Review Article

A New Insight on Feasibility of Pre-, Pro-, and Synbiotics-based Therapies in Alzheimer's Disease

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Abstract

Alzheimer's disease is a prevalent cause of dementia in the elderly population. The existing treatments in this issue are limited in efficacy besides having several adverse effects. Therefore, developing new therapeutic strategies is a major concern of scientists. This disease is closely linked to gut microflora through the brain–gut–microbiota axis. Targeting gut microbiota by pre-, pro-, and synbiotics supplementation can be effective for its treatment. Herein, we discuss the protecting effects of pre-, pro-, and synbiotics products against Alzheimer's disease based on comprehensive assessment of animal studies and performed clinical trials. Primarily, we briefly introduced involved pathogenesis, probable drug targets, and its correlation with gut microbiota. Subsequently, we debated preclinical and clinical research studies on the effect of pre-, pro-, and synbiotics agents on brain functionality, metabolic features, and biomarkers that are proven to have therapeutic effects. Searching the online databases revealed therapeutic capabilities of pre-, pro-, and synbiotics in Alzheimer's disease treatment by some mechanisms such as anti-oxidative stress, anti-inflammatory, prohibiting of apoptosis and DNA damage, insulin regulation, suppressing the aggregation of beta-amyloid (Aβ) and tau proteins, which can be considered as important outcomes of this application.

Keywords: *Alzheimer's disease, brain–gut–microbiota axis, memory impairment probiotic, neurodegenerative disease, prebiotic, synbiotic*

Introduction

The neurodegenerative aging-related diseases with progressive and uniformly fatal nature are considered an important risk for human health. Cell bioenergetics dysfunction is the most important characteristic feature of these types of disorders.[1-3] Neurodegenerative diseases cause irreversible neuron loss and gliosis, comprising types of disorders such as frontotemporal degeneration (FTD), Parkinson's disease (PD), and Alzheimer's disease (AD).[4-6] The most common type of dementia causing death in elderly individuals is AD, which represents the symptoms of personality changes, memory loss, and multiple cognitive impairments.[7,8] Hebert *et al.*[9] estimated the AD dementia global incidence in the older than 65 population, approximately 4.7 million cases in 2013, which is suspected to reach 130 million by 2050.[10] It has been shown that since a definite association exists between gut microbiota and neurological functions of the brain, the intestinal flora can be targeted for manipulation in neurodegenerative disorders such as AD.[11] The gastrointestinal (GI) microbiota, known as gut microbiota, is a complex community of billions of microorganism species including bacteria, viruses, fungi, archaea, and microbial genes present in the digestive tract ecosystem which has various quantities and compositions in different individuals.[12] The GI microbiome is the largest source of microorganisms in humans with almost 10^{14} microbes from 1000 different species creating a density of 10^{12} bacteria per mL. The estimated number of encoding genes from this population is approximately 4×10^{6} genes.[13,14] The alteration of this complex biomass, due to changes in dietary habits and environmental messages, causes many GI disorders and also can play an important role in the pathological basis of various diseases even outside of the GI tract.[15] For instance, gut microbiota can influence GI and brain functions. This communication is known as the gut–brain–microbiota axis. Probiotics-based bacteriotherapy seems to be a feasible way of achieving this goal.[11] The fast-growing body of studies suggests probiotic

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treatment as an effective way of cognition improvement.[16] Probiotics express their beneficial impact by balancing oxidative stress pathways and reducing apoptosis and inflammation events.[17]

Probiotics confer positive health benefits by affecting the GI microbiota and regulating the acquired immune system responses.[18] Different groups of probiotics were introduced as follows: *Lactobacillus* group such as *L. rhamnosus* GG, *L. sporogenes*, *L. reuteri* RC-14, *L. plantarum* 299v, *L. acidophilus*, *L. lactis*. *Bifidobacterium* group such as *B. bifidum*, *B. longum*, *B. infantis*, and *Streptococcus* group such as *S. thermophillus*, *S. lactis*, *S. fecalis*. In addition, nonbacterial organisms such as nonpathogenic yeast *Saccharomyces boulardii* is categorized as probiotic.[19] Probiotics express their beneficial impact by balancing oxidative stress pathways and reducing apoptosis and inflammation events.[17] Using probiotics is the novel approach in controlling and treatment of infections. Probiotic therapy as a long traditional history is a natural way to suppress the growth of pathogens and their unfavorable side effects.[20]

Due to substantial correlations of gut microflora with amyloids, degradation of gut barrier and vascular dehomeostasis, abnormality in brain-derived neurotrophic factor (BDNF), deregulation of neurotrasmitters conductivity, systemic and localized inflammation, dysfunction of mitochondria, and other factors, the gut microbiota modulation, especially probiotic supplement-therapy, is a viable possibility for AD management.[21]

In this review, we address performed examinations on animal studies and humans to determine the effect of pre-, pro-, and synbiotics products on cognitive function, microbiota alteration, AD-related biomarkers, and metabolic status by describing the analytical methods applied in these studies and we discuss the obtained major outcomes of each investigation.

Molecular Pathology of Alzheimer's Disease

AD is associated with many cellular changes including Aβ protein accumulation and aggregation, synapses damage by hyper-phosphorylation of τ protein, loss of cholinergic fibers, enhanced inflammatory responses of astrocytes, microglial cells, and mitochondrial dysfunction. Among these, Aβ plays the most important role in disease progression which may be diagnosed after 20 years.[22] Indicative features of AD on the microscopic level contain Aβ accumulation in neuronal cells, together with neurofibrillary tangles (NFTs) which are believed to be the reason for mitochondrial dysfunction.[23] The cholinergic nervous degeneration which takes place in AD is associated with the memory loss symptom of patients.[24,25] AD initiates with impairment in memory and based on its progression, it can be divided into three phases: the pre-clinical phase in which there is no change in cognitive ability, the mild cognitive impairment (MCI) phase, and the dementia phase.[26,27] The β-amyloid peptide is structurally an oligomer (Aβo), initiating Alzheimer's pathology.[28-30] The PrP^C is an essential receptor in the Aβo signaling pathway. Other effector proteins in this pathway include mGluR5, Fyn kinase, and Pyk2 kinase, which all can be pharmaceutically utilized targets for Alzheimer's treatment.[31] As mentioned above, amyloid-β, as a proteolytic product of β-amyloid precursor protein (APP), is the most important parameter in Alzheimer's etiology.[32] Early-onset AD is closely related to abnormalities of Aβ. The ε4 allele of apolipoprotein E is a major risk factor for late-onset AD which is a polygenic process.[33] The apolipoprotein E (APOE4) is the sturdiest genetic threatening factor responsible for AD. Possession of two copies of the APOE4 allele in individuals increases sporadic or familial AD risks and attenuates the age of commencement.[34] Previous findings indicated that APP and p-APP, PP2A, sirtuin 1, and inflammatory cytokines, containing interleukins (ILs) IL-6 and IL-8, may be responsible for the AD signaling network.[35,36] Other cellular and molecular mechanisms enclosed with APOE4 are Aβ aggregation, mitochondrial glucose metabolism, vascular function, insulin, and VEGF signaling, synaptic function, and lipid or cholesterol transport.[37]

Oxidative stress, reactive oxygen species (ROS), lipid peroxidation, DNA/RNA and protein oxidation, mitochondrial dysfunction, reduction in energy metabolism, calcium dyshomeostasis, and neuronal apoptosis have participated in the pathogenesis of AD.[38-40] In physiological disorders, mitochondria produce ROS such as $OH^{\cdot}$, $O2^{-}$, and H_2O_2, in addition to reactive nitrogen species, for instance, $ONOO^{-}$ and $NO^{\cdot}$. Dependably, glutathione peroxidase (GPX), superoxide dismutase (SOD), Catalase, and other enzymatic antioxidants can alleviate the harmful effects of these species.[41-43] Oxidative damage and inflammatory markers alter the regulation of microRNA expression related to AD.[44] A large number of inflammatory molecules were recognized to play a functional role in the pathogenesis of AD. IL-1β, IL-6, and TNF-α are the most common inflammatory molecules involved in etiologies of AD.[45,46] Pharmaceutical agents developed for retarding AD progression, are not effective enough to reach treatment goals. The multifactorial and complicated nature of AD is considered a major challenge for new drug development. Nowadays, efforts on new drug design for AD treatment focus on nine known targets associated with AD pathogenesis: acetylcholinesterase (AChE), beta-site amyloid precursor protein cleavage enzyme 1 (BACE-1), monoamine oxidases (MAOs), glycogen synthase kinase 3 β, N-methyl-D-aspartate receptors, the metal ion in the brain, H_3, 5-hydroxytryptamine, and phosphodiesterases (PDEs).[47] The multi-target treatment strategy can improve the poor prognosis of AD treatment.[48] The application of pre-, pro-, and synbiotics in AD treatment is founded upon these mentioned reasons.[49]

Gut Microbiota Role in the Pathogenesis of Alzheimer

Gut-specific microflora has a key role in central nervous system (CNS) neurochemistry in a way that germ-free animals treated with broad-spectrum antibiotics show major defective memory, recognition, and learning abilities.[50] This connection has been reported as a pathophysiology basis of neuropsychological disorders such as anxiety, autism, and AD.[51-53] It seems that there is a type of communication between gut microbiota and the brain, which has a critical impact on neurological processes and can lead to neurodegenerative disorders. This complex cross-talk is called the gut–brain axis. Although alteration in the microbial flora of the GI tract may lead to dysbiosis and AD development as a consequence, wise modification of microbiota pattern by beneficial microflora intervention has feasibility to be utilized in combating CNS disorders like AD.[54] This axis is a bidirectional relationship among the GI tract, brain, and gut microbiota through neuronal, endocrine, immune, and metabolic systems[55] [Figure 1].

In the survey of AD pathogenesis, two main hallmarks are recognized: the Aβ extracellular plaques and hyper-phosphorylated tau proteins forming intracellular NFTs. However, the underlying mechanisms of initiation of the mentioned molecular pathways remain unknown. The pathogenic microorganisms derived from the GI tract are known to be potential dangers for the exacerbation of AD.[56] The gut microbiota has a key role in processes like energy production from nutrients, vitamins' biosynthesis, defense, and protection system against pathogenic microbes, and immune system education.[57] Despite these beneficial features of gut microbiota, changes in the composition of the microbial population are associated with a variety of GI or extra-GI disorders such as inflammatory bowel disease (IBD), metabolic syndrome, and some neurological conditions.[58] Gut microbiota is inherited at birth and undergoes age-dependent qualitative changes. In the elderly population, gut microbiota composition may vary in individuals depending on the history of antibiotic administration, lifestyle, and specific diseases.[59] Gut microbiota can control intestinal permeability. Neurodegeneration may be initiated or increased if normal gut microbiota is damaged.[60,61] The amyloid hypothesis of AD pathophysiology was the commonly accepted reason for Alzheimer's development in the early 90s.[62] As a consequence of amyloid-β accumulation in the brain, the cascade of immune responses of innate immune cells in the CNS is triggered.[63] The activation of the immune pathway leads to chronic neuro-inflammation.[54] This inflammation may pose CNS to a severe risk by increasing permeability of the blood–brain barrier (BBB). The BBB dysfunctionality facilitates pathogen entrance into the CNS.[54]

Methods of Study Selection

Herein we directed systematic research conterminous to the conventional PRISMA guideline.[64] A literature search was directed up to January 13, 2021, on the electronic databases of Scopus, PubMed, and Web of Science. The search was accomplished by using the following search strings in the title/abstract/keywords: "Alzheimer's disease" AND "probiotic*" OR "prebiotic synbiotic*". Obtained articles were imported to EndNoteX9 reference management software. All articles were separately screened for, duplicity, and eligibility by two authors individually.

Inclusion Criteria

We included articles that encountered the following criteria: (1) published peer-reviewed articles; (2) research articles published up to 12 January 2021; (3) English language

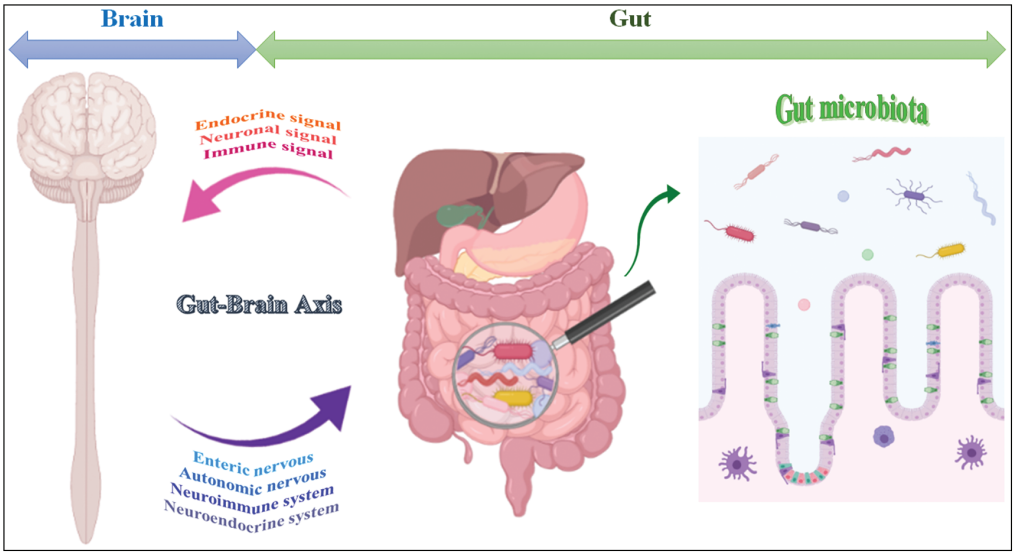

Figure 1: Schematic summary showing that AD is closely linked to gut microflora through the brain–gut–microbiota axis and bidirectional relationships between AD and microbiota through this axis

articles; (4) original preclinical and clinical studies; (5) articles containing sufficient data; and (6) articles evaluating the anti-AD effect of pre-, pro-, and synbiotics.

Exclusion Criteria

We excluded the articles that met the following criteria: (1) articles not in the English language; (2) articles comprising inadequate data; (3) review articles; (4) letters to the editor; (5) editorials; (6) hypothesis; (7) congress abstracts; (8) opinion articles; (9) articles described other neurological conditions less than AD or its related circumstances; (10) articles discussed only an unspecific mechanism involved in AD; (11) articles mentioned effects of pre-, pro-, and synbiotics only as a part of adjuvant-therapy; (12) articles assessed cognitive decline as a secondary happening of diseases rather than AD; and (13) articles which contained small sample sizes.

Data Extraction and Tabulation

Two individual researchers extracted the data from the nominated articles utilizing a data extraction form containing the first author, publication's year, microorganism, dose, duration, subject, and major outcomes [Tables 1–4].

Search Results

Of 424 recognized records, 139 records found a duplicate. A total of 233 articles were excluded through the first screening and 7 articles were excluded through the second screening. Finally, 41 articles were found eligible to enter into the present review article. The search process is summarized in Figure 2.

Animal Studies on the Efficacy of Probiotic Products in Alzheimer's Disease

Probiotics are helpful bacteria with beneficial features for the health of the recipient. Probiotic administration is a way of modulating gut flora for neuro-inflammation suppressing, therefore, it can be utilized as a therapeutic approach for AD.[65] Anti-AD possessions of probiotics can be evaluated in animal models of AD before performing clinical trials on the efficiency of a specific probiotic

Table 1: Summary of some animal studies on probiotic supplementation efficacy in Alzheimer's models.

Author/Date	Probiotic microorganism	Subject animal	Dose	Duration	Sample size	Major outcomes	Refs.
Nimgampalle *et al.* (2017)	*Lactobacillus plantarum* MTCC1325	Rats of Wistar strain (D-Gal-induced Alzheimer)	12×10^8 CFU/mL 10 mL/kg	60 d	48	↑Cognitive function ↓Gross behavioral activity ↑ACh ↓AChE	[66]
Cogliati *et al.* (2019)	*Bacillus Subtilis* NCIB3610	*Caenorhabditis elegans* (Transgenic)	50 µL of an overnight culture	30 d	10	↑Life expectancy ↓Neurodegeneration ↑Cognitive function ↓Aβ-induced paralysis	[71]
Wang *et al.* (2020)	*L. plantarum*	APP/PS1 mice (Transgenic) (Choline-treated)	1×10^9 CFU/mL	12 w	60	↑Cognitive function ↓Aβ ↑LTP	[73]
Sun *et al.* (2020)	*Clostridium butyricum* WZMC1016	APP/PS1 mice (Transgenic)	1×10^9 CFU/mL 200 µL	4 w	20	↑Cognitive function ↓Neurodegeneration ↓Aβ42 ↓Activation of microglia ↓IL-1β ↓TNF-α ↑Butyrate level	[74]
Abraham *et al.* (2019)	FRAMELIM® (*Bifidobacterium longum* and *L. acidophilus* lysates)	APP/PS1 mice (Transgenic)	120 mg/day	20 w	32	↑Cognitive function ↓Histological changes	[75]
Rezaei Asl *et al.* (2019)	Mixture of bacteria	Rats of Wistar strain (ICV injection of Aβ)	15×10^9 CFU	56 d		↑Spatial learning ↑Memory ↑LTP	[16]
Athari Nik Azm *et al.* (2017)	*L. acidophilus, L. fermentum, B. lactis, B. longum*	Rats of Wistar strain (ICV injection of Aβ)	10^{10} CFU/g 2 g/d	8 w	60	↓FPG ↓Insulin level ↓HOMA-IR	[87]

Table 2: Summary of some clinical trials on the effect of probiotics administration on Alzheimer patients

Author/ date	Probiotic microorganism	Dose	Duration	Participants number	Trial condition	Major outcomes	Refs.
Sanborn *et al.,* (2018)	*Lactobacillus rhamnosus* GG (*LrGG*)	10 billion CFUs	12 w	200	Double-blind RCT	Psychological status Cognitive function	[89]
Akbari *et al.* (2016)	Probiotic milk Multispecies probiotics (The genera *Lactobacillus* and *Bifidobacterium*)	2×109CFU/g (for each probiotic) 200 mL/day probiotic milk	12 w	60	Double-blind RCT	↑Cognitive function ↓MDA ↓hs-CRP ↓HOMA-IR ↓HOMA-B ↓TG ↑QUICKI	[92]
Kim *et al.* (2021)	*B. bifidum* BGN4 and *B. longum* BORI	1×10^9 CFU/d	12 w	53	Double-blind RCT	↑Cognitive function ↑BDNF	[94]

Table 3: Summary of studies on the utilization of some prebiotic agents for Alzheimer's animal models

Author/date	Subjects	Models	Prebiotic	Doses	Major effects/mechanisms	Refs.
Chen *et al.* (2017)	Rat	D-gal induced AD and Aβ25−35	FOS	50, 100 mg/kg/day, i.p.	Oxidative stress Inflammatory responses secretion of neurotransmitters Tau protein Aβ learning and memory apoptosis morphological changes histological changes, gut-brain axis	[100]
Xin *et al.* (2018)	Mouse	APP/PS1	FOS	50, 100 mg/kg/day, p.o.	Memory tissue swelling neuronal apoptosis Aβ gut-brain axis	[107]
Sun *et al.* (2019)	Mouse	APP/PS1	FOS	2% (w/w), p.o.	Gut microbiota-GLP-1/ GLP-1R pathway	[108]
Hoffman *et al.* (2019)	Mouse	E4FAD	Inulin	8% (w/w), p.o.	APOE4	[109]

Table 4: Summary of studies on synbiotic agents' effectiveness for Alzheimer's

Author/date	Subjects	Models	Synbiotic	Major effects/mechanisms	Refs.
Westfall *et al.* (2019)	Mouse	APP/PS1	TFLA + probiotics	Metabolic stability inflammatory factors immune signaling oxidative and mitochondrial stress PPARγ gut–brain axis	[113]
Pasinetti *et al.* (2020)	*In vitro* study	GIT	GSPE + probiotics	Tauopathy Aβ inflammation	[114]
Ton *et al.* (2020)	Human	AD	Kefir + probiotics	Serum protein oxidation cognitive declines mitochondrial dysfunction DNA damage apoptosis	[115]

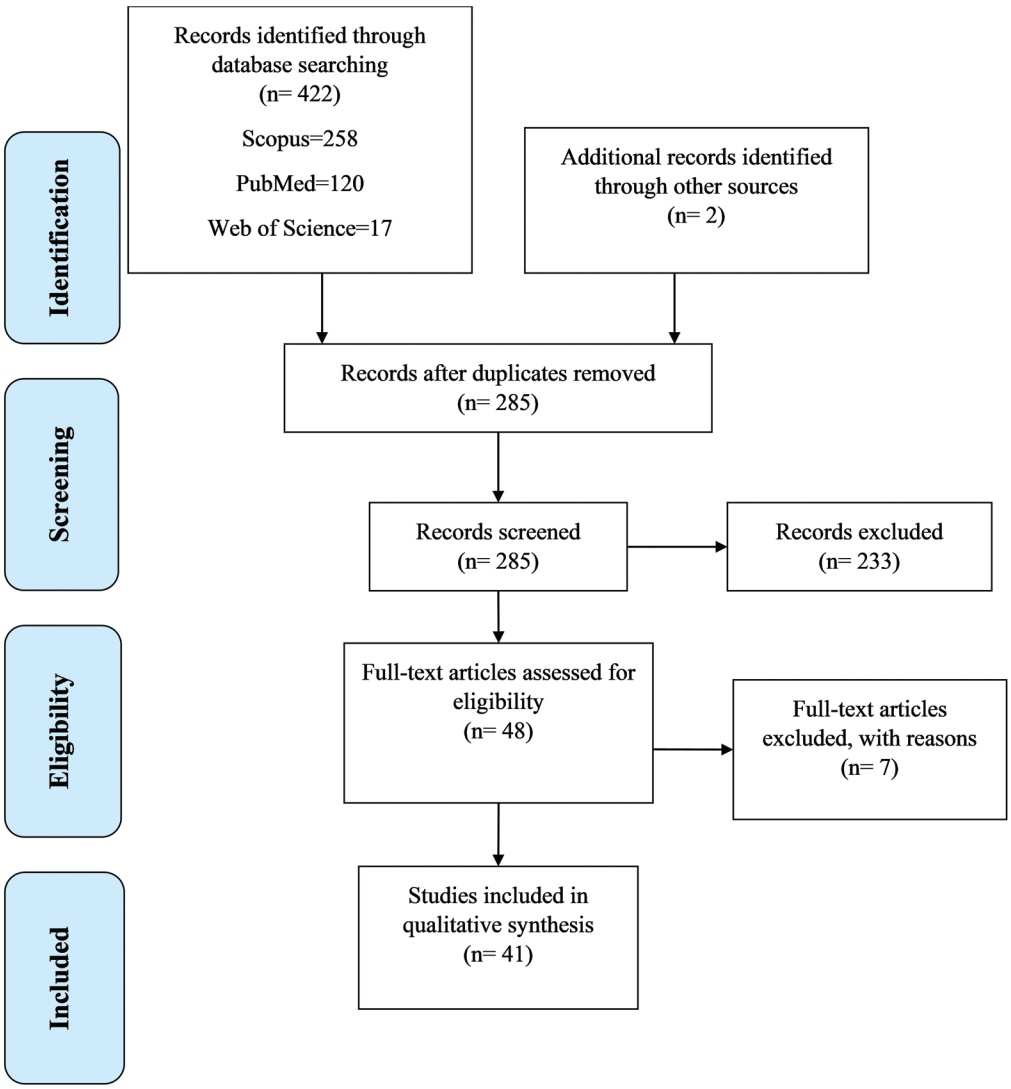

Figure 2: Flowchart describing of search process with 424 recognized records, of which 139 records found a duplicate. A total of 233 articles were excluded through the first screening, and 7 articles were excluded through the second screening

supplementation in patients with AD. An animal model of AD can be generated by prolonged intake of D-galactose with the mechanism of increasing ROS production leading to AD. Nimgampalle and Kuna[66] used the animal model of D-galactose-induced AD in rats to study *Lactobacillus plantarum* MTCC1325 efficiency for AD treatment. The morris water maze (MWM) experiment was performed for cognition measurement. Based on the obtained results, *L. plantarum* MTCC1325 improves cognition behavior and learning skills through the production of antioxidant agents and acetylcholine (Ach) and elevates this neurotransmitter in the hippocampus and cerebral cortex. The D-galactose model of AD was also used in another study in which the relief effect of *L. pentosus* var. *plantarum* C29 was explored.[67]

The AD model mice can be generated by lipopolysaccharide (LPS) administration. This model was used to study the therapeutic effect of engineered glucagon-like peptide-1 (GLP-1) producing *L. lactis* MG1363 to ameliorate memory impairment. This strain acted as TLR4/NF-κB pathway down-regulator, which reduces neuro-inflammation, and restored special learning of AD mice.[68] In another study, the LPS-induced AD was also treated by *L. helveticus* R0052 and *B. longum* R0175. This resulted in a significant reduction of pro-inflammatory cytokines.[11] The beneficial effects of probiotics on LPS-induced neuro-inflammation were also reported from probiotic-fermented cow's milk.[69] The ethanol precipitate of probiotics-fermented milk also presented anti-AD effects in both cell and animal studies.[70] Another predictive model for studying human neurological diseases is *Caenorhabditis elegans*. Cogliati *et al*.[71] used the transgenic *C. elegans* model to explore *Bacillus subtilis* NCIB3610 activity for delaying neuronal impairments. Three main weapons of *B. subtilis* to fight against AD are the anti-aging properties of this bacterium, production of quorum-sensing pentapeptide cerebrospinal fluid (named PhrC), and production of nattokinase. *Drosophila*

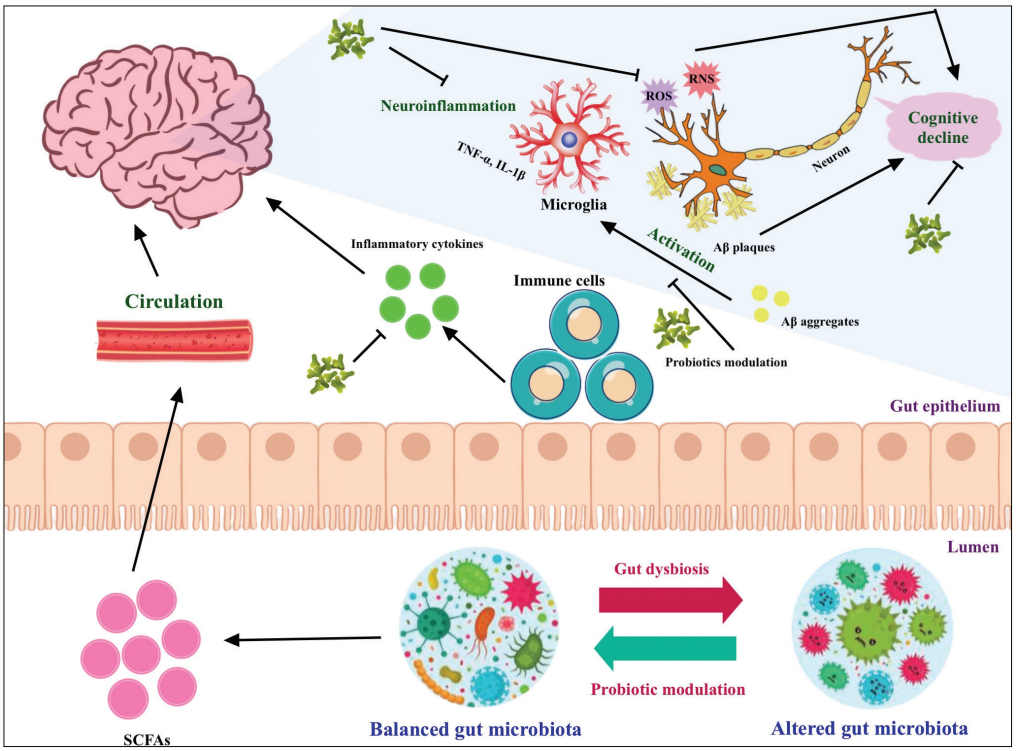

Figure 3: Schematic outline of the potential mechanisms of activity of probiotics for forestalling cognitive hindrance in AD. Probiotics or its bioactive metabolites, for example, SCFAs can further develop gut microbiota homeostasis and emphatically impact the neurotic elements engaged with the AD development like inflammatory response and oxidative pressure, accordingly enhancing cognitive dysfunction in AD

melanogaster is an insect AD model used to study AD-reversal effects of *L. plantarum* DR7 (DR7), rescuing the rough eye phenotype (REP) developed as a result of AD.[72]

In another study, APP/PS1 transgenic mice were used as AD models. The trimethylamine-N-oxide (TMAO) contribution in the AD process was explored, and the efficacy of the coadministration of *L. plantarum* and memantine on cognitive impairment was investigated. *L. plantarum* treatment decreased Aβ levels in the hippocampus and caused the reduction of TMAO synthesis.[73] Another example of APP/PS1 transgenic model application is the study of Sun *et al*.[74] They showed the effect of *Clostridium butyricum* WZMC1016 against AD-related neuro-inflammation by the metabolite butyrate. The third example of APP/PS1 model usage was a study carried out to investigate the effect of exercise training and a probiotic product, FRAMELIM®, to decrease AD progression. The mechanism of relief effect of these treatments is partly through microbial alteration.[75] The APP/PS1 model was also utilized to investigate the beneficial effect of *Akkermansia muciniphila* probiotic on memory and special learning.[76] The efficacy of combined and sole consumption of *B. bifidum* TMC3115 and *L. plantarum* 45 (LP45) were also explored in APP/PS1 mice by Wang *et al*.[77] Based on this study, combinational therapy significantly recovered spatial memory impairment. The 5XFAD transgenic mice is another AD model. This model was utilized to study *B. longum* NK46 probiotic's anti-inflammatory effect. This investigation revealed the blockage role of probiotic therapy on NF-κB and TNF-α pathways.[78] The other model, developed for AD, is a triple-transgenic mouse named 3xTg-AD. This model was utilized to assess SLAB51 (lactic acid bacteria and bifidobacterial mixture) probiotic preparation effect on AD's early stage. The administration of this formulation resulted in the renovation of hippocampus functions, improvement in cognitive function by increasing plasma levels of several gut hormones, for instance, ghrelin and leptin, partial repair of defected neuronal proteolytic pathways, diminished accumulation of Aβ aggregates, and anti-inflammatory impact through the alteration of inflammatory cytokines' plasma level.[79] Also, SLAB51 preparation is shown to reduce oxidative stress by activating the sirtuin 1 pathway.[80] The other investigation revealed the defected glucose metabolism amelioration mechanism by SLAB51 probiotics, which comprises glucose transporters' brain levels restoration, and modulation of pAMPK and pAkt, reducing the Tau phosphorylation.[81] The 3xTg-AD mouse was also used as a model to investigate the engineered probiotics' therapeutic effects in AD. In this study, animal models were treated by engineered *L. lactis* capable of expressing human p62 protein, which resulted in improved memory, reduced concentration of amyloid peptides, and lessened neuronal oxidative stress.[82] Another Alzheimer's model can be generated by ICV injection of amyloid-β for Wister rats. This model of AD was utilized to study the impact of probiotic supplementation, containing a mixture of *L. acidophilus*, *B. bifidum*, and *B. longum* on synaptic

plasticity. This supplementation showed a positive effect on antioxidant/oxidant biomarkers.[16,83] In 2018, a study was carried out on β-amyloid[1-42] intrahippocampal injected rats to investigate the role of *L. acidophilus*, *L. fermentum*, *B. lactis*, and *B. longum* in solving memory and learning deficits; also, oxidative stress biomarkers' concentration in the hippocampus were assessed. Results revealed that probiotics administration improved spatial memory and ameliorated SOD activity and malondialdehyde (MDA) levels.[84] In 2020, the obtained results from an investigation on Aβ1–40 injected rats consuming probiotics agreed with the previously mentioned study.[85] In another study, *Bifidobacteria* inhibited microglial activation and alleviated IL-1β, IL-4, IL-6, TNF-α, and INF-γ release in APP/PS1 mice.[86] Finally, Athari *et al.*[87] showed that insulin resistance as a major risk factor of AD was solved by probiotic supplementation. Based on obtained results, probiotics may be efficient for glycemic status control in AD. A summary of introduced studies, the examination conditions, and their major consequences are represented in Table 1.

Probiotic Supplementation in Patients with Alzheimer's Disease

Based on animal studies, manipulation of gut microbiota can seriously affect cognition, mood, and behavioral status. These findings suggest that probiotic administration may improve neurological outcomes in elderly individuals. There are several examples of the beneficial impacts of different probiotic products on the psychological condition of patients with AD. Here, some of these studies are summarized. According to many studies, neuro-inflammation plays a critical role in aging-related cognitive deficits and some of the probiotics have useful effects on minimizing this problem.[88] Sanborn *et al.* performed a double-blind randomized controlled trial (RCT) on 200 middle-aged and older healthy candidates to explore the influence of the probiotic *Lactobacillus rhamnosus* GG (LGG) on mood and cognition function. The authors believe that providing the mentioned information about the healthy sample response to the probiotic application will be valuable for the future preventive usage of LGG supplementation for this age group. The hypothesis testing was based on the MMRM analysis of obtained data from the NIH toolbox for the assessment of neurological and behavioral function.[89] One of the important features of LGG is its strong adhesive ability leading to the long-lasting activity of immunomodulatory and reduction of pro-inflammatory biomarkers such as IL-8. The reduced inflammation will lead to improved glycemic status, also several pro-inflammatory factors are known to be efficient in neurological conditions such as AD. The protective role of LGG on intestinal epithelial cells' antimicrobial agents' secretion is another mechanism of the mentioned beneficial outcomes. The LGG is indicated to be an effective agent for insulin resistance reduction based on animal studies.[90] Since AD pathogenesis is closely linked with serum levels of inflammatory/anti-inflammatory and oxidant/anti-oxidant biomarkers, a study was designed to investigate the responsiveness of these biomarkers to probiotic supplementation. For this aim, a twelve-weeks-double-blind RCT of the multispecies probiotics was performed on 60 patients with AD. Cognition measurement was done by TYM (TYM = 50 scores) method. The serum biomarkers containing total antioxidant capacity, glutathione, nitric oxide, 8-hydroxy-2′-deoxyguanosine, MDA, and cytokines (TNF-α, IL-6, and IL-10) were assessed and compared before and after the treatment. The TYM test revealed that most of the participants in this trial were suffering from severe AD. It was concluded that biochemical indicators and cognitive function of severe patients with AD are insensitive to probiotic therapy. Therefore, the indication of probiotic supplements has no beneficial effect on severe type AD.[91] Despite the previously described trial, another study proved that probiotic consumption positively affects cognitive function and related metabolic deficits. This study was performed on 60 participants with AD to examine the efficacy of 12 weeks of administration of probiotic milk containing *L. acidophilus*, *L. scasei*, *B. bifidum*, and *L. sfermentum* on cognition and biochemical parameters. The assessment method for cognition was the mini-mental state exam (MMSE). The intervention could improve MMSE scores significantly. Some features of the metabolic profile also have been altered. The MDA, hs-CRP, HOMA-IR, HOMA-B, and serum triglycerides levels were significantly varied and the quantitative insulin sensitivity check index (QUICKI) was significantly increased compared to the placebo-controlled group. No considerable effects were found on glycemic status, inflammation factors, and other lipid profiles.[92] *Bifidobacterium breve* A1 has been reported as a therapeutic agent for cognitive impairment in animal studies.[93] In a double-blind RCT of 12 weeks on 63 individuals consumption of probiotics comprising *B. bifidum* BGN4 and *B. longum* BORI promoted mental flexibility and mitigated stress in healthy older adults, due to the alterations in gut microbiota which can be considered in patients with AD in the future.[94] Accordingly, a double-blind RCT of 12-week application of this probiotic for 121 AD elderly subjects was performed. The assessment of cognition was based on two scales containing MMSE and assessment of neuropsychological status (RBANS). There was a significant improvement in the probiotic group in terms of MMSE total score and the "immediate memory" subscale of RBANS.[95] Kim *et al.* designed a double-blind placebo-controlled RCT to determine the impact of probiotic supplementation on 63 healthy elderly participants for 12 weeks. The gut microflora alteration, brain function, and BDNF were measured before and after the treatment. Based on the obtained results, blood BDNF concentration was increased in the probiotic group and the probiotic administration could improve mental flexibility

along with microbiota shifting.[94] A summary of introduced studies, the study's design, and their major outcomes are represented in Table 2.

A Comprehensive Overview of Prebiotic Supplementation in Alzheimer's Disease

Prebiotics are fiber compounds served as food, helping efficient benefits regarding the microorganisms and probiotics present in the GI tract.[65] The known prebiotics, such as fructooligosaccharides (FOS), galactooligosaccharides (GOS), and inulin, are under-investigation for the induction of manipulating microbiota and their association with neurological disturbances.[96-100] Prebiotics enhance the short-chain fatty acids production and reduce the toxic-fermentated products. In addition, they increase the Th1/Th2 ratio, and enhance gut-associated lymphocyte population and intestinal IgA secretion consequently.[101] It is commanding to develop drugs or foods with possession of prebiotic properties from natural origins. *Morinda officinalis* as a natural herb in traditional Chinese medicine comprises various active constituents. Approximately 49.79–58.25% of saccharides are present in *M. officinalis* and most of them are oligosaccharides.[102-106] Findings from pretreatment with oligosaccharides extracted from *M. officinalis* (OMO) were indicated on two models of rats AD encountering with D-galactose and Aβ25-35. OMO could promote learning and memory dysfunction in rats following the MWM test, ameliorated SOD and Catalase, and abrogated MDA generation; in this manner represented the OMO administration could enhance antioxidant activities in D-galactose-induced deficient rats. OMO significantly increased Na+/K+-ATPase and ACh levels in the brain tissue of D-galactose treated rats. OMO administration increased Shannon, npShannon, abundance-based coverage estimator (ACE), Chao1, and decreased Simpson values in the D-galactose-induced group. Besides, OMO restored GM-CSF, TNF-γ, 1L-10, IL-12, IL-17α, 1L-4, TNF-α, and VGEF to the normal in Aβ1−42-induced deficient rats. OMO administration normalized some monoamine neurotransmitters (norepinephrine, DA, 5-hydroxytryptamine, and 5-Hydroxyindoleacetic acid) in Aβ1−42-induced deficient rats. The KEGG pathway showed that the differentially expressed genes were predominantly enriched in numerous signaling pathways such as PI3K-Akt, PPAR, B cell receptor, interaction in the cytokine-cytokine receptor, chemokine, extracellular matrix-receptor receptor interaction phagosome, antigen processing and presentation, and cell adhesion molecules (CAMs).[100]

Besides, the effects of OMO administration were evaluated in the AD model of APP/PS1 transgenic mice. Utilization of ultra-high-pressure liquid chromatography with a linear ion trap-high resolution/orbitrap/mass was beneficial to study the metabolites existing in mouse serum.[107] Evaluation of MWM, OFR, and ORT tests showed that the administration of prebiotic FOS improved cognitive deficits, upregulated synapsin I and PSD-95 expressions, and mitigated phosphorylated JNK. Furthermore, FOS improved GLP-1 and reduced GLP-1R levels in the transgenic mice regarding gut microbiota.[108] Besides, pre-treatment with inulin caused to ameliorate beneficial microbiota in APOE4 transgenic (E4FAD) mice. Inulin also abridged the expression of the inflammatory gene in the hippocampus. These findings suggested that dietary inulin intervention can diminish metabolic disorders contributed by the APOE ε4 genotype.[109] FOS supplementation in D-galactose-induced oxidative injuries in BALB/cJ mice, normalized MDA, SOD, protein carbonyl, and 8-oxo-deoxyguanosine levels in plasma, liver, and hepatic mitochondria, cerebral cortex, and hippocampus.[110] R13 molecule as a prodrug form of 7,8-dihydroxyflavone (7,8-DHF) with prebiotic function agonized the tropomyosin receptor kinase B (TrkB) receptor. R13-induced *L. salivarius* antagonized the C/EBPb/AEP signaling pathway, which led to alleviate gut leakage, oxidative stress, and suppressed the amyloid aggregations in the gut of 5xFAD mice.[111] It seems that the OMO, FOS, and inulin can be good candidates as therapeutic agents in the managing of numerous neurological disorders [Table 3 and Figure 3].

Application of Synbiotics in Alzheimer's Disease Treatment

Synbiotics are a combination of probiotic and prebiotic components. Consumption of a synbiotic containing *B. longum* as a probiotic and an insulin-based prebiotic in older people showed valuable points in a randomized, double-blind, placebo-controlled crossover study. The pro-inflammatory response was regulated by symbiotic supplementation. Synbiotic applications can be operative in the promotion of the composition and metabolic actions of colonic bacterial populations and immune factors in elderly people.[112] The synbiotics increase viability, motility, saving Aβ deposition, and AChE activity. These effects were thanks to the synbiotic's combinatorial action on gut–brain axis signaling pathways including metabolic stability, immune signaling, oxidative and mitochondrial stress feasibly over pathways connecting PPARγ.[113] A recent study designated a novel synbiotic containing, *L. plantarum*, *L. fermentum*, and *Bifidobacteria longum* subspecies *infantis* with a polyphenol plant extract from the GI tonic Triphala (TFLA; *Emblica officinalis*, *Terminalia bellirica,* and *Terminalia chebula*) with helpful effects in transgenic APP/PS1 mice model of AD. Probiotics containing *L. Plantarum*, *B. infantis*, and *L. salivarius* in combination with polyphenolic metabolites 3-hydroxybenzoic acid and 3-(3'-hydroxyphenyl) propionic acid derived from grape seed polyphenolic extract (GSPE) were used through *in vitro* GI tract model. The synbiotic could penetrate the BBB and prevent the aggregation of Aβ, tauopathy, and neuro-inflammation.[114] A recent uncontrolled clinical trial evaluated patients with AD nominated by suitability sampling. The selected synbiotic was fermented milk using grains of kefir encompassing

Candida famata, *C. krusei, Acetobacter* sp., *Acetobacter aceti*, *Enterococcus faecium*, *L. fermentum*, *L. delbrueckii*, *L. fructivorans*, *Leuconostoc sp.*, and *L. kefiranofaciens*. Kefir ameliorated cognitive deficits via modulation of systemic inflammation, oxidative stress, mitochondrial dysfunction, DNA damage, and apoptosis. Thereby kefir may be a justifiable adjuvant therapy alongside the AD progression.[115] The summary of these studies is displayed in Table 4.

Effect of Prebiotic Polysaccharides on Probiotics and Alzheimer's Disease

Several non-digestible oligosaccharides and polysaccharides can be considered as a nutritive substrate that established the host gut flora by stimulating the growth of limited number of bacterial strains.[116-118] Prebiotic polysaccharides boost the development and/or activity of beneficial bacteria in the intestine.[119] Zaporozhets *et al.* analyzed prebiotic properties of polysaccharides of seaweeds on intestinal microflora and showed that they have selectively induced the growth of colonic *bifidobacteria*, improved intestinal bacterial disorders, and decreased inflammation.[120] Wang *et al.* identified two polysaccharide fractions (RP1 and RP2) from rapeseed and introduced them as novel prebiotics. They also showed that these polysaccharides stimulated acid production by *Bifidobacteria* and L*actobacilli*.[121] Chen *et al.* found that the polysaccharides isolated from *Grateloupia filicina* and *Eucheuma spinosum* have a substantial prebiotic effect by promoting *Bifidobacterium* proliferation.[122] Lee *et al.* introduced a polysaccharide derived from brown algae *Ecklonia* with prebiotic capability, which can improve the innate immune response of fish olive flounder infected with pathogen bacteria by enhancing of prebiotic bacteria growth.[123] A recent study discovered that crude polysaccharides derived from *Sphallerocarpus gracilis* increased the acidifying activity of *L. rhamnosus*, *L. plantarum*, and *S. thermophiles* during fermentation of milk.[124] Intake of high polysaccharide prebiotics may aid in the maintenance of a healthy gut microbiota, which is linked to increased short-chain fatty acids synthesis, mucus secretion, and pathogen reduction. Subsequently, a well-functioning gut immune system and immunological homeostasis have beneficial effects on brain function. Anti-inflammatory metabolites provide signals to the brain's central immune system, which may help maintain brain function and prevent the beginning or progression of AD. It was revealed that diets with prebiotic carbohydrates in patients with AD reduce the number of detrimental bacterial, such as *Bilophila*, which are effective in the prevention of AD.[125] Chen *et al.* looked into the effects of prebiotic oligosaccharides on AD. They found that *M. Officinalis* has the ability to produce FOS with a positive effect on the microbiota–brain–gut axis in AD.[100] It seems that the prebiotic oligosaccharides and polysaccharides prevent the onset or progression of AD by stimulation of the beneficial microorganisms' growth.

The Role of Local Probiotics on Alzheimer's Disease

Probiotics regulate the pH level in the body, help maintain the integrity of the intestinal lining, act as an antibiotic, and enhance BDNF.[126] Apart from brain neurotrophic factor, probiotics provide a good prognosis in the treatment of memory deficits and psychiatric disorders by directly modifying brain biochemical components.[127] The most common probiotic microorganisms used in dairy products are *Lactobacillus* and *Bifidobacterium* species. Since they are free of LPSs, they do not induce any form of inflammation after consumption.[128] *Lactobacilli* are of great commercial importance due to their use in the production of a wide range of dairy products, meat, and fermented vegetables.[129] Recently, we investigated the probiotics population of Lighvan cheese as the most famous traditional cheese in Iran using phenotypic and phylogenetic methods. We identified twenty-eight bacterial species belonged to *Lactobacillus* genus including *L. fermentum* (100%) and *L. casei* group (*L. casei, L. paracasei*, and *L. rhamnosus*) (99.0%–100%) and showed that *Lactobacillus* species. Is the dominant population of probiotics in Lighvan cheese.[129] Local dairies are the most important carriers to deliver probiotics. Based on previous studies *Lactococcus*, *Streptococcus*, *E.*, *B. clavus*, and *E. faecium* SF68 are used as probiotics in local fermented foods.[130]

Limitations and Future Recommendations

Owing to the lack of knowledge about AD pathophysiology, investigations that emerged in this study may offer new gates between gut microbiota and AD. Several well-designed clinical and mechanistic investigations are needed to clarify the underlying cascades and to prepare an effective and safe probiotic formulation for impeding the initiation or progression of AD. Emerging innovative probiotic medications are being investigated and intended to attenuate accompanying adverse effects while enhancing therapeutic effectiveness.

Though prevailing research shows that probiotics have prodigious therapeutic potential in AD, numerous obstacles should be overcome before probiotic medication is prescribed in medical practice. The US-FDA has now approved a limited list of probiotics that are recognized to be safe for commercial consumption in food and probiotic supplements. However, the FDA has not approved any claims for probiotics that associate with disease prevention or management of existing medical disorders. The most negative sides of probiotic supplementation in AD are their temporary and unpredictability in colonizing the gut mucosa. In addition, depending on the individuals, certain probiotics may fail to develop in a pre-existing stable gut milieu.

Several pre-, pro-, and synbiotics have been proven to improve microbiome stability, with resultant advantages to brain health that are especially beneficial in combating neurodegenerative pathologies like AD. By considering the aforementioned studies about feasible indications of pre-, pro-, and synbiotics as possible treatments for AD, there is still much work to be done for clarifying their functional mechanisms and the intersection between AD and microbiome research.

According to a recent analysis conducted by Xiang *et al.*,[131] probiotics supplementation in patients with AD/MCI was safe based on the evaluation of hematological and blood biochemical tests. However, more studies are needed to guarantee the safety, purity, and potency of probiotic treatments for AD to be regulated at the pharmaceutical or biological product level.

Conclusion

AD with signs of memory loss, cognitive impairment, and personality changes is a multifactorial disorder with a 5%–7% prevalence in most countries. The gut microbiota dysbiosis is believed to be closely linked with AD pathogenesis. According to this fact, microflora modification and improvement can be considered as a therapeutic strategy of AD treatment. Some pre-, pro-, and synbiotics are known to have a beneficial impact on AD-associated biomarkers and metabolic features can improve cognitive function and behavioral appearance based on animal and human studies. Several mentioned agents act as inhibitors of neuro-inflammation with consequent relief impact on AD symptoms. Altogether, pre-, pro-, and synbiotics' administration is a potential way of AD treatment or prophylaxis. Nevertheless, more RCTs should be conducted in the future. These RCTs should consist of numerous features entailing the duration of the trial should not be less than 24 months; specific parameters and scores (ADAS-Cog) should be assessed; adequate sample size should be considered in the trials. Since hallmarks are a late clinical manifestation of AD, in addition to the neuropsychological assessment, early diagnostic markers should be measured.

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Conflicts of interest

There are no conflicts of interest.

Authors' contributions

VE, MT, and AR were involved in the conceptualization; validation of resources and data extraction. MT, VE, AR, AF, AS, HF, and VT performed writing the manuscript. VE, VT, and MT reviewed and edited the manuscript. All of the authors read and approved the final manuscript.

Ethical approval

Not applicable.

Consent for publication

Not applicable.

Data availability

The datasets used and/or analyzed during this study are available from the corresponding author on reasonable request.

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