushman, F.D. (2008). The macaque gut microbiome in health, lentiviral infection, and chronic enterocolitis. *PLoS Pathogenes,* 4(2), e20. https://doi.org/10.1371/journal.ppat.0040020.

Morris, M.C., Evans, D.A., Bienias, J.L., Tangney, C.C., & Wilson, R.S. (2004). Dietary fat intake and 6-year cognitive change in an older biracial community population. *Neurology,* 62(9), 1573-1579. https://doi.org/10.1212/01.wnl.0000123250.82849.b6.

Nazlıkul, H.s., & Acarkan, T. (2014). Bağırsak ve enterik sinir sisteminin regülasyondaki önemi. *Bilimsel Tamamlayıcı Tıp Regülasyon ve Nöral Terapi Dergisi,* 8(1), 1-7.

Nguyen, T.L., Vieira-Silva, S., Liston, A., & Raes, J. (2015). How informative is the mouse for human gut microbiota research? *Disease Models Mechanisms,* 8(1), 1-16. https://doi.org/10.1242/dmm.017400.

Orel, R., & Trop, T.K. (2014). Intestinal microbiota, probiotics and prebiotics in inflammatory bowel disease. *World Journal of Gastroenterology,* 20(33), 11505-11524. https://doi.org/10.3748/wjg.v20.i33.11505.

Özer, M., Özyurt, G., & Harsa, Ş.T. (2019). Probiyotik ve prebiyotiklerin bağırsak-beyin aksına etkisi. *Akademik Gıda,* 17(2), 269-280.

Pedersen, R., Ingerslev, H.C., Sturek, M., Alloosh, M., Cirera, S., Christoffersen, B., Moesgaard, S.G., Larsen, N., & Boye, M. (2013). Characterisation of gut microbiota in ossabaw and göttingen minipigs as models of obesity and metabolic syndrome. *PLoS One*, 8(2), e56612. https://doi.org/ 10.1371/journal.pone.0056612.

Pistollato, F., Sumalla Cano, S., Elio, I., Masias Vergara, M., Giampieri, F., & Battino, M. (2016). Role of gut microbiota and nutrients in amyloid formation and pathogenesis of Alzheimer disease. *Nutrition Reviews*, 74(10), 624-634. https://doi.org/10.1093/nutrit/nuw023.

Porsteinsson, A.P., Isaacson, R.S., Knox, S., Sabbagh, M.N., & Rubino, I. (2021). Diagnosis of early Alzheimer's disease: clinical practice in 2021. *The Journal of Prevention of Alzheimer's Disease,* 8(3), 371-

386. https://doi.org/10.14283/jpad.2021.23.

Rezaeiasl, Z., Salami, M., & Sepehri, G. (2019). The effects of probiotic Lactobacillus and Bifidobacterium strains on memory and learning behavior, long-term potentiation (LTP), and some biochemical parameters in β-amyloid-induced rat's model of Alzheimer's disease. *Preventive Nutrition and Food Science,* 24(3), 265-273. https://doi.org/10.3746/pnf.2019.24.3.265

Saka, E. (2010). Pathophysiology of Alzheimer's diease: experimental and genetic findings. *Turkish Journal of Geriatrics,* 13(3), 21-26.

Scheltens, P., De Strooper, B., Kivipelto, M., Holstege, H., Chételat, G., Teunissen, C.E., Cummings, J., & van der Flier, W.M. (2021). Alzheimer's disease. *Lancet,* 397(10284), 1577-1590. https://doi.org/10.1016/S0140-6736(20)32205-4.

Taşdemir, A. (2017). Probiyotikler, prebiyotikler, sinbiyotikler. *Sağlık Akademisi Kastamonu,* 2(1), 71-88. https://doi.org/10.25279/sak.300045.

Thursby, E., & Juge, N. (2017). Introduction to the human gut microbiota. *Biochemical Journal,* 474(11), 1823-1836. https://doi.org/10.1042/BCJ20160510.

Ton, A., Arpini, C., & Campagnaro, B. (2018). Alzheimer's disease: a brief update on the influence of gut microbiota and the impact of functional food. *International Journal of Food Microbiology,* 2(1), 11-15.

Tully, A.M., Roche, H.M., Doyle, R., Fallon, C., Bruce, I., Lawlor, B., Coakley, D., Gibney, M.J. (2003). Low serum cholesteryl ester-docosahexaenoic acid levels in Alzheimer's disease: a case–control study. *British Journal of Nutrition,* 89(4), 483–489. https://doi.org/10.1079/bjn2002804

Turner, P.V. (2018). The role of the gut microbiota on animal model reproducibility. *Animal Models and Experimental Medicine,* 1(2), 109-115. https://doi.org/10.1002/ame2.12022.

Yılmaz, K., & Altındiş, M. (2017). Sindirim sistemi mikrobiyotasi ve fekal transplantasyon. *Nobel Medicus,* 13(1), 9-15.