INTERNAL DISEASES

Role of the oral microbiota in the development of Alzheimer's disease*

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Dementia and, in particular, Alzheimer's disease (AD), affects millions of people around the world and its prevalence is steadily rising annually. Some risk factors for AD, such as age, cannot be modified, while others could possibly be corrected. In recent years, many studies are tackling the problem of the oral and gut microbiota as a provoking factor for AD and other neurodegenerative diseases, but their relationship and specific pathophysiological mechanisms remain understudied. The microbiota of the oral cavity can be of particular importance due to the specificity of microorganisms and their localization, as well as the possibility of provoking neuroinflammation, which requires further study. This review covers the specific features of the oral microbiota, current views on the pathophysiological role of the oral microbiota in the development of AD, as well as the beneficial role of probiotics. The study of this issue can have an important practical application both for the early diagnosis of AD, and for its further treatment.

Keywords: Alzheimer's disease, oral cavity, microbiota, probiotics, neurodegenerative diseases.

Introduction

Age-associated diseases are becoming more and more urgent problem, significantly reducing the quality and duration of life of the elderly. Being the most common cause of dementia in developed countries, Alzheimer's disease (AD) is becoming more and more widespread nosology. Nowadays, oral bacteria, their structural components and metabolites have been considered as one of the prominent risk factors for AD. The deposition of beta-amyloid, which is one of the key components in the AD development, occurs long before the clinical manifestation of the disease and, according to recent data, can be triggered by several risk factors, including microbiota. Understanding the role of the oral cavity bacteria, their components and metabolites in the pathogenesis of AD may contribute to the early diagnosis of dementia, as well as the development of new approaches to the management of elderly and senile patients with cognitive impairment.

Aim of the study: to investigate the possible pathogenic role of the oral bacteria in the development of Alzheimer's disease, which can be applied to develop therapeutic strategies for preventing and slowing the progression of this disease.

Features of the microbial composition of the oral cavity

The oral cavity (OC) in humans includes the lips, the cheeks, the hard and soft palate, as well as the muscular diaphragm that makes up its bottom. The OC also includes the alveolar ridges, the gums, the teeth, the tongue, the palatine and the lingual tonsils. Different areas of the OC differ in their anatomical, physiological and physicochemical properties, which leads to a non-uniform distribution of microorganisms [1]. One milliliter of saliva contains approximately 108 microbial cells [2]. Several studies have identified up to 700 different taxa of prokaryotes in saliva [3], while a typical healthy microbiome consists of approximately 100-200 different bacterial species [4].

The microbiota of the OC is mostly presented with such genera as *Streptococcus, Actinomyces, Veillonella, Granulicatella, Gemella, Corynebacterium, Rothia, Fusobacterium, Porphyromonas, Prevotella, Capnocytophaga, Neisseria, Haemophilus, Treponema, Lactobacteria*. The OC has a number of well-defined "niches" formed on various surfaces in the mouth. According to numerous studies, the microbiomes of each area of the OC (tongue, gums, palate, subgingival and supragingival plaque, etc.) have a general similarity, but at the same time, they have their own ratio of the abovementioned bacterial genera [5; 6]. For example, the subgingival region is inhabited mainly by anaerobes of the genus *Actinomyces* and *Fusobacterium nucleatum* [7; 8], on the back of the tongue mainly *Streptococcus salivarius, Rothia mucilaginosa,* and various species of the genus *Eubacterium* [9] are described, in saliva and in the mucous membrane of the cheeks, higher concentrations of microorganisms such as *Firmicutes* are found [10; 11]. The composition of the MB is also different when considering the "cross section" of the microbial film. Closer to the enamel surface, an increased number of bacteria of the genus *Actinomyces* is observed in dental plaque, and the radially located bacteria of the genus *Corynebacterium* structure the biofilm, creating a habitat for other organisms [6].

In addition, individual differences are observed in the composition of MB of the OC, due to the environment, genetic characteristics, age and lifestyle of a particular person. Changes in the availability of oxygen, nutrients and the pH-mediated effect of saliva can

promote the growth of various organisms [12], and conversely, these organisms can participate in the construction of their own small niche [13] through the formation of biofilms and nutrients. However, due to such property of the MB as "functional redundancy", individual characteristics do not significantly affect its normal functioning.

However, when the ability of the MB as an ecosystem to resist and recover is impaired, there is a pathological change in its composition with the development of inflammatory diseases of the OC, associated partly with the presence of oral cavity infections, partly with the formation of a systemic inflammatory response observed in a number of somatic diseases [14–16]. At the same time, OC communicates with the respiratory and digestive systems and has a rich blood supply, which suggests the potential participation of oral MB in the development of other systemic diseases. An increasing number of studies demonstrate the connection between internal organ diseases and changes in the MB of the OC. This, in turn, suggests that a change in the composition of the latter can serve as a potential biomarker in the diagnosis of some systemic diseases.

Role of the oral microbiota in the development of Alzheimer's disease

The results of recent studies have demonstrated the relationship of inflammatory diseases of the OC with the development and progression of AD [17–19]. In particular, a number of clinical and experimental studies have revealed a relationship between periodontitis and a progressive decline in cognitive functions in AD [20]. On the one hand, patients with dementia have difficulties in maintaining oral hygiene and impaired oral motility, which is a risk factor contributing to the development of inflammatory diseases. On the other hand, it cannot be denied that some features of the microbial composition of the oral cavity can provoke the development and progression of AD [14].

The most studied pathogenic bacteria of the oral cavity associated with AD are *P. gingivalis, T. denticola, T. forsythia, T. socranskii, A. actinomycetemcomitans, C. rectus, F. nucleatum, E nodatum, A. naeslundii, and C. pneumonia* [15]. *P. gingivalis* DNA was found during autopsy of the brain of AD patients [16], while *Borrelia burgdorferi* was the first microorganism isolated from the blood and cerebrospinal fluid of AD patients [17]. Another bacterium often found in the brain tissue and cerebrospinal fluid of patients with AD is *Treponema denticola*, which can move both through the systemic blood flow and along the neuronal pathways. The latter assumption is supported by the fact that in a number of patients this microorganism was isolated from the trigeminal ganglia [18; 19].

AD is believed to be largely associated with neuroinflammation, which can be enhanced by systemic inflammation. According to the recent data, inflammatory diseases of the OC, being a chronic peripheral infection, cause a significant systemic inflammatory response. In addition, it is assumed that oral MB can influence the development of AD due to the invasion of microorganisms into the brain tissue and stimulation of the local immune response [21]. Presumably, the penetration of the OC bacteria into the central nervous system is performed via the bloodstream, followed by penetration through the blood-brain barrier (BBB), which may become more permeable with age. The other possibilities include involvement of the perivascular spaces, as well as the olfactory and trigeminal nerves [21; 22].

Unique neuropathological features of AD include extracellular accumulation of beta-amyloid (βA) peptide and intracellular accumulation of hyperphosphorylated tau protein

[23; 24]. Using the example of intestinal MB, it has been demonstrated that bacteria inhabiting the intestine can secrete significant amounts of amyloid and lipopolysaccharides, which can play a role in modulating signaling pathways and the production of proinflammatory cytokines associated with the pathogenesis of AD [25].

It is assumed that when the composition of oral MB is disrupted, the emerging invasion of microorganisms into the brain tissue leads to the disruption of calcium transport in neurons, causes neuroinflammation, and contributes to the accumulation of βA due to the deposition of its own amyloid peptides and stimulation of βA production by the glial cells [26]. For example, in vitro *Borrelia burgdorferi* stimulates glial and neuronal cells to synthesize βA and tau protein [17].

However, as shown by the study by Laugisch et al., although the entry of bacterial components into the brain through the systemic circulation is an important mechanism in the progression of AD, it is still not a triggering factor [22]. Nevertheless, from the point of view of the amyloid hypothesis that the accumulation of βA is the reason for the development of AD, bacteria and pathogens that trigger or increase the production of this substance may serve as the primary cause of the progression of the disease.

Currently, lipopolysaccharide (LPS) are considered to play one of the main roles in the development of a number of neurodegenerative diseases, including AD. Zhan et al. demonstrated that the administration of LPS obtained from gram-negative bacteria, followed by ischemia-hypoxia, leads to the formation of plaque-like aggregates of β-amyloid in the rat brain (β-A) [27].

It is believed that the influence of LPS on the development of AD is realized through several mechanisms [28–30]. As potential endotoxin, LPS activates toll-like receptors 4 (TLR4) of endothelial cells, triggering the nuclear factor kappa-light-chain-enhancer of activated B cells (NFkB) transcription factor, which leads to the assembly the NLRP3 (NOD-, LRR- and pyrin domain-containing protein-3) inflammasome, which mediates the synthesis of the pro-inflammatory cytokine IL-1β (interleukin-1β) [31]. Research by Dempsey et al. showed that inhibition of NLRP3 significantly reduces β-A levels and improves cognitive function in patients with AD [32].

Besides, by disrupting the structure of myelin, LPS can increase the level of degraded myelin basic protein (dMBA). This protein is described in amyloid plaques in a complex with β-A. It is assumed that it promotes the formation of amyloid plaques. LPS can also act on the blood-brain barrier (BBB), inhibit the apolipoprotein E receptor, decreasing the clearance of β-A, and thereby contribute to its accumulation. LPS has also been shown to induce hyperphosphorylation of the tau protein.

In addition to LPS, other bacterial toxins may play a role in the development of AD. For example, *P. gingivalis* synthesizes toxic proteases called gingipain, which have also been found in brain tissue, cerebrospinal fluid, and saliva in AD patients, and high levels of which are correlated with tau protein and ubiquitin levels. A possible mechanism of action of these proteases is a damaging of the tight junctions of endothelial cells, which may increase the BBB permeability for bacteria and inflammatory mediators. It has been shown, that oral administration of low molecular weight inhibitors gingipain (COR388) reduces β-A production and neuroinflammation [33].

Some bacteria are able to synthesize special proteins of the outer membrane — porins. *F. nucleatum* produces porin FomA (major outer membrane protein A), *T. pallidum* expresses the TprC/D and TprI proteins with porin-like activity, *T. denticola* contains

a surface antigen (Msp), which demonstrates the activity of adhesin and porin. It has been shown that porins can move from bacteria to cell membranes, causing damage and, as a result, ionic imbalance. Thus, bacterial porins, disrupting the permeability of nerve cell membranes, can contribute to β-A "leakage", its circulation, accumulation and toxic effects. In addition, porins can cause excess calcium intake into cells, contributing to their death [34].

Possible role of probiotics in correcting Alzheimer's disease

The above-described probable relationship of human MB with the development of AD opens the question of the possible use of probiotics in the prevention and therapy of neurodegenerative processes. Probiotics are viable microorganisms that, when used in adequate amounts, are capable of exerting a therapeutic effect on various pathological processes. Their influence on the qualitative and quantitative composition of the microbiota is performed through both direct and indirect effects [35]. So probiotics are able to influence MBs, inhibiting the growth of pathogenic microorganisms by developing their own antimicrobial compounds, competition for nutrients and sites of attachment to host tissues. For example, in patients with chronic periodontitis, prescribing probiotics with *Lactobacillus reuteri* show a decrease in the number of *P. gingivalis* in saliva [36], as well as a decrease in the concentration of *A. actinomycetemcomitans, P. gingivalis,* and *P. inermedia* in the supragingival plaque [37]. In addition, probiotic bacteria are able to alter the production of cytokines and thereby influence the general and local immune response [38]. Szkaradkiewicz et al. has been shown that the use of a probiotic with *L. reuteri* in addition to conventional treatment leads to a decrease in inflammatory cytokines, including TNF-alpha, IL-1 beta and IL-17 [39].

The bacteria that are part of many probiotics and have a beneficial effect on the prognosis in AD include *Bifidobacterium spp.*, which reduce the manifestations of the inflammatory process and the concentration of pro-inflammatory cytokines [40]. It has been demonstrated *in vitro* that certain types of lactobacilli and bifidobacteria produce neurotransmitters such as gamma-aminobutyric acid (GABA) and acetylcholine, which may have a beneficial effect on cognitive and behavioral aspects [41].

Bonfili et al. in their 2017 study on laboratory animals of the 3xTg-AD line, predisposed to the development of AD, showed that the use of the probiotic SLAB51, which affects the composition of the intestinal MB and its metabolites, significantly reduces cognitive deficit in the animals under study by slowing down the processes of neurodegeneration. According to the authors, the improvement of cognitive processes occurred due to the partial restoration of two impaired neuronal proteolytic pathways — the ubiquitin proteasome system and autophagy [40]. Abraham et al. demonstrated on animal models that treatment with probiotics in combination with exercise can slow down the progression of AD, which can presumably be mediated by changes in the microbiome [42].

In the study of oral administration of the strain *A1 Bifidobacterium breve* (*B. breve A1)* on behavior and physiological processes in AD mice, a partial reduction in the cognitive deficit observed in AD mice was also noted. In addition, consumption of *B. breve A1* suppressed the expression in the hippocampus of inflammation and immunoreactive genes, which are induced by β-amyloid [43].

Separate studies of the effect of probiotic supplementation on cognitive function and metabolic status in people with AD have shown a significant improvement in mental state and a positive effect of probiotics on some metabolic parameters, such as, for example, C-reactive protein, insulin resistance, triglycerides, inulin sensitivity index [44].

It should be noted that most of the studies on the effect of probiotic therapy on the development of AD concerned the investigation of the intestinal microbiota. To date, there is a small number of the published data confirming the improvement in the condition of patients with asthma during therapy with probiotics for their existing inflammatory disease of the oral cavity. Nevertheless, based on the possible role of the oral microbiota in the progression of neurodegenerative diseases, it is assumed that oral probiotics may play a positive role in the prevention and correction of cognitive impairment in elderly patients, which requires further research.

Conclusion

Alzheimer's disease is a neurodegenerative disease, where various pathophysiological aspects are still remaining understudied. A sufficient amount of data suggests a possible relationship between the gut and oral microbiota and the development of AD. Further study of the features of the oral MB in patients with AD may contribute to the development of methods for the early diagnosis of the disease based on the identification of certain types of bacteria in the oral cavity and their structural components associated with AD.

The data accumulated to date on the possible relationship between AD and MB, the effect of MB on brain activity and its ability to cause brain dysfunction, open up prospects for the search for new methods of prevention and therapeutic action using pro/prebiotics. The results of *in vitro* studies, in animal models, as well as a few studies among patients with AD indicate a beneficial effect of the use of probiotics on the cognitive and behavioral aspects of AD. Studies of the oral cavity microbiota as a therapeutic target in the treatment of neurodegenerative diseases, including AD has great interest and prospects for further development. The probiotics administration on the microbiome of the gastrointestinal tract, including the oral cavity, may improve the quality of life of patients and slow down the AD progression.

References

1. Sharma N., Bhatia S., Singh Sodhi A., Batra N. Oral microbiome and health. *AIMS Microbiol.* 2018, vol. 4, no. 1, pp. 42–66.
2. Marsh P. D., Do T., Beighton D., Devine D. A. Influence of saliva on the oral microbiota. *Periodontology*, 2000, vol. 2016, no. 70, pp. 80–92.
3. Dewhirst F. E., Chen T., Izard J., Paster B. J., Tanner A. C. R., Yu W. H., Lakshmanan A., Wade W. G. The human oral microbiome. *J. Bacteriol.*, 2010, vol. 192, no. 19, pp. 5002–5017.
4. Paster B. J., Olsen I., Aas J. A., Dewhirst F. E. The breadth of bacterial diversity in the human periodontal pocket and other oral sites. *Periodontology*, 2000, vol. 2006, no. 42, pp. 80–87.
5. Zarco M. F., Vess T. J., Ginsburg G. S. The oral microbiome in health and disease and the potential impact on personalized dental medicine. *Oral Diseases*, 2012, vol. 18, pp. 109–120.
6. Welch J. L. M., Rossetti B. J., Rieken C. W., Dewhirst F. E., Borisy G. G. Biogeography of a human oral microbiome at the micron scale. *Proc. Natl. Acad. Sci. USA*, 2016, vol. 13, no. 6, E791–800.
7. Chistiakov D. A., Orekhov A. N., Bobryshev Yu. V. Links between atherosclerotic and periodontal disease. *Experimental and Molecular Pathology*, 2016, vol. 100, pp. 220–235.

8. Lu M., Xuan S., Wang Z. Oral microbiota: A new view of body health. *Food Science and Human Wellness*, 2019, vol. 8, pp. 8–15.

9. Zhang Y., Wang X., Li H., Ni C., Du Z., Yan F. Human oral microbiota and its modulation for oral health. *Biomedicine and Pharmacotherapy*, 2018, vol. 99, pp. 883–893.

10. Xu X., He J., Xue J. Wang Y., Li K., Zhang K., Guo Q., Liu X., Zhou Y., Cheng L., Li M., Li Yu., Li Ya., Shi W., Zhou X. Oral cavity contains distinct niches with dynamic microbial communities. *Environ. Microbiol.*, 2015, vol. 17, no. 3, pp. 699–710.

11. Segata N., Haake S. K., Mannon P., Lemon K. P., Waldron L., Gevers D., Huttenhower C., Izard J. Composition of the adult digestive tract bacterial microbiome based on seven mouth surfaces, tonsils, throat and stool samples. *Genome Biol.*, 2012, vol. 13, no. 6, R42.

12. Luftig R. Bacteriology of Humans: An Ecological Perspective. *Microbe Mag.*, 2009, vol. 4, no. 6, pp. 298–298.

13. Laubichler M. D., Renn J. Extended evolution: A conceptual framework for integrating regulatory networks and niche construction. *J. Exp. Zool. Part B Mol. Dev. Evol.*, 2015, vol. 324, no. 7, pp. 565–577.

14. Rosier B. T., Marsh P. D., Mira A. Resilience of the Oral Microbiota in Health: Mechanisms That Prevent Dysbiosis. *Journal of Dental Research*, 2018, vol. 97, pp. 371–380.

15. Lucchese A., Bondemark L., Marcolina M., Manuelli M. Changes in oral microbiota due to orthodontic appliances: a systematic review. *J. Oral. Microbiol.*, 2018, vol. 10, no. 1, 1476645.

16. Olsen I. The oral microbiome in health and disease. In: *Oral Infections and General Health: From Molecule to Chairside*. Springer International Publishing, 2015, pp. 97–114.

17. Poole S., Singhrao S. K., Kesavalu L., Curtis M. A., Crean S. J. Determining the presence of periodontopathic virulence factors in short-term postmortem Alzheimer's disease brain tissue. *J. Alzheimer's Dis.*, 2013, vol. 36, no. 4, pp. 665–677.

18. Sudhakara P., Gupta A., Bhardwaj A., Wilson A. Oral Dysbiotic Communities and Their Implications in Systemic Diseases. *Dent. J.*, 2018, vol. 6, no. 2, p. 10.

19. Chen C. K., Wu Y. T., Chang Y. C. Association between chronic periodontitis and the risk of Alzheimer's disease: A retrospective, population-based, matched-cohort study. *Alzheimer's Res. Ther.*, 2017, vol. 9, no. 1, pp. 1–7.

20. Wu Z., Nakanishi H. Connection between periodontitis and Alzheimer's disease: Possible roles of microglia and leptomeningeal cells. Journal of Pharmacological Sciences. *Japanese Pharmacological Society*, 2014, vol. 126, pp. 8–13.

21. Bell J. S., Spencer J. I., Yates R. L., Yee S. A., Jacobs B. M., DeLuca G. C. Invited Review: From nose to gut — the role of the microbiome in neurological disease. *Neuropathol. Appl. Neurobiol.*, 2019, vol. 45, no. 3, pp. 195–215.

22. Laugisch O., Johnen A., Maldonado A., Ehmke B., Bürgin W., Olsen I., Potempa J., Sculean A., Duning T., Eick S. Periodontal Pathogens and Associated Intrathecal Antibodies in Early Stages of Alzheimer's Disease. *J. Alzheimers Dis.*, 2018, no. 66 (1), pp. 105–114.

23. Hardy J., Selkoe D. J. The amyloid hypothesis of Alzheimer's disease: Progress and problems on the road to therapeutics. *Science*, 2002, vol. 297, pp. 353–356.

24. Iqbal K., Grundke-Iqbal I. Discoveries of Tau, abnormally hyperphosphorylated tau and others of neurofibrillary degeneration: A personal historical perspective. *Journal of Alzheimer's Disease*, 2006, vol. 9, pp. 219–242.

25. Pistollato F., Cano S. S., Elio I., Vergara M. M., Giampieri F., Battino M. Role of gut microbiota and nutrients in amyloid formation and pathogenesis of Alzheimer disease. *Nutr. Rev.*, 2016, vol. 74, no. 10, pp. 624–634.

26. Sureda A., Daglia M., Argüelles Castilla S., Sanadgol N., Fazel Nabavi S., Khan H., Belwal T., Jeandet P., Marchese A., Pistollato F., Forbes-Hernandez T., Battino M., Berindan-Neagoe I., D'Onofrio G., Nabavi S. M. Oral microbiota and Alzheimer's disease: Do all roads lead to Rome? *Pharmacological Research*, 2020, vol. 151, 104582.

27. Zhan X., Cox C., Ander B. P., Liu D., Stamova B., Jin L. W., Jickling G. C., Sharp F. R. Inflammation combined with ischemia produces myelin injury and plaque-like aggregates of myelin, amyloid-β and AβPP in adult rat brain. *J. Alzheimer's Dis.*, 2015, vol. 46, no. 2, pp. 507–523.

28. Zhan X., Stamova B., Sharp F. R. Lipopolysaccharide associates with amyloid plaques, neurons and oligodendrocytes in Alzheimer's disease brain: A review. Frontiers in Aging Neuroscience. *Frontiers Media S. A.*, 2018, vol. 10. https://doi.org/10.3389/fnagi.2018.00042.

29. Kotrova A. D., Shishkin A. N., Semienova O. I., Slepykh L. A. The role of gut microbiota in the development of metabolic syndrome. *Exp. Clin. Gastroenterol.*, 2019, vol. 172, no. 12, pp. 101–108. (In Russian)

30. Yakovlev M. U. Elementy endotoksinovoi teorii fi ziologii i patologii cheloveka. *Fiziol. Cheloveka*, 2003, vol. 4, no. 29, pp. 476–485. (In Russian)

31. Minter M. R., Taylor J. M., Crack P. J. The contribution of neuroinflammation to amyloid toxicity in Alzheimer's disease. *Journal of Neurochemistry*, 2016, vol. 136, pp. 457–474.

32. Dempsey C., Rubio Araiz A., Bryson K. J., Finucane O., Larkin C., Mills E. L., Robertson A. A. B., Cooper M. A., O'Neill L. A. J., Lynch M. A. Inhibiting the NLRP3 inflammasome with MCC950 promotes non-phlogistic clearance of amyloid-β and cognitive function in APP/PS1 mice. *Brain Behav. Immun.*, 2017, vol. 61, pp. 306–316.

33. Dominy S. S., Lynch C., Ermini F., Benedyk M., Marczyk A., Konradi A., Nguyen M., Haditsch U., Raha D., Griffin C., Holsinger L. J., Arastu-Kapur S., Kaba S., Lee A., Ryder M. I., Potempa B., Mydel P., Hellvard A., Adamowicz K., Hasturk H., Walker G. D., Reynolds E. C., Faull R. L. M., Curtis M. A., Dragunow M., Potempa J. Porphyromonas gingivalis in Alzheimer's disease brains: Evidence for disease causation and treatment with small-molecule inhibitors. *Sci. Adv.*, 2019, vol. 5, no. 1, eaau3333.

34. Aguayo S., Schuh C. M. A. P., Vicente B., Aguayo L. G. Association between Alzheimer's disease and oral and gut microbiota: Are pore forming proteins the missing link? *Journal of Alzheimer's Disease*, 2018, vol. 65, pp. 29–46.

35. Meurman J. H. Probiotics: Do they have a role in oral medicine and dentistry? *European Journal of Oral Sciences*, 2005, vol. 113, pp. 188–196.

36. Teughels W., Durukan A., Ozcelik O., Pauwels M., Quirynen M., Haytac M. C. Clinical and microbiological effects of Lactobacillus reuteri probiotics in the treatment of chronic periodontitis: A randomized placebo-controlled study. *J. Clin. Periodontol.*, 2013, vol. 40, no. 11, pp. 1025–1035.

37. Vivekananda M. R., Vandana K. L., Bhat K. G. Effect of the probiotic Lactobacilli reuteri (Prodentis) in the management of periodontal disease: a preliminary randomized clinical trial. *J. Oral Microbiol.*, 2010, vol. 2, no. 1, 5344.

38. Allaker R. P., Stephen A. S. Use of Probiotics and Oral Health. *Curr. Oral Heal. Reports.*, 2017, vol. 4, no. 4, pp. 309–318.

39. Szkaradkiewicz A. K., Stopa J., Karpinski M., Karpinski K. Effect of Oral Administration Involving a Probiotic Strain of Lactobacillus reuteri on Pro-Inflammatory Cytokine Response in Patients with Chronic Periodontitis. *Arch. Immunol. Ther. Exp.*, 2014, vol. 6, no. 62, pp. 495–500.

40. Bonfili L., Cecarini V., Berardi S., Scarpona S., Suchodolski J. S., Nasuti C., Fiorini D., Boarelli M. C., Rossi G., Eleuteri A. M. Microbiota modulation counteracts Alzheimer's disease progression influencing neuronal proteolysis and gut hormones plasma levels. *Sci. Rep.*, 2017, vol. 7, no. 1, pp. 1–21.

41. Barrett E., Ross R. P., O'Toole P. W., Fitzgerald G. F., Stanton C. γ-Aminobutyric acid production by culturable bacteria from the human intestine. *J. Appl. Microbiol.*, 2012, vol. 113, no. 2, pp. 411–417.

42. Abraham D., Feher J., Scuderi G. L., Szabo D., Dobolyi A., Cservenak M., Juhasz J., Ligeti B., Pongor S., Gomez-Cabrera M. C., Vina J., Higuchi M., Suzuki K., Boldogh I., Radak Z. Exercise and probiotics attenuate the development of Alzheimer's disease in transgenic mice: Role of microbiome. *Exp. Gerontol.*, 2019, vol. 115, pp. 122–131.

43. Kobayashi Y., Sugahara H., Shimada K., Mitsuyama E., Kuhara T., Yasuoka A., Kondo T., Abe K., Xiao J. Therapeutic potential of Bifidobacterium breve strain A1 for preventing cognitive impairment in Alzheimer's disease. *Sci. Rep.*, 2017, vol. 7, no. 1, 13510.

44. Akbari E., Asemi Z., Kakhaki R. D., Bahmani F., Kouchaki E., Tamtaji O. R., Hamidi G. A., Salami M. Effect of probiotic supplementation on cognitive function and metabolic status in Alzheimer's disease: A randomized, double-blind and controlled trial. *Front Aging Neurosci.*, 2016, vol. 8, p. 256.

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