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Research Article

The Effects of Probiotic Supplementation on Alzheimer's Disease

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Abstract

Alzheimer's Disease (AD) is the leading cause of dementia and is fastly becoming one of the deadliest and most serious diseases of this century. It is a pathology that mostly affects the elderly, with still uncertain causes, largely affecting the cognition of patients. Recognition of multiple causative genes and means of protection, identification of new imaging tests with biomarkers, and screening of disease-modifying treatments is important for society. The understanding of the gut-brain axis relationship to reduce the symptoms of this disease has become more and more famous, in this perspective, the study of probiotics is of great value. The objective of this work is to review, through an analysis of clinical studies, the impact of the use of probiotics on the reduction of AD symptoms. This is an integrative literature review, with studies published in the last 5 years in English and Portuguese, with searches consulted in the specialized databases SCIELO and PUBMED, the latter including MEDLINE, with their respective descriptors in Health Sciences - DeCS: Probiotics (probiotics); Alzheimer's; symptoms (symptoms) using the Boolean operator (AND). At the end of the search, 18 articles related to the proposed theme were analyzed. It was verified that there is a symptomatic reduction of AD both in humans and in mice and rats, mainly in cognitive functions, mood, learning capacity, long and short-term memory with different probiotic classes. It is known that AD has many pathways of development, but a diet with different probiotics can significantly reduce neuroinflammation and neurodegeneration.

Keywords: Probiotics, Alzheimer's, Symptoms

Introduction

Alzheimer's disease (AD) is a neurodegenerative disease with an insidious onset, starting from Mild Cognitive Impairment (MCI) with a progressive deficit in behavioral and cognitive functions, including memory, comprehension, language, attention, reasoning, and judgment. There is no cure for AD, although there are treatments available that may improve some symptoms [1].

Regarding to the current scenario, in the last century with the considerable increase in the number of elderly people, has also been an increase in the number of diseases characterized by dementia, increasingly worrying professionals involved in the health area, as there is an urgent need to control the symptoms and diagnostic optimization, in an attempt to guarantee a good quality of life for these elderly people [2]. In this context, as of 2000, AD occurs in 1.6% of the population aged 65 to74 years, in the group aged 75 to 84 years the number of patients reaches 16% and, in individuals over 84 years it increases to 42%. In addition to the senile form of AD, there is the familial (pre-senile) form, which is associated with genetic predisposition and is characterized by early development (at 45-50 years) and an aggressive course of the disease. The progression form of AD, particularly the inflammatory reaction and oxidative stress, probiotics proven to restore homeostasis of the intestinal microbiota and delay the progression of AD, thus improving cognitive decline.

Probiotics are live microorganisms that provide health benefits when consumed in adequate amounts. They regulate the pH level in the body, help preserve the integrity of the intestinal lining, act as antibiotics, and increase brain-derived neurotrophic factor [3]. As they are free of lipopolysaccharides, they do not induce any form of inflammation after ingestion. Probiotics are known to be one of the best preventive measures against cognitive decline in AD. Numerous in vivo trials and recent clinical trials have proven the efficacy of selected bacterial strains in slowing the progression of AD. It has been proven that probiotics modulate the inflammatory process, combat oxidative stress, and modify the intestinal microbiota [4]. Therefore, it is proposed that the microbiota-gut-brain axis is of paramount importance for the pathogenesis of several neurodegenerative diseases. Therefore, the aim of this integrative review was to analyze the existing scientific evidence in the literature whether the use of probiotics has a positive impact on the reduction of AD symptoms.

Methodology

To reach the proposed objective, the following steps of the integrative review method were followed: identification of the problem, search in the literature, evaluation and analysis of the data obtained. In each article, the aspects that answered the central question were sought: Does the use of probiotics positively impact the reduction of symptoms of Alzheimer's disease? The research tool called Pico was used to aid research and search for evidence, considering P (population) as the population with Alzheimer's; I (Intervention/Interest) such as the use of probiotics; Co (context) with improvement of symptoms in the use of probiotics. For the search and selection of articles, the specialized databases SCIELO and PUBMED were consulted, the latter including MEDLINE, with their respective Descriptors in Health Sciences - DeCS: Probiotics (probiotics); Alzheimer's; symptoms (symptoms) using the Boolean operator (AND). Therefore, the phrase used: Probiotics and Alzheimer and symptoms. Articles in Portuguese or English, published in up to 5 years, that is, in the period from 2018 to 2022, that were complete and available for free access, were included. Literature review studies or studies that had another design outside the purpose of the research were excluded, in addition to filtering only by clinical trials. In this process, 30 articles remained, of which 18 were selected by manual search to ensure the inclusion of the most relevant to the topic.

Results

Table 1: Characterization of the articles according to author, year, experimental group, probiotics used and main findings.

Authors	Experimental Group	Probioticos	Main Findings
Sun, et al. (2020)[28]	Mice	*Bifidobacterium, Acidobacterium* and *Clostridium butyricum*	Significantly improves cognitive deficits, neurodegeneration and microglia-mediated neuroinflammation through regulation of the Gut Microbiota.
Kim, et al. (2021)[37]	Humans	*Bifidobacteriumbifidum* BGN4 and *Bifidobacteriumlongum* BORI	Improved mental flexibility, cognitive and stress testing than placebo group
Kobayashi, et al. (2019)[38]	Humans	*Bifidobacterium breve* MCC1274	Beneficial effects on cognitive function in elderly with memory complaints. Improvement in immediate and delayed memory subscales.
Bonfili, et al. (2019)[34]	Mice	*Bifidobacterium, Lactobacillus* and *Actinobacteria* together with fecal transplantation	Counteracts the time-dependent increase in hemoglobin glycation and the accumulation of advanced glycation end products, consistently with improved memory.
Bernier, et al. (2021)[29]	Humans	*Bifidobacterium breve* MCC1274	Inverse correlation of HbA1c with improvement in RBANS total score. It was proven to have anti-inflammatory properties, reducing the symptomatic condition.
Asaoka, et al. (2022)[33]	Humans	*Bifidobacterium breve* MCC1274 (A1)	Increased cognition and helps prevent brain atrophy in elderly with CCL. Significant comparative improvement of the MMSE subscales "time orientation" and "writing". There were no marked changes in the overall composition of the gut microbiota by probiotic supplementation.
Chiasseu, et al. (2017)[22]	Mice	*Bifidobacterium breve* MCC1274 (A1)	It was observed that the accumulation of tau protein in the retina preceded the aggregation in the brain. After the addition of probiotics to the diet, the levels of A β 40 and A β 42 decreased significantly, preventing brain pathologies (dementia, Alzheimer's and recent memory loss)
Tan, et al. (2022)[45]	Mice	*Bifidobacterium e Lactobacillus acidophilus*, Vitamins A and D and w3 fatty acid	Inhibition of tau hyper-phosphorylation in the cortex and hippocampus of 3xTg-AD mice, Improved learning capacity and memory

Tamtaji, et al. (2019)[46]	Humans	Co-supplementation of probiotics containing *Bifidobacterium bifidum, Bifidobacteriumlongum e Lactobacillus acidophilus*	Improved cognitive function and some metabolic profiles, such as reduced serum triglyceride and insulin levels.
Leblhuber, et al. (2018)[23]	Humans	*Bifidobacterium lactis* W51, *Bifidobacterium bifidum* W23, *Lactobacillus salivarius* W24, *Lactobacillus casei* W56, *Lactococcus lactis* W19 and *Lactobacillus acidophilus* W22.	The results show that supplementation of Alzheimer's disease patients with multi-species probiotics influences the composition of gut bacteria and tryptophan metabolism in serum. The correlation between neo-pterin concentrations and tryptophan breakdown points to the activation of macrophages and/or dendritic cells.
Abraham, et al. (2019)[31]	Mice	*Bifidobacterium breve* A1	It has been shown that exercises or probiotic treatments alone are not effective in improving spatial memory. The combined effects of these treatments increase brain performance Decreased size and number of beta-amyloid plaques in the hippocampus.
Mehrabadi, et al. (2020)[25]	Rats	*Bifidobacterium infantis,Lactobacillus reuteri* and *Lactobacillus rhamnosus*	Spatial memory significantly improved in the treatment group as measured by the MWM Reduction of Aβ plaques in mice with AD. MDA decreased and SOD increased in the treatment group. In addition, they reduced IL-1β and TNF-α as markers of inflammation in AD rat model.
Xiao, et al. (2020)[43]	Humans	*Bifidobacterium breve* A1	Improved dominance of immediate, visual/spatial, and delayed memory. Bifidobacterium breve A1 is a safe and effective approach to improving memory functions in individuals suspected of MCI.
Abdelhamid, et al. (2022) [24]	Mice	*Bifidobacterium breve* MCC1274, given orally for four months	It attenuated microglial activation and elevated synaptic protein levels in the hippocampus. These findings suggest that Bifidobacterium breve MCC1274 can mitigate AD-like pathologies in WT mice by decreasing Aβ42 levels, inhibiting tau phosphorylation, attenuating neuroinflammation, and improving synaptic protein levels.
Athari, et al. (2019)[21]	ratos	*Bifidobacteria* and *Lactobacilli*	Significant improvement in spatial memory, including shorter escape latency and distance traveled and longer time spent in the target quadrant. There was also improvement in biomarkers of oxidative stress, such as increased malondialdehyde levels and superoxide dismutase activity after β-amyloid injection.
Pan, et al. (2021)[39]	humanos	*Bifidobacterium breve* MCC1274	Prevented memory impairment, decreased hippocampal amyloid-β levels, attenuated microglial activation, and suppressed pro-inflammatory cytokine expression levels in the brain of AppNL-GF mice
Wang J, et al. (2020)[42]	camundongos	*Lactobacillus plantarum* and *memantine*	It was revealed that choline-associated supplementation improves specific behavioral, neurological, and cognitive deficits. However, higher choline intake is associated with poorer brain health and cognitive function among adults
Ton, et al. (2020)[26]	humanos	*Lactobacillus reuteri, Lactobacillus rhamnosus kefir grains*	By continuous dietary supplementation with fermented milk containing these agents. A cytometric analysis showed an absolute/relative decrease in several markers analyzed during the study: inflammatory, genetic, and imaging.

In this integrative review, 18 scientific articles were used, all consisting of clinical trials, which demonstrated a close relationship between the administration of probiotics and the attenuation of Alzheimer's symptoms, and, as an experimental group, 9 chose rats or mice and 9 chose humans. The experiments carried out with rodents were successful in research due to the similarity of the microbiota composition of these species with that of humans in response to supplementation. Table 1 includes the summary of the articles included (the authors, year of publication, experimental group, probiotic administered and the main results of the 18 articles included) in this integrative review (Table 1).

Discussion

Although Alzheimer's disease is widely researched, its origin is still not well understood since there is no ideal and affordable biomarker for its diagnosis [5]. The pathology presents a multifactorial character, with genetic and environmental factors being pointed out as causative elements [6] and becoming increasingly recognized as a disease of metabolic origin [7-9]. Regarding the pathology, older age remains the major risk factor, usually manifesting in people older than 65 years of age [10-16]. However, other studies have highlighted several factors, unrelated to age, as primary contribu-

tors to the development of the disorder, such as cortisol elevation [17]; sedentary lifestyle [18]; inadequate sleep [2]; as well as the prolonged use of some medications such as antibiotics [18,19]. Today, to be characterized as Alzheimer's, besides the clinical picture of dementia, there must be, in the patient's brain, the formation of plaques and tangles. The main histopathological changes of AD, according to [20], according to the amyloid theory, beta-amyloid peptide comes from a larger protein found in the fatty membrane surrounding nerve cells and, because of their chemical composition, they clump together and form extracellular plaques commonly in the limbic system that can block signaling between neurons at the synapse [21]. However, the histopathological findings highlight the influence of tau protein hyper-phosphorylation as a component of AD, as alterations in Tau phosphorylation and misclassification correlated with substantive defects in anterograde axonal transport that preceded neuron death. The studies by [22-26], reaffirmed the importance of the brain-intestine axis in AD and showed that probiotics have direct beneficial effects on symptom relief, besides the potential to prevent cognition-related disorders.

In this segment, [27] concluded that probiotic intervention affects the reduction of neurofibrillary tangles of Tau protein. Allied to this issue, [22] observed, from studies conducted in the retina, that the accumulation of Tau in this region precedes aggregation in the brain and can already be visualized at 3 months of age, long before the onset of behavioral deficits. Therefore, an alternative is created to optimize the way it is prevented, treated, and diagnosed. Physiologically, Tau protein is responsible for the stability and function of the intraneuronal microtubule system. In addition, neurofibrillary tangles are intracytoplasmic aggregates of paired helical filaments composed of hyperphosphorylated Tau protein. These clusters promote impaired anterograde axonal transport in vivo, a feature that precedes neuronal dysfunction and cell death. Associated with the benefit of the bifid bacterium genus elucidated by *Sun, et al.,* (2020); *Berniner, et al.,* (2021) [28,29] and [24], there were other relevant findings. [23] state that the accumulation of Aβ is caused by gut dysbiosis and decrease in anti-inflammatory species, such as *Faecalibacterium prausnitzii*. Therefore, an understanding is created that besides positively affecting, the imbalanced bacterial flora is a potential factor for aggravating neurodegenerative symptoms, because of the inflammatory gut and CNS relationship. Regarding inflammation, [30] explains that Aβ deposition causes activation of the microglia, which then releases inflammatory factors, leading to inflammatory apoptosis of the nerve cells and promoting brain atrophy.

Extending the findings regarding biomarkers, [21,23-26] concluded that the level of plasma Aβ 11, indole-3-pyruvic acid (a metabolite of tryptophan), and Enterobacteriaceae (Proteobacteria), can distinguish CCL patients from those with AD. This analysis regarding markers has rich potential for use since it allows non-invasive methods to diagnose predisposition or early stages of AD and to expect cognitive decline. Regarding the use of antibiotics, [27] shows their impacts on the dysbiosis of the gut microbiota and the possibility of leading to an expansion of pathogenic populations. In this regard, persistent use over decades results in an overall imbalance of the body, leading to elevation of pro-inflammatory cytokines and chemokine - a crucial factor for the development of cognitive impairment [31-46].

Conclusion

This study identified the benefits of treating AD with the use of probiotics. Thus, with the use of probiotics, such as *bifidobacterial* and *lactobacilli*, there is a clear improvement in cognitive function and neuroinflammation, in addition to improving the learning and memory capacity of the participants. However, there were some limitations during the development of the work because of how recent the research is and how difficult it is to conclude, thus restricting the number of studies. Therefore, this review points out the need for more studies on the subject because it is a disease that affects thousands of elderly people and because of the perspective of aging of the world population, which creates an increasing problem. Thus, with the use of probiotic-based treatments, it is possible to move towards an effective procedure against AD.

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Conflict of Interest

No conflict of interest.

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