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Impact of gut microbiota modulation on cognitive decline: a systematic review

Impacto da modulação da microbiota intestinal no declínio cognitivo: uma revisão sistemática

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ABSTRACT

Introduction: Dementia, especially Alzheimer's disease (AD), is a growing public health challenge. Research focuses on the gut-brain axis, where the gut microbiota is crucial for cognitive function. Dysbiosis is linked to inflammation and oxidative stress, contributing to cognitive decline. Interventions with probiotics and prebiotics are promising.

Objective: This review aims to evaluate their impact on cognitive function.

Method: This systematic review followed PRISMA guidelines and the PICO framework. The target population was adults with cognitive decline. The main intervention was gut microbiota modulation via probiotics and prebiotics (including fermented foods and fecal transplant). Comparison groups received placebo or standard treatment. Primary outcomes were cognitive improvements; secondary outcomes included neuroprotection and reduced neuroinflammation. Study quality was assessed using the Cochrane Risk of Bias tool.

Result: Were included 24 randomized clinical trials and 4 narrative reviews, showing positive results from dietary, probiotic, prebiotic, and symbiotic interventions in managing AD and mild cognitive decline. There was improvement in general cognitive function, memory, synaptic plasticity, and increased blood-brain derived neurotrophic factor. Microbial metabolites influenced the central nervous system, affecting barriers and immunity. Specific Bifidobacterium strains reduced inflammatory markers and improved cognition.

Conclusion: Gut microbiota modulation by probiotics and prebiotics shows a promising role in mitigating cognitive decline, especially in AD and mild cognitive decline. Interventions with specific Bifidobacterium were associated with cognitive improvements, reduced neuroinflammation, and increased blood-brain neurotrophic factor.

KEYWORDS: Cognitive decline. Gut microbiota. Probiotics. Prebiotics. Alzheimer's disease. Mild cognitive impairment. Gut-brain axis. Neuroinflammation. Neurodegeneration. Brain-derived neurotrophic factor. Dysbiosis.

Central Message

Modulation of the intestinal microbiota by probiotics and prebiotics has demonstrated therapeutic potential in delaying cognitive decline, with evidence of improvement in cognitive functions, reduction of neuroinflammation and increase in neuroprotective markers. Although studies still present methodological limitations and heterogeneity, the findings support the microbiota as a viable target for preventive and therapeutic strategies in Alzheimer's disease and other forms of mild cognitive impairment.

Perspective

This article is based on an interdisciplinary perspective between neurology, microbiology and public health, proposing that the modulation of the intestinal microbiota through interventions with probiotics and prebiotics may represent a promising and still underexplored strategy to delay cognitive decline in adults and the elderly. The study considers the microbiota-intestine-brain axis as a relevant therapeutic target, especially in view of population aging and the projected increase in cases of dementia, especially Alzheimer's disease.

RESUMO

Introdução: A demência, especialmente a doença de Alzheimer (DA), é um crescente desafio de saúde pública. A pesquisa se concentra no eixo intestino-cérebro, onde a microbiota intestinal é crucial para a função cognitiva. A disbiose está ligada à inflamação e ao estresse oxidativo, contribuindo para o declínio cognitivo. Intervenções com probióticos e prebióticos são promissoras.

Objetivo: Esta revisão teve como objetivo avaliar seu impacto na função cognitiva.

Método: Esta revisão sistemática seguiu as diretrizes PRISMA e a estrutura PICO. A população-alvo foram adultos com declínio cognitivo. A principal intervenção foi a modulação da microbiota intestinal via probióticos e prebióticos (incluindo alimentos fermentados e transplante fecal). Os grupos de comparação receberam placebo ou tratamento padrão. Os desfechos primários foram melhorias cognitivas; os desfechos secundários incluíram neuroproteção e neuroinflamação reduzida. A qualidade do estudo foi avaliada usando a ferramenta Cochrane Risk of Bias.

Resultado: Foram incluídos 24 ensaios clínicos randomizados e 4 revisões narrativas, mostrando resultados positivos de intervenções dietéticas, probióticas, prebióticas e simbióticas no manejo da DA e declínio cognitivo leve. Houve melhora na função cognitiva geral, memória, plasticidade sináptica e aumento do fator neurotrófico derivado do hematoencefálico. Os metabólitos microbianos influenciaram o sistema nervoso central, afetando as barreiras e a imunidade. Cepas específicas de Bifidobacterium reduziram os marcadores inflamatórios e melhoraram a cognição.

Conclusão: A modulação da microbiota intestinal por probióticos e prebióticos mostra papel promissor na mitigação do declínio cognitivo, especialmente na DA e no declínio cognitivo leve. Intervenções com Bifidobacterium foram associadas às melhorias cognitivas, redução da neuroinflamação e aumento do fator neurotrófico.

PALAVRAS-CHAVE: Declínio cognitivo. Microbiota intestinal. Probióticos. Prebióticos. Doença de Alzheimer. Comprometimento cognitivo leve. Eixo intestino-cérebro. Neuroinflamação. Neurodegeneração. Fator neurotrófico derivado do cérebro. Disbiose.

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INTRODUCTION

The World Health Organization defines dementia as an umbrella term for various diseases affecting memory, thinking, and the ability to perform daily activities. This condition is caused by diseases or injuries that directly or indirectly impact the brain. Currently, the most common form of dementia is Alzheimer's disease (AD), accounting for 60% to 70% of cases.[1]

From an epidemiological perspective, cognitive decline is associated with aging, posing a significant public health challenge. The most affected population includes individuals over 65 years of age, and the WHO estimates that more than 55 million people (8.1% of women and 5.4% of men in this age group) live with dementia. Projections indicate that this number will rise to 78 million by 2030 and 139 million by 2050.[2]

Given this scenario, research on strategies to delay disease onset has intensified in the last decade. A major focus has been the study of the gut-brain axis — a bidirectional system connecting the nervous system to the gastrointestinal tract, mediated by immune, neural, metabolic, and endocrine pathways. In this context, the gut microbiota has gained prominence due to its impact on cognitive function and neural homeostasis.[2]

Dysbiosis — changes in the composition and diversity of the gut microbiota — has been linked to inflammatory processes, blood-brain barrier impairment, and oxidative stress.[3] Based on this, strategies such as probiotic and prebiotic administration have been investigated as promising alternatives for the prevention and treatment of cognitive disorders.[4]

This systematic review aims to evaluate the impact of probiotic and prebiotic interventions on cognitive function in adults and older adults, contributing to the understanding of their therapeutic potential in mitigating cognitive decline.

METHOD

This study is a systematic review conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

The research question was guided by the PICO framework (Population, Intervention, Comparison, Outcome), as follows:

Population (P): Adults experiencing cognitive decline, including mild cognitive impairment (MCI), Alzheimer's disease, dementia, and age-related cognitive dysfunction. Keywords for this population included: "Cognitive decline", "Mild cognitive impairment", "MCI", "Alzheimer*", "Dementia", "Neurodegeneration", "Cognitive dysfunction", "Age-related cognitive decline", "Memory impairment", "Executive dysfunction", "Neurocognitive disorders", "Brain aging", "Cognitive deficits", and "Cognitive disorders".

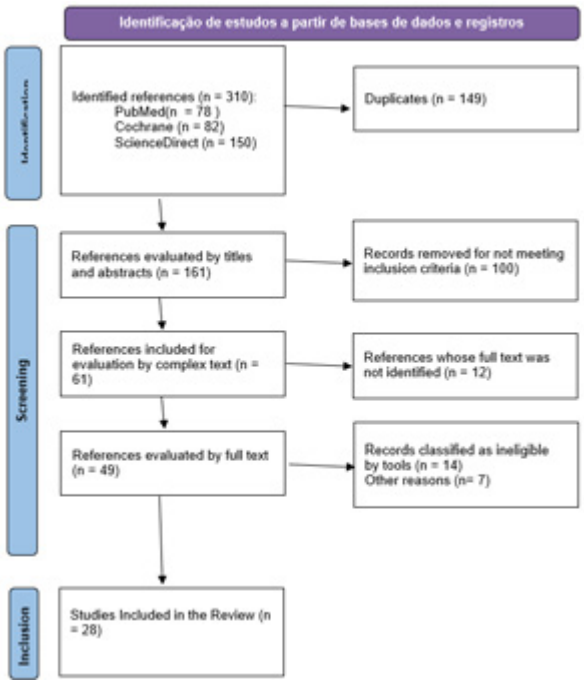

FIGURE — Flowchart PRISMA

Intervention (I): Evaluated the modulation of gut microbiota through probiotic and prebiotic supplementation. This included the use of specific strains such as Lactobacillus, Bifidobacterium, and Saccharomyces, as well as dietary interventions involving fermented foods, symbiotics, and fecal microbiota transplantation. Keywords related to the intervention included: "Gut microbiota", "Intestinal microbioma", "Microbial composition", "Microbioma modulation", "Dysbiosis", "Microbiota-gut-brain axis", "Probiotic therapy", "Prebiotic therapy", "Symbiotics", "Lactobacillus", "Bifidobacterium", "Saccharomyces", "Fermented foods", and "Fecal microbiota transplantation".

Comparison (C): The comparison group consisted of individuals receiving placebo, standard care, or usual diet without probiotic or prebiotic supplementation. Keywords included: "Placebo", "Standard care", "Usual diet", "No iIntervention", "Control group", "Sham treatment", and "Non-supplemented diet".

Outcome (O): The primary outcomes evaluated were improvements in cognitive function, memory performance, and executive function. Secondary outcomes included neuroprotection, reduction of neuroinflammation, brain atrophy prevention, changes in biomarkers (amyloid beta, Tau protein), neurotransmitter level alterations, and modifications in gut metabolites. Keywords included: "Cognitive function", "Memory performance", "Executive function", "Attention", "Neuroprotection", "Neuroinflammation", "Brain atrophy", "Amyloid beta", "Tau protein", "Biomarkers", "Neurotransmitter levels", "MRI", "fMRI", "Gut metabolites", "Inflammatory markers", and "Oxidative stress".

Inclusion criteria

The inclusion criteria required that studies involve adults experiencing cognitive decline, utilize probiotic or

prebiotic interventions, and report on cognitive function, neuroinflammation, or biomarker outcomes. No time or language restrictions were applied. Data extraction was performed by two independent reviewers, and any discrepancies were resolved through discussion and consultation with a third reviewer. The quality of the included studies was assessed using the Cochrane Risk of Bias tool.

DISCUSSION

Randomized clinical trials (n = 24) were included, being placebo-controlled (n = 20) and double-blind (n = 17), added with narrative reviews (n = 4) for theoretical support of interventions.

These articles (n = 28) were selected for review and showed positive results between dietary interventions, probiotics, prebiotics and symbiotics in the therapeutic management of patients with AD or mild cognitive decline (MCI)[5], these being the neurological pathologies most present in the literature on this subject. Cognitive tests such as the MMSE (Mini-Mental State Examination)[6], ADAS-Cog (Alzheimer's Disease Assessment Scale - Cognitive subscale)[6] and the Geriatric Depression Scale (GDS)[7] were used to evaluate the interventions, magnetic resonance imaging tests using the Regional Analysis System + Specific Fecal Samples for Alzheimer's Disease (VSRAD)[8], structural analysis of the fecal microbiota using 16S RNA gene sequencing and bioinformatics[7,9], and an enzyme-linked immunosorbent assay for blood-brain derived neurotrophic factor (BDNF).[7]

The metabolism of lipopolysaccharides, amyloid peptides, bacterial metabolites (short-chain fatty acids, branched amino acids, and neurotransmitters), and functional byproducts (bile acids)[10] have been associated with signs of neuroinflammation, intestinal barrier disintegration, neuronal oxidative stress[11], neurotransmitter regulation.[12] This investigation evaluated the therapeutic potential and delay of dementia, and in clinical and preclinical studies, there was a significant improvement in general cognitive function, spatial and non-spatial memory, synaptic plasticity, as well as an increase in BDNF levels.[13]

Metabolites derived from the intestinal microbiota modulate the central nervous system through immunological, enteroendocrine and enteric nervous system pathways. These interactions promote changes in the function of the intestinal barrier, peripheral immune responses and the integrity of the blood-brain barrier, largely mediated by metabolites derived from tryptophan metabolism - such as kynurenine, serotonin, tryptamine and indoles - as well as trimethylamine and its N-oxide (TMAO). In addition, these metabolites regulate neuronal homeostasis, neurogenesis and the processes of maturation and activation of glial cells.[14]

Mild cognitive decline is well studied and represents an early stage of cognitive impairment with a much higher risk of progression to dementia. Its development is closely related to non-modifiable factors (genetics, gender) and modifiable factors such as lifestyle, associated with epigenetics. Microglial hyperactivity and neuronal damage and central nervous system neuroinflammation predispose to cognitive impairment in ageing.[15]

Thus, the intestinal microbiota has received increasing attention for this clinical condition, demonstrating the benefit of dietary fiber sources for their ability to improve intestinal health, cognitive functioning, mood, glycemia, immunogenicity and inhibition of phosphorylation. The aim is to test the effects of a probiotic intervention on the composition and function of the gut microbiota in humans with or at risk of dementia due to AD, in addition to collecting preliminary biomarker and cognitive data.

In addition, there has been a greater focus on the study of probiotics from specific strains, such as Bifidobacterium longum BB68S,8 Bifidobacterium brevis MCC1274[6], Bifidobacterium bifidum BGN4 or Bifidobacterium longum BORI[7], Bifidobacterium animalis subsp. lactis GCL250[5,16] have been shown to reduce inflammatory markers, improve cognitive function and modulation of the central nervous system (microbiota-gut-brain axis), strengthening this promising alternative for promoting healthy and safe cognitive ageing. Some microbiological analyses have identified taxa related to DLB, such as Prevotella ruminicola, Bacteroides thetaiotaomicron and Bacteroides xylanisolvens, where a comparative study of groups of patients with DLB vs. cognitively intact patients was carried out, revealing the taxa as early predictors of DLB, in order to promote a pleasant aging.[17]

Part of the analysis identified well-designed clinical trials, of high quality but low scale for the proportion of a feasible causal relationship. Despite this, all the articles support the thesis of this review. Overall, the importance of specifically studying the composition of each patient's intestinal microbiota, studying epigenetic influences, lifestyle, medications in use and associated comorbidities when considering this type of treatment is emphasized.[13,18,19]

Recent evidence increasingly points to the fact that modulation of the gut microbiome, particularly through probiotic supplementation, can have a positive effect on cognitive function in older adults. In randomized and controlled clinical trials, regular probiotic intake was shown to significantly improve the overall cognitive performance of elderly individuals, even among those undergoing what is considered normal aging. These benefits included improvements in memory, attention, and executive functions, as well as a favorable impact on mood, with reductions in depressive and anxious symptoms.[7]

In elderly participants diagnosed with mild cognitive impairment, a condition often preceding the development of dementias such as Alzheimer's disease, probiotic intervention not only appeared to stabilize cognitive decline but also partially reversed some already established deficits. In these populations, the use of probiotics was particularly associated with marked improvements in tasks requiring short-term memory, verbal fluency, and concentration capacity.[18]

Among patients with established Alzheimer's disease, a randomized controlled study evaluated the impact of supplementation over 12 weeks and found positive

effects not only in cognitive testing but also in central biological markers of brain health. There was a significant increase in serum levels of brain-derived neurotrophic factor (BDNF), a critical protein for neuronal plasticity, the formation of new synaptic connections, and neuronal survival. At the same time, a reduction was observed in systemic inflammatory markers and biomarkers of oxidative stress, factors widely recognized as contributors to the progression of neurodegenerative diseases.[11]

Another line of investigation evaluated the combination of probiotics with dietary fiber, reinforcing that an integrated dietary approach could potentiate the beneficial effects on the microbiome and cognition. In this context, the continuous ingestion of Bifidobacteria associated with fibers resulted in marked improvement in domains such as working memory and inhibitory control, suggesting that synergistic intervention in the intestinal environment is a particularly effective strategy.[16]

In parallel to the clinical trials, recent literature reviews have consolidated the understanding that the gut microbiome has a direct influence on brain aging. The diversity and balance of the microbiota are considered critical factors for preserving cognitive function throughout life. Dysbiosis, or an imbalance in the microbial composition of the gut, has been associated with an increased risk of neurodegeneration, intensification of inflammatory processes in the central nervous system, and compromise of the blood-brain barrier integrity, facilitating the entry of pro-inflammatory agents into the brain.[15]

The interactions between the gut and the central nervous system seem to involve complex mechanisms, including the release of neuroactive microbial metabolites such as short-chain fatty acids, modulation of the immune system, and bidirectional communication through the gut-brain axis. Among these mechanisms, the production of substances directly influencing neuroinflammation and neuronal signaling emerges as one of the most relevant pathways for understanding how intestinal alterations can impact mental and cognitive health.[20]

Overall, the available data reinforce that intervention in the gut microbiome, whether through the administration of isolated probiotics, their combination with prebiotics, or other nutritional strategies, represents a promising approach for both the prevention and treatment of cognitive decline associated with aging and neurodegenerative diseases. The results also highlight the need for future research to clarify the optimal supplementation protocols, including the specific strains to be used, treatment duration, and patient profiles that would benefit most from such interventions.

This study synthesized the available evidence on the efficacy of dietary, probiotic, prebiotic and symbiotic interventions in the management of individuals with AD or mild cognitive impairment, highlighting the importance of these interventions in the treatment and prevention of these conditions. The evidence gathered indicates that the modulation of the intestinal microbiota has a significant influence on the pathophysiology of neurodegenerative diseases, particularly through the interaction of the microbiota-intestine-brain axis.

Cognitive tests such as the Mini-Mental State Examination (MMSE)[6], the Alzheimer's Disease Assessment Scale - Cognitive Subscale (ADAS-Cog)[7] and the Geriatric Depression Scale (GDS) were used to assess cognitive outcomes. Methods such as brain magnetic resonance imaging (using the Regional Analysis System + Fecal Samples Specific for AD - VSRAD)[8], microbiota analysis by 16S rRNA gene sequencing[7,9] and enzyme-linked immunosorbent assays for brain-derived neurotrophic factor (BDNF)[7] complemented the biomarker analysis.

The pathophysiological mechanisms involved include preserving the integrity of the intestinal and blood-brain barriers, regulating peripheral and central immunity, modulating tryptophan metabolism - impacting the production of serotonin, kynurenine, tryptamine and indoles - as well as interfering with the synthesis of neuroactive metabolites such as trimethylamine N-oxide.[14] These events culminate in the modulation of oxidative stress, the reduction of neuroinflammation and the preservation of synaptic plasticity, fundamental aspects for the maintenance of cognitive functions.

In addition, the regulation of metabolites derived from the intestinal microbiota, such as lipopolysaccharides, amyloid peptides, short-chain fatty acids, branched amino acids, neurotransmitters and bile acids, associated with neuroinflammation, disintegration of the intestinal barrier and neuronal oxidative stress, is also relevant.[11,12] The improvement observed in general cognitive function, spatial and non-spatial memory, together with the increase in BDNF levels, supports the biological plausibility of the proposed mechanisms of action.

Probiotic interventions have been shown to be effective in reducing inflammatory markers, improving cognitive parameters and favorably modulating the intestinal microbiota, especially those using strains such as Bifidobacterium longum BB68S[8], Bifidobacterium brevis MCC1274[6], Bifidobacterium bifidum BGN[4] and Bifidobacterium animalis subsp. lactis GCL250[5], presenting a satisfactory safety profile.[16] Some microbiological analyses have also identified microbial taxa related to MCI, such as Prevotella ruminicola, Bacteroides thetaiotaomicron and Bacteroides xylanisolvens, with the potential to act as early predictors of mild cognitive decline.[17]

Mild cognitive impairment represents a critical window of opportunity for preventive and therapeutic interventions, and its development is influenced by both non-modifiable factors (such as genetics and gender) and modifiable factors, such as lifestyle, diet and exposure to epigenetic influences. Recent literature highlights the importance of personalized approaches, taking into account the particularities of each individual's gut microbiota composition, lifestyle habits, comorbidities and medication use.

However, some limitations should be considered. Part of the analysis identified well-designed clinical trials of high methodological quality, but with a low scale for inferring robust causal relationships. Furthermore, the heterogeneity between the studies in terms of the strains used, dosages, intervention time and microbiota

assessment methods, requires caution when interpreting the findings and generalizing the results.

In this sense, modulation of the intestinal microbiota through probiotics, prebiotics, symbiotics or dietary interventions is emerging as a promising, low-cost alternative with a potential impact on public health, especially in the face of an ageing population and an increase in the incidence of neurodegenerative diseases. In order to consolidate these interventions as effective therapeutic tools, multicenter, randomized clinical trials with greater methodological robustness and long-term follow-up are needed.

CONCLUSION

This discussion highlights the promising role of gut-microbiota modulation via probiotics and prebiotics in mitigating cognitive decline, particularly in AD and mild cognitive impairment. Probiotic interventions — especially those using specific Bifidobacterium strains — have been associated with reductions in neuroinflammatory markers, strengthened blood–brain barrier integrity, elevated BDNF levels and modulation of key gut-derived metabolites, leading to measurable improvements in cognitive performance, memory, executive function and sleep quality. These discoveries underscore the crucial need for further research into microbiota-targeted therapies as a potential strategy for managing AD and improving patient outcomes. Our study demonstrated that probiotic treatment improved cognitive function and sleep quality in older adults with mild cognitive impairment, providing important insights into the clinical prevention and management of cognitive decline. Despite these encouraging findings, heterogeneity in trial design, small sample sizes and variability in strains, dosages and outcome measures limit definitive causal inferences. Moving forward, personalized approaches that integrate individual microbiota profiles, genetic background, lifestyle factors and comorbidities — combined with standardized intervention protocols and robust cognitive assessments — will be essential. Large-scale, multicenter, long-term trials are critical to validate these results and translate gut–brain axis modulation into evidence-based strategies for dementia prevention and healthy aging.

Author´s contribution

Conceptualization: All authors
Writing (original draft): All authors
Writing (proofreading and editing): All authors

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