Probiotics for Mild Cognitive Impairment

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Alzheimer's disease (AD) is the most common neurodegenerative disease, hallmarks of which include amyloid plaques and neurofibrillary tangles. Accumulating evidence from animal studies supports the potential role of probiotics and prebiotics in alleviating neurodegenerative diseases.

Keywords: probiotics ; Alzheimer's disease ; mild cognitive impairment ; cognition ; meta-analysis

1. Introduction

Alzheimer's disease (AD) is the most common neurodegenerative disease, hallmarks of which include amyloid plaques and neurofibrillary tangles [1]. Despite the existence of treatments that can alleviate these symptoms, no therapeutic approach has been proven to completely halt AD progression [2]. According to the 2020 World Alzheimer Report, the current annual healthcare cost for AD treatment is $1 trillion, which is predicted to double by 2030.

Due to the gradual nature of AD progression, it is imperative to explore and develop intervention strategies for early-stage AD [1]. In the past decade, an increasing number of randomized control trials (RCTs) have demonstrated promising findings regarding dietary interventions for AD, especially probiotic and prebiotic supplementation, which has been shown to delay AD progression [3][4]. Regulation of the gut–brain axis has been proposed as an evolving therapeutic approach for neurodegenerative disorders such as AD [5]. With the accumulation of knowledge regarding the changes in gut microbiota in patients with AD in recent years, research has increasingly focused on more specific 'gut-microbiota-targeted' intervention strategies for AD progression.

According to the consensus statement of the International Scientific Association for Probiotics and Prebiotics (ISAPP), probiotics are defined as 'live microorganisms that, when administered in adequate amounts, confer a health benefit on the host' [6]; the definition of a prebiotic is "a substrate that is selectively utilized by host microorganisms conferring a health benefit" [7]; and the definition of a synbiotic is "a mixture comprising live microorganisms and substrate(s) selectively utilized by host microorganisms that confers a health benefit on the host" [8]. Given their ability to modulate the structure and composition of the gut microbiota and impart health benefits, probiotics and prebiotics supplementation provide a novel approach for the prevention or treatment of certain diseases. In fact, several studies have provided compelling evidence supporting the neuroprotective effects of probiotics and prebiotics in neurological disorders [9][10][11].

Consistent with the burgeoning interest, several reviews of the efficacy of probiotic supplementation for neurological disorders/AD have been published, including one systematic review [12] and three meta-analyses [13][14][15]. Despite providing comprehensive evaluations of the early literature in this field and their importance for guiding clinical trials, these reviews have several limitations. For example, the meta-analyses yielded contradictory findings, with one reporting no ameliorative effect of probiotics on cognitive function [13] and the other two reporting improvement in cognitive function after the administration of probiotics [14][15]. These meta-analyses only included studies published before 2018 that investigated the beneficial effects of probiotics and prebiotics. We update the data by adding evidence from recently published studies [16][17][18], including one study that evaluated the protective effects of a synbiotic [16]. Furthermore, two of the three meta-analyses [14][15] included a study that combined mild cognitive impairment (MCI) and AD as a single outcome in their quantitative analyses, which might have yielded inaccurate findings. Notably, Jenifer et al. [13] only included three studies in their meta-analysis and did not assess publication bias, which might account for the high between-study heterogeneity reported. In addition, Cristofer et al. [15] did not include a subgroup analysis in their meta-analysis, despite observing high between-group heterogeneity. They also missed the most authoritative biomedical database, Embase, when searching for eligible literature.

2. Current Insights on Probiotics for Mild Cognitive Impairment

In this meta-analysis, we include the most recent RCTs of probiotic and prebiotic supplementation for MCI and AD. Compared with placebo or control interventions, probiotic supplementation considerably improved cognitive function in the participants with MCI, but it only caused a modest cognitive improvement in those with AD. Furthermore, subgroup analyses conducted to explain the high heterogeneity across the included studies revealed that the extent of cognitive improvement is associated with the number of probiotic strains used (single or multiple), the dosage and duration of the intervention and the severity of the disease (AD or MCI). Collectively, these findings align with the previously reported neuroprotective effects of probiotics and prebiotics in neurological disorders [9][10][11].

In addition to cognitive improvement, probiotic supplementation altered the fecal microbiota structure and composition in AD patients. A recent study in a Chinese cohort found the diversity of fecal microbiota was significantly declined in AD patients; it also found reductions in the abundances of specific microbial communities to be associated with the disease severity of AD and MCI [19]. Similarly, a US study reported decreased fecal microbial diversity in patients with AD [20]. However, only one study [21] included in our review reported the changes of gut microbiome composition after probiotic administration. Given that microbiota-targeted interventions using probiotics/prebiotics can improve cognition through the microbiota–gut–brain axis, more attention should be paid to fecal microbiota analyses in future studies.

In the past decade, emerging studies have suggested that dietary probiotic intervention also play a beneficial effect in emotion, cognition, systemic and neural indices in disease states [22]. In addition to the clinical trials for AD and MCI reviewed in this study, several recent studies have evaluated the effects of specific probiotics on depression, anxiety and Parkinson's disease. For example, in a randomized, double-blind, placebo-controlled clinical trial [23], daily probiotic administration for 12 weeks considerably improved the MDS-UPDRS scores in patients with Parkinson's disease. Another recent study [10] reported that daily administration of probiotics led to a slight but significant change in symptoms of depression and anxiety, whereas prebiotic administration showed no effect.

Evidence from other investigations also support similar beneficial effects of probiotic administration on disorders of the gut–brain axis. For example, in one RCT [24], healthy volunteers randomly received a mixture of multiple probiotics or placebo for 4 weeks. Compared with the placebo, probiotic consumption significantly reduced reactivity to sad mood in the volunteers. Another study in physically healthy subjects also found that the consumption of a probiotic-containing yogurt for 3 weeks substantially improved mood [25]. An early study of irritable bowel syndrome also provided evidence of the beneficial systemic and immunological effects of probiotics [26]. Interestingly, only individuals with irritable bowel syndrome who received *Bifidobacterium infantis* 35,624 exhibited a normalization of the interleukin-10 to interleukin-12 ratio. These findings suggest that the widely acknowledged immunological benefits of probiotics are more strain-specific than previously thought [27].

Notably, the well-studied *Bifidobacterium* and *Lactobacillus* spp. are most frequently used as potential psychobiotics [28][29]. However, not all probiotics have psychobiotic potential. Thus, given the fact that the salutary effects of probiotics on AD are strain-specific, a more efficient probiotic screening method is warranted to develop effective probiotic strategies for AD.

According to the ISAPP definition of probiotics, consuming adequate amounts of probiotics can confer certain health benefits. However, the ISAPP does not specify the functional dose and frequency of probiotic supplementation. Over the past decade, organizations and agencies, such as the ISAPP [6], Health Canada [30], the World Gastroenterology Organization [31] and the Italian Ministry of Health (IMH) [32], have attempted to establish a recommended dosage of probiotics. To ensure safe and effective use of probiotics, the IMH has claimed that the minimum number of viable probiotic cells in food-based probiotics and dietary supplements should be 1×10^9 CFU per day. Consistently, in our study, all of the included probiotic-treated studies consumed a daily probiotic dose of 1×10^9 CFU or more. Despite the considerable research progress in the field of probiotic, determining the most effective dose of specific probiotic strains for different disease conditions remains a challenge. Given that certain probiotic strains have synergistic effects on the gut microbiota, multistrain probiotics that promise high efficacy should receive more attention in future studies.

Some limitations in the experimental design of the studies included in this systematic review must be acknowledged. First, some of the trials [16][33] had a small sample size, which might restrict the accuracy of the findings. Second, none of the included studies ruled out the interference of other dietary supplements, such as antibiotics, Mediterranean-style diets, other probiotics or fermented foods. Such dietary supplements may have a direct effect on the gut microbiota and metabolic profiles, which can in turn influence the gut–brain axis and related disorders. For instance, the results of a high-quality meta-analysis suggested that Mediterranean diets are negatively correlated with the risk of developing MCI and AD

[34]. Therefore, such factors should be taken into consideration in future studies. Third, the included studies assessed cognitive function using a variety of rating scales. As the rating scales have different sensitivities and specificities for cognitive impairment, one or more gold-standard rating tools should be established to ensure the stability and reliability of results across studies. Fourth, to better distinguish patients with AD and without dementia, a commonly used clinical diagnosis criteria such as the NINCDS-ADRDA should be used. However, only four of our included studies [16][33][35][23] applied the NINCDS-ADRDA criteria. Fifth, none of the included studies ruled out the interference of other lifestyle interventions that can improve cognitive status and possibly even prevent cognitive impairment, dementia and AD [36], such as mental activities and exercise and specific multinutrient interventions [4]. Sixth, only two of the included studies [17] [37] grouped the patients according to disease severity and evaluated the effects of probiotics on them separately. Evidence from previous researches have shown that the health effect of probiotics may differ among different diseases stages [21][37]. Consistently, our findings suggest that probiotic intervention at early stages of AD, such as MCI, could improve cognitive function and delay disease progression. Lastly, four of the included studies [17][33][35][23] did not report the adverse effects of probiotic administration. Although probiotics have a demonstrable history of safe use as dietary supplements, elderly people have decreased immunity and a high risk of serious adverse effects, such as gastrointestinal side effects, systemic infections and skin complications. Therefore, future studies are encouraged to report the adverse effects of probiotic supplementation [38]. By addressing all of these limitations in the design of future probiotic intervention-based studies, the beneficial effects of probiotics on AD could be more comprehensively and systematically clarified.

This systematic review has some noteworthy strengths. First, the systematic review and meta-analysis strictly followed the recommendations of the Cochrane handbook and the results were rigorously reported in accordance with the PRISMA statement. Second, we applied a random-effects model and performed sensitivity and subgroup analyses to adequately capture the heterogeneity among the study results. Third, we fully discussed the limitations of the experimental design of the included studies, addressing these methodological limitations may guide future researches.

Despite these strengths, our systematic review has some limitations. First, despite exhaustive literature searches, we might have missed some eligible studies. Second, the features of some included studies may have potential risk of bias due to commercial funding and defects in the experimental design. Third, the format of the data reported by some studies was not suitable for our analyses. Lastly, in terms of the high heterogeneity indicated, our findings should be interpreted with caution.

3. Conclusions

Collectively, the results of this meta-analysis indicate that probiotics, when supplemented at adequate amounts for 12 weeks or longer, may improve cognitive function in MCI or AD individuals. However, given the insufficient evidence from current RCTs, further work concerning long-period, large-scale RCTs are warranted to investigate the neuroprotective effects of probiotics in different stages of AD.

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