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Narrative Review

Modulation of gut microbiome in the treatment of neurodegenerative diseases: A systematic review

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SUMMARY

Background and aims: Microbiota plays an essential role in maintaining body health, through positive influences on metabolic, defensive, and trophic processes and on intercellular communication. Imbalance in intestinal flora, with the proliferation of harmful bacterial species (dysbiosis) is consistently reported in chronic illnesses, including neurodegenerative diseases (ND). Correcting dysbiosis can have a beneficial impact on the symptoms and evolution of ND. This review examines the effects of microbiota modulation through administration of probiotics, prebiotics, symbiotics, or prebiotics' metabolites (postbiotics) in patients with ND like multiple sclerosis (MS), Alzheimer's disease (AD), Parkinson's disease (PD) and amyotrophic lateral sclerosis (ALS).
Methods: PubMed, Web of Science, Medline databases and ClinicalTrials.gov registry searches were performed using pre-/pro-/postbiotics and ND-related terms. Further references were obtained by checking relevant articles.
Results: Although few compared to animal studies, the human studies generally show positive effects on disease-specific symptoms, overall health, metabolic parameters, on oxidative stress and immunological markers. Therapy with probiotics in various forms (mixtures of bacterial strains, fecal microbiota transplant, diets rich in fermented foods) exert favorable effects on patients' mental health, cognition, and quality of life, targeting pathogenetic ND mechanisms and inducing reparatory mechanisms at the cellular level. More encouraging results have been observed in prebiotic/postbiotic therapy in some ND.
Conclusions: The effects of probiotic-related interventions depend on the patients' ND stage and pre-existing allopathic medication. Further studies on larger cohorts and long term comprehensive neuropsychiatric, metabolic, biochemical testing, and neuroimaging monitoring are necessary to optimize therapeutic protocols in ND.

1. Introduction

Neurodegenerative diseases result from progressive, selective damage to neuronal populations, glial cells and interneuronal connections in the brain and spinal cord. Synaptic dysfunction and neuronal functional alterations lead to destruction and loss of neurons with decreased grey/white matter density, identifiable by imaging methods [1]. Selective loss of neuronal mass in the central nervous system is manifested by impaired cognitive function (leading to dementia), emotional and personality disorders and/or motor disorders - leading to inability to coordinate voluntary movements (ataxia). Both genetic and epigenetic factors (lifestyle, diet, long-term exposure to toxic substances, infections, trauma) have been implicated in the etiology of neurodegenerative diseases. Diseases caused by familial transmission of defective genes to offspring generally have a lower incidence and earlier onset (e.g. Huntington's disease, rare cases of motor neuron disease or Alzheimer's disease).

The ND with the highest incidence are dementias (most prevalent being Alzheimer's disease), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS) and multiple sclerosis (MS). The prevalence of AD in the population aged over 85 years is 30%, with the incidence rate increasing from 0.5% per year in the population aged 65–75 years to 6–8% per year in the population aged over 85

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years [2]. In the case of Parkinson's disease, the incidence is 2% among people over 65 years [3]. With increase of elderly population, the prevalence of ND is expected to escalate. Current allopathic treatments have not led to satisfactory results, at best succeeding to slow down the diseases' progression and there is currently no effective therapy to cure or halt the disease. In this context, it becomes imperative to explore and develop complementary approaches leading to more effective therapies.

Numerous studies over the last two decades have highlighted the essential role of the microbiota (the community of all microorganisms including fungi, protozoa, viruses, and bacteria living in the body of an individual) in maintaining health, and the role of the microbiota–brain axis in the development of neurodegenerative pathology [4]. The gut flora accounts for about 90% of the total microbiota [4,5], with an estimated human: bacterial cell ratio close to 1: 1 and is mainly composed of 6 clusters - *Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria, Fusobacteria* and *Verrucomicrobia*. Health maintenance has been associated with a great diversity of microbial flora, in a delicate balance with the host. Alterations in the composition of gut flora leading to loss of this balance, called dysbiosis, has been implicated in the development of chronic diseases, from intestinal disorders such as irritable bowel syndrome, or celiac disease [6,7], to metabolic disorders (e.g. type 2 diabetes, obesity), cardiovascular diseases, or neurological disorders [8,9]. Studies in animals and in humans revealed that interventions to correct microbiota, consistent with the health status, have had beneficial effects on the condition/disposition of patients and on cognitive function. These results have stimulated research into developing new protocols that target the microbiota to treat neurodegenerative diseases.

1.1. The role of gut microbiota in health and disease

The gut flora is essential in maintaining the health of the host, participating in defensive, trophic, and metabolic processes. It is implicated in defense against pathogens by stimulating regeneration of the intestinal epithelium and improving the mechanical and biological barrier function of the intestinal wall, as well as by competing for attachment sites and nutrient sources, producing antimicrobial substances (e.g. hydrogen peroxide, H_2O_2) and generating an acidic environment, unfavorable for the growth of pathogenic bacteria [4,10].

The gut microbiome has also trophic functions through the ability to ferment complex carbohydrates (cellulose, pectin, starch, etc.), and proteins, producing short/branched chain fatty acids (S/BCFA), which are important energy source for colonocytes [11]. Propionic, butyric, and acetic acids (in a 1:1:3 ratio) are the predominant SCFA produced in the gut, with a regulatory role in the immune system and in inflammatory response and in maintaining and restoring epithelial integrity. Butyrate has beneficial anti-inflammatory, anti-carcinogenic, and protective intestinal barrier effects, improving the tight junctions of epithelial cells and through its role in mucin synthesis. SCFA are taken up by intestinal epithelial cells and are involved in gene expression, cell differentiation, proliferation, and apoptosis [11].

Gut flora also participates in metabolism through de novo synthesis of essential vitamins like B12, synthesized by lactic acid bacteria [11], folate (important in vital metabolic processes, DNA synthesis and repair), other B vitamins, and vitamin K. Bacterial metabolites are also involved in cell signaling including modulation of inflammation and gut motility, and in lipid and glucose metabolism. Through production and release of neuroactive compounds such as neurotransmitters (glutamate, GABA, dopamine, serotonin, etc.), neuropeptides, cytokines, chemokines, other metabolites (S/BCFA, peptidoglycans, etc.) that reach the brain through blood circulation, other cells, or transporter molecules, intestinal microbiome influences cerebral function and mental health [12,13]. It also provides up to 10% of the body's energy requirements through its metabolites and helps maintain the integrity of the blood–brain barrier by synthesizing junctional proteins, such as occludin and claudin-5, which are involved in regulating the permeability of endothelial tissues [14].

With advancing age, the gut microbial ecology changes (increased abundance of Gram-negative bacteria and proliferation of other pathogens), together with its metabolite spectrum. For example, increased levels of lipo-polysaccharides (LPS) - endotoxins of Gram-negative bacteria, can cause intestinal inflammation [15]; lower level of SCFA diminish mucus production by epithelial cells, leading to increased intestinal permeability for pathogens and to systemic inflammation - a vulnerability factor for many age-related pathologies [15,16].

1.2. Pathogenetic mechanisms of neurodegenerative diseases

The primary regions affected in various ND are different and the neuronal circuits subsequently affected by degeneration include both specific and common brain circuits, reflecting the characteristic clinical picture of each disease [17]. Beyond genetic risk factors, Castillo Ximena and collaborators [18] propose four main pathogenetic mechanisms as the origin of neurodegeneration, briefly described in the following.

a) **Pathological processes at the cardiovascular level**, which induce blood vessels damage and through a defective neurovascular coupling affect nervous tissue perfusion, neuronal excitability thresholds [19,20], and impair cellular homeostasis; this leads to accumulation of neurotoxic proteins (amyloid beta, immunoglobulins, plasmins, thrombins, albumin) in the parenchyma [24,25] and over time to brain dysfunction and athrophy [21]. Cerebral small vessels disease induces white matter lesions (demyelination), lacunar infarcts and cerebral microhemorrhages visible by MRI imaging [22], associated with dementia, motor and balance disorders [23,26–28].

b) **Cellular senescence** amplified with aging [29,30], through activation of the associated secretory phenotype (ASP) (which includes various signaling factors like proinflammatory cytokines, chemokines, proteases, metalloproteinases, growth modulators, angiogenic factors, microRNAs, mitochondrial DNA, small molecule metabolites) that confers resistance against immune clearance [31–35], induces passive senescence in nearby or distant normal cells, impairs tissue regeneration and contributes to tissue aging and neurodegenerative and cerebrovascular diseases [36,37]. Senescence in various brain cell types induces different deficiencies or dysfunctions - in microglia and astrocytes can lead to inflammation and impaired trophicity, in oligodendrocytes to reduced myelin sheath, affecting nerve impulse transmission, whereas senescence of endothelial cells can affect the blood–brain barrier. Removal of senescent cells in animal models of PD has been shown to attenuate neurodegeneration, suggesting a cause–effect relation [38,39].

c) **Defective trophic body-brain interactions**, arise in altered peripheral cell homeostasis and induce changes in composition of extracellular vesicles (EV), involved in neuron-target cell communication. EV that travel from peripheral organs to the brain, can modulate neuronal physiology and have been implicated in the propagation of misfolding proteins [40], affecting neurons and over time initiating processes leading to neuronal death during aging [40]. For example, metabolic disorders such as diabetes and obesity can contribute to neurodegenerative processes in the central nervous system.

d) **Long term gut dysbiosis**, with excessive proliferation of pro-inflammatory bacteria and their characteristic compounds with neurotoxic potential (e.g. lipopolysaccharides, LPS, located on the outer surface of the gram-negative bacteria [47,48]), affects the brain through the gut–brain axis. Increased permeability of the intestinal epithelium with aging [41] favors translocation of bacteria and their metabolites across the intestinal barrier to other organs, including the brain [42], where an exacerbated immune response can lead to neurodegeneration; also, high plasma LPS levels can result in excessive metabolic endotexemia accompanied by an inflammatory response with increased release of pro-inflammatory cytokines [49]. Observation of gut dysbiosis [43,44], with an increased abundance of pro-inflammatory bacteria [45,46] and LPS levels [50–53] in PD, AD, ALS patients compared to healthy individuals, as well as an excess of propionate disrupting neurotransmitter systems (dopamine, serotonin, glutamate) [54,55] in AD patients, support the hypothesis of an infectious etiology of ND [56–58].

1.2.1. Subcellular morpho-functional alterations

To understand the etiopathogenesis of ND at the subcellular level and to create the framework for an individualized therapeutic approach, Wilson et al. [59] proposed a model, describing changes in different neuronal segments: 1) pathological protein aggregation, 2) defects at the synapse and neuronal network level; 3) defective proteostasis; 4) abnormalities at the cytoskeleton level; 5) disturbed energy homeostasis; 6) DNA/RNA defects; 7) inflammation; 8) neuronal death. These changes may interact with each other, amplifying destructive effects and conferring a specific clinical picture for each ND.

1.3. The main factors that influence microbiota

Gut microbial colonization begins in utero by maternal microbiota transferred via amniotic fluid and placenta [60] and is affected by childbirth delivery method and infant feeding (breast- or formula-fed), becoming similar to the gut flora of an adult by the age of 3 years [61–64]. Early life microbial colonization influences brain development and maturation, determines immune and metabolic programming and influences the risk of later-life chronic illnesses, including ND [65].

A major factor that impacts the microbiota throughout life is diet. A balanced diet, like the Mediterranean one, rich in compounds with anti-inflammatory properties, antioxidants, polyunsaturated acids, polyphenols, vitamins, and fibers, increases the *Bifidobacterium* and *Lactobacillus* populations that improve cognitive function and decreases the *Clostridium* and *Bacteroides* populations, with pathogenic potential [66,67].

Other important factors affecting gut flora are antibiotics that favor gut colonization with antibiotic-resistant pathogenic bacterial strains, impacting diversity and metabolism, humoral and cellular immune response [68,69], as well as exposure to environmental toxicants containing mercury, arsenic, cadmium, chromium, cobalt, nickel, or to pesticides that affect composition of the microbiota, its metabolites and the intercellular signalling pathways in which it is involved. Xenobiotics can be metabolised by gut flora, resulting in compounds with enhanced or attenuated toxicity. For example, methyl mercury is demethylated by intestinal bacteria, resulting in inorganic mercury with lower toxicity [70]. Food additives can also unintentionally alter the gut flora. Artificial sweeteners such as saccharin, acesulfame, sucralose and aspartame have been implicated in the development of glucose intolerance, chronic inflammation and obesity [70]. Prolonged mental and physical stress also influences the gut microbiota via the gut–brain axis, which consists of multiple communication pathways between the brain and the gastrointestinal tract. These bidirectional communication pathways include the hypothalamic-pituitary- adrenal (HPA) axis, the sympathetic and parasympathetic autonomic nervous system, vagus nerve and gut flora [15,16]. The enteric nervous system contains a neural network of approximately 500 million neurons, which extends throughout the entire digestive tract and communicates via the same neurotransmitters as the central nervous system, which is why it has also been referred to as the “second brain” [12]. Endocrine, neurocrine and inflammation-related signals generated by the gut microbiota and specialized cells in the gut influence the brain, which in turn can influence the composition and activity of the gut flora.

1.4. Interventions to modulate gut microbiota

The main long term approach to influence gut microbiota for therapeutic purposes is adherence to diets rich in fruits and vegetables, with fibres (prebiotics), postbiotics and foods naturally containing probiotics (e.g. yoghurt, kefir). Prebiotics are currently defined as selectively fermented ingredients (by gut flora), non-absorbable in the GI tract, that influence intestinal microbiota, with benefits for the host health [71]. Probiotics are defined as live and viable microorganisms which, when administered frequently and in adequate quantities, have beneficial effects on the health of the host organism [72]. They can be encapsulated and administered orally or by fecal microbiota transplant (FMT) from a healthy donor (as a solution administered via nasogastric tube or colonoscopy, or orally in capsules). Microbiota can also be influenced through “smart probiotics”, genetically engineered to synthesize certain chemicals (e.g. anti-inflammatory cytokines, enzymes, or certain proteins to cover deficiencies), or by therapy with bacteriophages - viruses that selectively target and destroy specific bacteria, like pathogenic, antibiotic-resistant ones.

Probiotics that confer mental health benefits to the host when consumed in a certain amount by interacting with commensal gut bacteria are defined as psychobiotics [72–75]. Bacteria used predominantly in the therapy of nervous system diseases are gram-positive bacteria (e.g. *Bifidobacterium* and *Lactobacillus* species), which do not contain lipopolysaccharides, thus reducing the risk of an immunological response. Psychobiotics can influence psychological, emotional and cognitive processes through the hypothalamic-pituitary-adrenal (HPA) axis, involved in stress response and controlling inflammation [75]. Prolonged stress causes an excess of glucocorticoids, with immunosuppressive effect, which can lead to dysbiosis, which in turn can also activate the HPA system, with increased sensitivity to stress, impaired memory and cognition; correction of gut flora imbalance, can ameliorate these effects. Moreover, through SCFA, psychobiotics can influence the maturation, morphology and immunological function of microglial cells – the effector cells of the innate immune system in the central nervous system. Also, they can regulate interneuronal communication through synthesis of neurotransmitters that control neuronal excitation-inhibition balance and synthesis of proteins such as brain-derived neurotrophic factor (BDNF), which influences neuronal growth and survival, and synaptic plasticity, being essential in learning and memory [74].

2. Aims

The present study provides a narrative review of the published results on the effects of microbiota modulation in patients with the most prevalent ND's, using prebiotics, probiotics, postbiotics or symbiotics administered in various forms — through diet, fermented foods, commercial or custom made mixtures of bacterial strains, plant-derived oligosaccharides administered orally as capsules or solutions, bars rich in dietary fibers, beneficial bacterial metabolites, or fecal microbiota transplant, Fig. 1. Effects on specific symptoms, on gut microbiota composition, metabolic parameters and biomarkers of inflammation and oxidative stress, cognitive, mood and behavioral changes are analyzed and potential future directions are outlined. Neurodegenerative diseases included in the study are Alzheimer's disease and other dementias, Parkinson's disease, multiple sclerosis, and motor neuron disease (MND), including amyotrophic lateral sclerosis. Diseases caused by genetic defects (e.g. Huntington's disease, familial MND) are not considered in this review.

3. Methods

3.1. Search strategy

The search for published articles was carried out initially until July 2023 and then updated until February 2024 using Pubmed, MEDLINE and Web of Science databases. Two lists of related terms were elaborated. List 1 included the terms “probiotic”, “prebiotic”, “symbiotic”, “psychobiotic”, “*lactobacillus*”, “bifidobacteria” “yoghurt”, “kefir”, “fermented”, “fibre” “food”, “*bifidobacterium*”, “microbiota”, “gut microbiome”, “brain-gut axis”, “mycobacteria”, “gut bacteria”, “commensal bacteria”, “gut micro/flora”, “*enterococcus*”, “*streptococcus*”. List 2 included the terms ‘neurodegenerative disease’, ‘dementia’, 'Alzheimer's disease', ‘multiple sclerosis', 'Parkinson's disease’, ‘motor neuron disease’, ‘amyotrophic lateral sclerosis'. Each search included one term from list 1 AND one term from list 2. In order to facilitate the selection of relevant articles for this synthesis from the large number of articles present in the databases, additional filters have been introduced. Only “classical article” “clinical trial protocol”, “randomized controlled trial”, “research articles”, “multicenter study”, “observational study”, “case reports” or “short communications” type of studies were selected; book chapters, reviews and abstracts were excluded. Only articles relating to human subjects were selected, whereas animal studies were excluded. The Web of Science search included articles from the following fields: microbiology, nutrition and dietetics, gastroenterology, immunology, neuroscience, applied microbiology in biotechnology, research experiments in medicine, nursing, oncology, pharmacology, and psychiatry.

Other complementary sources for papers were bibliographic references of articles included in the study and of previously published review articles, as well as the clinical trials registry ClinicalTrials.gov. In this database, under condition/disease - the terms neurodegenerative disease, dementia, multiple sclerosis, Parkinson's disease, motor neuron disease, were entered sequentially and under type of intervention/treatment — the terms probiotic, psychobiotic, prebiotic, symbiotic, postbiotic, dietary fibers. As additional filters, we required the age category of study participants to be between 18 and 64 years or over 65 years and we selected only studies with results. The identification of articles for the present synthesis followed the PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols) guidelines, [76,77]. We included in the review the studies that involved administration of fermented foods and which provide details regarding the bacterial composition and detailed conditions of preparation and/or number of colony forming units (CFU's). Information on the type of study - correlational or interventional, cross-sectional or cross-over, whether there was a control group or placebo administration, randomisation, whether the study was double-blind, whether there were any conflicts of interest (e.g. study authors were shareholders in companies marketing probiotics) was examined.

4. Results

4.1. Search results

The results of the selection process of the articles included in the synthesis are presented in the diagram in Fig. 2. The search of the mentioned databases (PubMed, MEDLINE, Web of Science) in the absence of filters led to the identification of 9113 published studies, with a further 6 studies identified by examining the bibliographic resources of the relevant articles. The search on ClinicalTrials.gov did not identify any studies with published (preliminary) results.

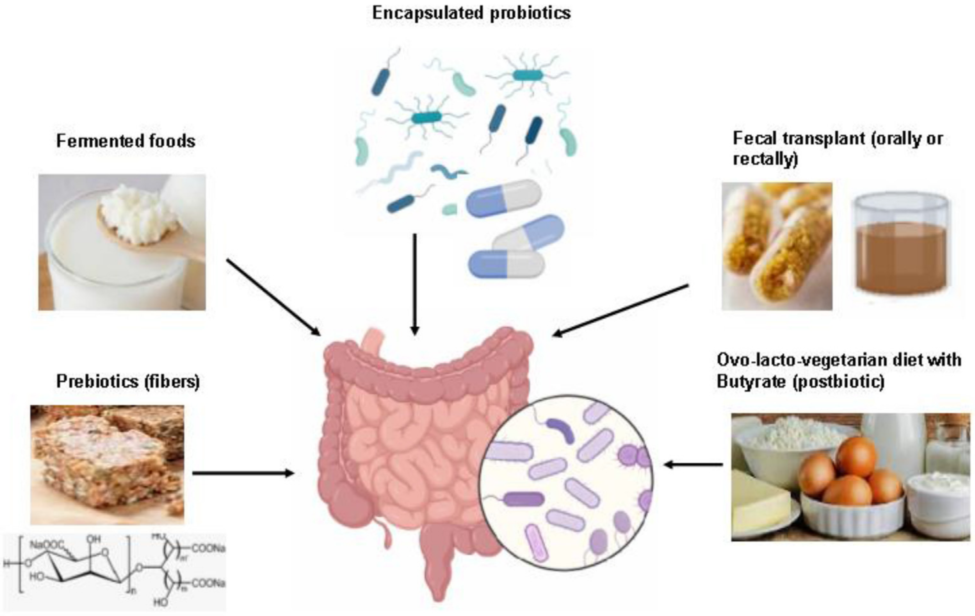

Fig. 1. Modulation of gut microbiota through probiotic/prebiotic/postbiotic therapies.

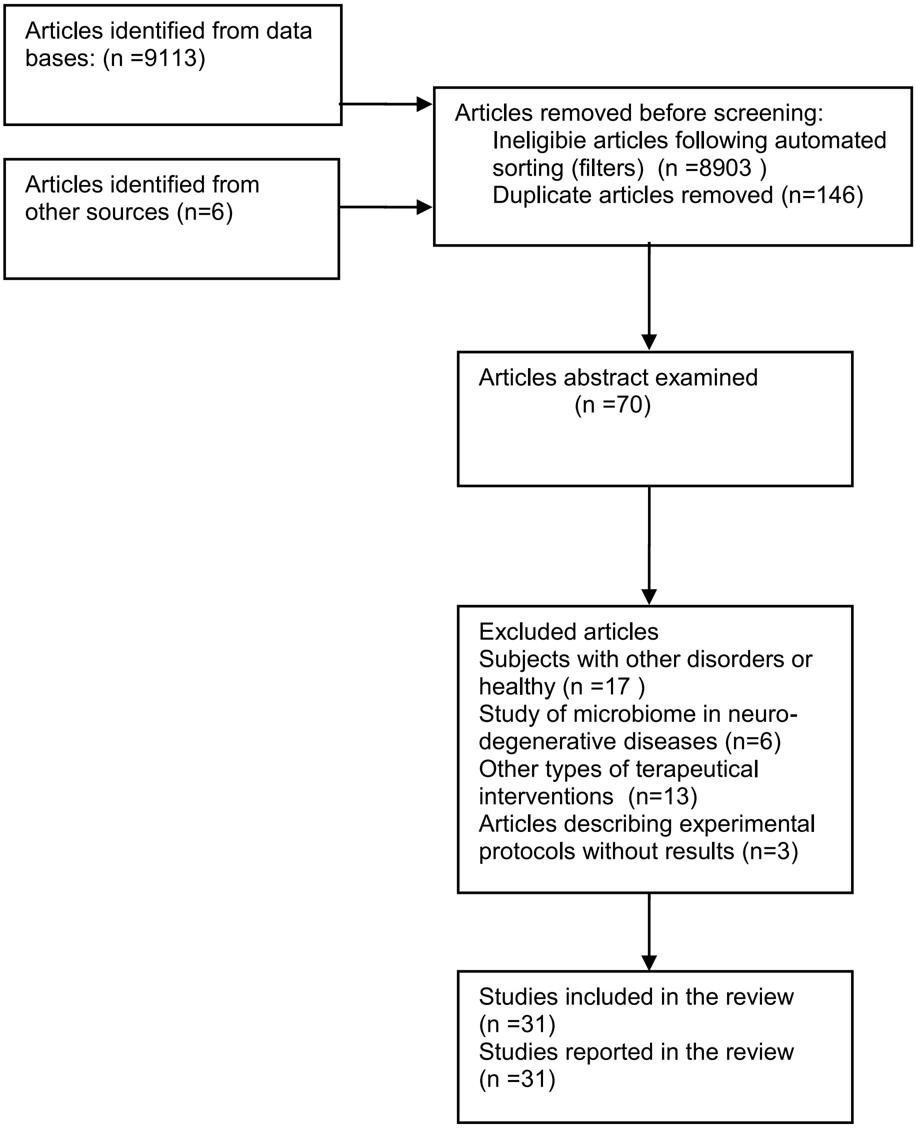

Fig. 2. PRISMA diagram illustrating the selection procedure of the articles included in the review.

Out of a total of 9119 studies retrieved, 8903 articles were removed following the application of the above mentioned filters. Furthermore, after exclusion of the duplicates, 70 articles remained for consideration. Following abstract reading, 17 studies were excluded due to focusing on healthy participants, on people with mild cognitive impairment, or on patients with other conditions (diabetes, obesity, etc.). Other 6 articles focusing on microbiome composition in patients with various ND, without involving any restoration intervention, were excluded. Thirteen articles describing other types of interventions on the microbiota (e.g. physical exercise, electroacupuncture, etc.) were also excluded, as well as other 3 articles describing experimental protocols for probiotics based therapies only, without results. The remaining 31 articles were examined in detail and included in the present review. For each of these studies, relevant information was extracted - type of experimental design, number and age of participants, type of intervention (amount of probiotic species or pre-/postbiotic used), duration and route of administration, main results obtained, and limitations, Tables 1–4. The data have been grouped by type of ND to facilitate an overview of outcomes for each disease.

4.2. Multiple sclerosis (MS, or RRMS-relapsing-remitting multiple sclerosis)

Six studies have investigated the effect of probiotic administration in patients with multiple sclerosis - three randomised double-blind, placebo-controlled trials (RCT) [79,82,83], a pilot study in a small number of patients [78] and a clinical trial with a control group of healthy subjects [80,81], Table 1.We included in the review besides randomized clinical trials (RCT), pilot studies as their results can provide the basis for future larger RCT.

One such pilot study on 5 MS patients [78], revealed a decrease of the number of lesions observed on MRI images following the treatment with *Trichiuris suis* eggs, but with a tendency to increase again two months after treatment cessation. Increased eosinophils number and high-sensitivity C-reactive protein (hs-CRP) level was also observed in the first 2 months, followed by a decrease in the last month of treatment, probably reflecting the initiation of an anti-inflammatory response following an initial inflammatory response. The results recommend a larger randomised clinical trial to confirm the findings.

Table 1
Studies investigating microbiota modulation in multiple sclerosis patients.

Study/Study design	Sample features –number, sex (m/f), age	Therapy – product used, dose, frequency, duration	Main results	Limitations
Fleming et al. MSJ, 2011 [78] Pilot study	- 5 MS patients - 4 f/1m, 24-42	- *Trichiuris suis* ova 2500 ova orally, - 1 time every 2 weeks, for 3 months	- ↓ # of new lesions on MRI compared to pre-treatment - initial ↑ hs-CRP and # of eosinofils in first 2 months, then ↓	Small number of patients, no statistical analysis
Kouchaki et al., 2017 [79] RCT, double-blind, placebo controlled	- 30 MS patients control lot (5m/25f) age 33.8 ± 8.9 - 30 MS patients therapy lot (5m/25f) age 34.4 ± 9.2	- Mix of *Lactobacillus*: *L. acidophillus, L. casei, L. fermentum, & Bifidobacterium bifidum*, each 2 × 10^9 CFU/g - 1 capsule/day, for 12 weeks	- ↓ disability (EDSS score), improved mental health (↓BDI, DASS scores) and general health (GHQ-28 score) - ↓ inflammation markers (hs-CRP) -↓ glycemia and insulinemia, ↑ in NO in the treated vs. control group	- no assessment of cognitive deficit, not studied if changes persisted after the end of treatment
Tankou et al., 2018 [80]; Thankou et al., 2018 [81] Comparison with healthy individuals, both groups received the probiotics	- 9 MS pacients (44.4%m, 55.6%f); age 50 ± 10 - 13 healthy persons (38.5% m, 61.5%f), age 35 ± 14	- Probiotic VSL3-900 × 10^9 CFU/sachet, mix of *Lactobacillus* (*L. paracasei* DSM 24734, *L. plantarum* DSM 24730, *L. Acidophilus* DSM 24735, *L. delbruckei sbsp. bulgaricus* DSM 24734), *Bifidobacterium* (*B. Longum* DSM 24736, *B. Infantis* DSM 24737, *B. breve* DSM 24732), *Streptococcus (S thermophilus* DSM 24731) - 2 sachets of VSL3, twice/day (3600 billions CFU) for 2 months (commercially Vivomixx/Visbiome)	- Changes in microbiota - recover of affected species in MS and deplete of ones causing dysbiosis; - anti-inflammatory peripheral immune response (↓ frequency of monocytes); - down-reg. of pro-inflammatory genes MALT-1 & LGALS-3 in MS group; modifications do not persist after treatment cessation	Small number of patients; no correlations of measured parameters with clinical data.
Rahimlou et al., 2020 [82] RCT placebo controlled	- 33 MS patients placebo lot (12m/21f) 39.9 ± 8.76 - 32 patients (6m/26f) therapy lot 42.15 ± 11.98	- Probiotic (Protexin), min 2 × 10^9 UFC/capsule mix of 14 strains (*Bacillus subtilis* PXN 21, *Bifidobacterium: bifidum* PXN 23, *breve* PXN 25, *infantis* PXN 27, *longum* PXN 30, *Lactobacillus: acidophilus* PXN 35, *delbrueckii* ssp. *bulgaricus* PXN 39, *casei* PXN 37, *plantarum* PXN 47, *rhamnosus* PXN 54,*helveticus* PXN 45, *salivarius* PXN 57, *Lactococcus lactis* ssp. *lactis* PXN 63, *Streptococcus thermophilus* PXN 66) - 2 capsules/day, for 6 months	- ↓ level of depression (BDI score), ↓ fatigue (FSS, fatigue severity scale) ↓ reduced pain ratings, ↑ BDNF serum level, ↓ IL-6 in treated group, nonsignificant differences in NGF level	- no data regarding the persistence of effects following the cessation of the treatment
Tamtaji et al., 2017 [83] RCT, double-blind, placebo controlled	- 20 patients in placebo group 34.9 ± 8.9 - 20 patients in probiotic group 32.8 ± 9.2	- Mix of *Lactobacillus: L. acidophillus, L. casei, L. fermentum, & Bifidobacterium bifidum*, each 2 × 10^9 CFU/g - 1 capsule/day, for 12 weeks	- ↓ IL-8, TNF-α pro-inflammatory gene expression in the probiotic vs. control group; no observed influence on gene expression for for IL-1, PPAR-γ si LDLR, implicated in insulin and, respectively, in lipid homeostasis	- fecal microbiota composition not examined, nor other genes implicated in metabolic signaling/ imflammation (e.g. GLUT-4, NF-kB)

Legend: EDSS- Expanded disability status scale; BDI- Beck depression inventory (Beck AT et al., Archives of Gen Psychiatry,1961); GHQ-28 – General Health Questionnaire (Goldberg DP et al., Psychol Medicine, 1979); DASS- Depression Anxiety and Stress Scale (Crawford JR, Brit J of Clin Psychol. 2004); LDLR-low density lipoprotein receptor (receptor LDL); LGALS-3 – lectin galactoside-binding soluble-3 (gene encoding galectin-3); NGF-nerve growth factor; hs-CRP-high sensitivity C reactive protein; IL-interleukin; PPAR-γ -peroxisome proliferator-activated receptor gamma; TNF-α- tumor necrosis factor alpha; GLUT-4 – glucose transporter type 4; NF- kB – nuclear factor kappa-light chain enhancer of activated B cells; ↑-increase; ↓ - decrease.

Two studies [79,83] using the same type of probiotics (mix of *Lactobacillus* and *Bifidobacterium* species, administered for 12 weeks, reported positive clinical effects, like improvements in psycho–emotional parameters - reduction in depression, anxiety and stress, improvement in overall health, as well as decrease in insulin resistance and improvement in lipid metabolism [79], and down-regulation of the expression of some pro-inflammatory genes, corresponding to IL-1, IL-8, TNF-α [83]. These findings are consistent with those obtained by Rahimlou and colleagues [82], which also reported reduced pain ratings and fatigue following treatment with commercial probiotic Protexin for 6 months and an increase in BDNF (brain-derived neurotrophic factor), which exerts a protective effect against demyelination in MS [86]. Excessive pro-inflammatory cytokines are associated with accentuated peripheral and central inflammation and involved in myelin and axon damage. By reducing inflammation, probiotic therapy has the potential to slow disease progression. Also, an increase in the level of nitric oxide (NO) was detected, compound which in physiological concentrations exerts many beneficial actions; these include anti-inflammatory effects by inhibiting the action of pro-inflammatory

Table 2
Studies investigating microbiota modulation in Alzheimer's disease patients.

Study/Study design	Sample features –number, sex (m/f), age	Therapy – product used, dose, frequency, duration	Main results	Limitations
Agahi et al., 2018 [87], RCT double- blind, placebo controlled	- 23 AD patients (10m/13 f) - control lot - 25 AD patients (7 m, 18 f) - therapy lot - age range 65–90 - 83.5% severe cases	- Capsule 1-mix of *Lactobacillus fermentum,L. plantarum* & *Bifidobacterium lactis* (total 3×10^9 CFU) - Capsule 2- mix of *Lactobacillus acidophilus, Bifidobacterium bifidum* & *B.longum* (total 3×10^9 CFU) - 1 capsule of each probiotic every 2 days for 12 weeks	- ns differences post-/pretherapy in memory tests performance ("Test your memory"), in serum NO, total antioxidant capacity (TAC), MDA levels, cyokines (IL-10 Il-6, TNF-α) and 8-OHdG level	- Small number of patients, relatively low probiotic concentration for severe cases of AD
Leblhuber et al., 2019 [88] Clinical trial	- 20 AD patients (11 m/9 f) - mean age 76.7 ± 9.7 age range 60–93	- Omnibiotic Stress Repair (Alergosan, Austria) *Lactobacillus: L. casei* W56, *L. acidophilus* W22, *L. paracasei* W20, *L. plantarum* W62, *L. salivarius* W24, *Lactococcus lactis* W19, and *Bifidobacterium lactis* W52 & W51, *B. bifidum* W23; 7.5×10^9 CFU - Aqueous suspension (1 sachet in 125 ml water) of probiotic, administered daily for 28 days	- ↓ concentration of fecal zonulin, ↑ *faecalibacterium prausnitzii*, ↑ serum biomarkers of immune activation (kynurenine, neopterin) post- vs. pretreatment - ns effect on cognitive function (MMSE), or trypyophan breakdown)	- small number of patients, no control group, conflict of interest one of the authors
Tamtaji et al., 2019 [89], RCT, 3 groups: control -placebo, therapy with Selenium only and therapy with Se + probiotic	- 26 AD patients control group, age 78.5 ± 8.0 - 26 patients Selenium group, age 78.8 ± 10.2 - 27 AD patients Se + probiotic group age 76.2 ± 8.1	- Mixture of *Lactobacillus acidophillus, Bifidobacterium bifidum* and *Bifidobacterium longum*, each 2×10^9 UFC/g, Selenium 200 μg - 1 probiotic capsule + Selenium 200 μ g, for 12 weeks	- ↑ MMSE score, ↓ hs-CRP, TAC, and GSH level, ↑insulin sensitivity - ↓ insulin resistance, ↓ triglycerides, VLDL-, LDL, total-/HDL cholesterol in Se + probiotics vs. placebo and Se + placebo groups - improved expression of TNF-α, PPAR-γ and LDLR genes - ns fasting plasma glucose, gene expression for IL-8,TGF-β	- small number of patients
Ton et al., 2020 [90] Uncontrolled clinical trial	- 13 AD patients (11f/2m), age 78 ± 3 women 78 ± 7 men	- Fermented product by inoculating pasteurized milk with 4% kefir grains containing the species *Acetobacter aceti, Acetobacter* sp., *Lactobacillus delbrueckii, Lactobacillus fermentum, Lactobacillus fructivorans, Enterococcus faecium, Lactobacter Faecium, Canfiranos, Faecium Faecium, Candida Famacidida* and *Candida krusei,* culture incubation at 25°C-28 °C 24 h, filtered and refrigerated at 2°C-6°C for 24 h administered mixed with organic strawberries-500 g fruit/2L fermented milk. - Administration - 2 ml/kg/day for 90 days	- Post-treatment improvement of cognitive functions (memory, visuo-spatial & abstraction skills, linguistic, executive skills tests) - ↓ pro-inflammatory cytokines level TNF-α, IL-8, IL12p70, ↓ markers of oxidative stress (O2-, H2O2, ONOO-); ↓ DNA fragmentation and apoptosis (↓ of PARP-1 marker, Poly ADP-ribose polymerase 1); ↑ NO bioavail-ability and p53 protein expression	- small sample
Akbari et al., 2016 [91] RCT, double-blind, placebo-controlled	- control lot 30 AD patients (24 f/6 m); age 82 ± 1.69 - therapy lot 30 AD patients (26f/6m); age 77.67 ± 2.62	- 200 ml milk with probiotic mixture (*Lactobacillus: L. acidophillus, L. casei, L. fermentum,* and *Bifidobacterium bifidum*, each 2×10^9 CFU/g) - Daily administration of 200 ml milk with probiotics, for 12 weeks	- ↑ MMSE score, ↓ hs-CRP, MDA, TG &HOMA-IR levels, ↑ insulin sensitivity in therapy vs. control lot - ns changes in HDL, LDL cholesterol, insulin, NO, TAC, GSH	- limited cognitive assessment (MMSE only)
Chen X et al., 2023 [92] Open-label study	- 5 patients (2 m/3f); age 54-80 - 2 patients with AD, 1 with FTD, 2 with MCI	- Capsules with fecal microbiota from healthy donors, mixed with saline solution, then filtered and mixed with glycerol, 1 g/capsule	- improved cognitive scores (MoCA, ADAS-Cog) in MCI patients, maintenance at the pre-treatment level in dementia patients	- small group of participants, no control, diet may have influcenced the results

Table 2 (*continued*)

Study/Study design	Sample features –number, sex (m/f), age	Therapy – product used, dose, frequency, duration	Main results	Limitations
		- 40 capsules, 3 times/day for one day	- 7 up-reg,28 down-regulated metabolites; changes persist after 180 days	
Xiao S et al., 2021 [93] RCT double-blind placebo-controlled multicenter phase III trial	- 818 patients (50–85) - 408 AD patients GV-971 group - 410 AD patients – placebo	- Sodium oligomannate GV-971, 900 mg (450 mg b.i.d.), or placebo for 36 weeks	- significant↑ in ADAS-Cog12 scores in treated vs. placebo lot at 4 weeks, sustained through the study; effect on mild/moderate AD - few cases of severe AD in the group - ns ADCS-ADL, NPI scores - adverse effects nasopharingitis and hyperlipidemia higher in GV-971 lot	- placebo unspecified; no report on persistence of effects 4 weeks post-treatment and on [^{18}F]-FDG-PET results (subset of patients)
Hsu et al., 2024 [131], RCT double-blind, active-controlled trial	- 16 AD patients in the treatment group age 75.4 ± 8.0 - 16 AD patients in the active control group, age 75.8 ± 7.3	- Mix of probiotics: *Bifidobacterium: B. longum* subsp. *infantis* BLI-02, *B. breve* Bv-889, *B. animalis* subsp. *Lactis* CP-9,*B. bifidum* VDD088, and *Lactobacillus plantarum* PL-02 in equal proportions 1:1:1:1 (Glac Biotech Co., Ltd., Taiwan) - 1 capsule daily, containing 1×10^{10} CFU for the treatment group and 5×10^{7} CFU for placebo group for 12 weeks	- ↑ serum BDNF and SOD levels - ↓ pro-inflammatory IL-1β &cortisol in therapy vs. control group - ns differences in cognition (MMSE, ADAS-Cog, ADL scores); preference for non-deterioration in probiotic lot - ↑ abundance of *Bifidobacterium*, *Ruminococcus*, *Clostridium* and *Akkermansia*, ↓ of *Megamonas* in probiotic group	- small number of patients, some on DSSM that can influence probiotic therapy results - diagnostic of AD patients not based of confirmation of Aβ and tau proteins (PET or CSF exam)

Legend:FTD-fronto-temporal dementia; MCI – mild cognitive impairment; MMSE - Mini-Mental State Examination; MoCA test –Montreal Cognitive Assessment; ADL-activities of daily living; ADAS-Cog-Alzheimer's Disease Assessment Scale-Cognitive Subscale; CIBIC + - Clinician's Interview-Based Impression of Change with Caregiver Input); ADCS-ADL- Alzeimer's Disease Cooperative Study-Activities of Daily Living; NPI-Neuropsychiatric Inventory; MDA-malondialdehide; HOMA-IR-homeostasis model for assessment estimated level of insulin resistance; HOMA-B- homeostasis model assessment for B-cell function; QUICKI- quantitative insulin sensitivity check index; TAC - total oxidant capacity; GSH – glutathione; NO- nitric oxide; TG-triglicerides; SOD-superoxid dismutase; LDLR-low density lipoprotein receptor; ↑-increase; ↓ - decrease, ns - non-significant.

cytokines, endothelial protective and antiatherogenic effects and reduction of reactive oxygen species through action at the mitochondrial level [84].

Two months of therapy with a commercial probiotic VSL 3 (Visbiome or Vivomixx) (Table 1), induced changes in microbiota, with enrichment of depleted species and reduction of species associated with dysbiosis in MS, such as *Blautia* and *Dorea*. An anti-inflammatory effect was also observed at the peripheral level – a diminished frequency of intermediate monocytes and a decrease in expression of some pro-inflammatory genes (MALT1 and LGALS3) in monocytes. Of note, immunomodulatory effects do not persist 3 months after treatment cessation [80,81].

4.3. Alzheimer's disease (AD)

Eight studies have investigated the effect of probiotics on Alzheimer's disease - five randomised trials [87,89,91,93,130], two without a control group [88,90] and one open-label case series including two AD patients, one with frontotemporal dementia and two with mild cognitive impairment [92], Table 2. Administration of probiotics (*Lactobacillus* and *Bifidobacterim* species) in combination with 200 mg Selenium/day for 12 weeks [89] in AD patients improved cognition, insulin metabolism and lipid profile (triglyceride level and VLDL-, LDL-, total-/HDL-cholesterol ratio) and up-regulated expression of LDLR (low-density lipid receptor) and PPAR-γ (peroxisome proliferator-activated receptor gamma) genes, which play a role in the regulation of metabolism and inflammation [94]. Selenium and placebo administration also improved insulin and lipid metabolism parameters, compared to placebo group, but the effect was modest compared to Se and probiotics.

In a comprehensive study on 13 AD patients given kefir-fermented milk for 90 days, Ton et al. [90] recorded marked improvement in cognitive function, reflected by improved scores on a complex battery of cognitive tests including the Mini Mental State Examination (MMSE), which assesses global cognitive status, tests of short-term memory (Immediate Memory Test and Delayed Memory Test), language (Boston Naming Test), verbal fluency, attention (Trail Making Test A), visuo-constructive skills through the clock drawing test. They also found a decrease in plasma levels of some pro-inflammatory cytokines like TNF-α, IL-8, IL12p70 and an improvement in the balance between pro- and anti-inflammatory cytokines. Consistent results were obtained following daily administration of 200 ml of milk with probiotics for 12 weeks, namely improvement of cognitive performance (MMSE score), of carbohydrate metabolism by decreasing insulin resistance (but not serum insulin), and lipid metabolism by decreasing triglyceride fraction (but not HDL, LDL, cholesterol) [91]. Levels of antioxidants such as glutathione (GSH) and NO did not change, whereas AD patients treated with a mix of *Bifidobacterium* and *Lactobacillus plantarum* strains for the same duration showed an increased superoxide dismutase (SOD) and BDNF [130]. Fecal transplantation in the form of orally administered capsules was effective even after 180 days in improving cognitive function in patients with mild cognitive impairment and in maintaining cognitive level in patients with dementia [92].

Finally, a large multicentric study on non-medicated AD patients in China [93], revealed a relatively modest, but significant improvement of the cognitive abilities (of 2 points in Alzheimer's Disease Assessment Scale–Cognitive Subscale, ADAS-Cog12) of the

Table 3
Studies investigating microbiota modulation in Parkinson's disease patients.

Study/Study design	Sample features –number, sex (m/f), age	Therapy – product used, dose, frequency, duration	Main results	Limitations
Barichella et al., 2016 [95] RCT, double-blind, placebo-controlled	- therapy group 80 PD patients (41 m, 39 f); age71.8 ± 7.7 - placebo group 40 PD patients (24m, 16 f); age 69.5 ± 10.3	- Fermented milk with prebiotics (fructooligo-saccharides) and probiotics: *Streptococcus salivarius* subsp *thermophilus, Enterococcus faecium, Lactobacillus: L. rhamnosus GG, L. acidophilus, L. plantarum, L. paracasei, L. delbrueckii* subsp *bulgaricus* and *Bifido-bacterium (breve and animalis subsp lactis*), 250 × 10^9 CFU - 125 g of fermented milk with prebiotics and probiotics, at breakfast, for 4 weeks - control group- 125 g fermented milk without prebiotics and probiotics	- Improvement of constipation by increasing the number of complete stools/week and increasing the number of stools by at least one/week in weeks # 3 and 4 in the treated group, compared to the control group	- possible influence of consumption of laxatives during the study
Becker et al., 2022 [96] Open-label clinical trial	3 groups: - 25 PD patients with dietary counselling, PD + DC (13 m, 12 f) median/age range 66/ 47-80 - 30 healthy controls treated with resitant starch Co + RS (12m, 18 f); 61.5/40-76 - 32 PD patients treated with resistant starch PD + RS, (18 m, 14f); 64.5/42–84	- Commercial dietary supplement SymbioIntest, SymbioPharm GmbH, Herborn, Germany - Oral administration of 5g prebiotic twice/day in the Co + RS and PD + RS groups, for 8 weeks	- ↓ severity of depression and non-motor symptoms (BDI and NMSQ scores), ↓ calprotectin concentration, ↑ butyrate conc. in PD + RS post- vs. pre-treatment - no changes in the number of stools.	- no examination of the therapy influence on microbiota
Borzabadi et al., 2018 [97] RCT, double-blind, placebo controlled	- placebo group 25 PD patients (16 m, 9 f); age 66.7 ± 10.7 - therapy group 25 PD patients (17 m, 8 f); age 66.9 ± 7.0	- Mixture of *Lactobacillus acidophillus, Bifidobacterium bifidum, Lactobacillus reuteri si Lactobacillus fermentum*, 2 × 10^9 CFU/g each -1 capsule/day for 12 weeks	- down-regulation of genes expression for IL-1, IL-8 and TNF-α, up-regulation of TGF-β and PPAR-γ in blood mononuclear cells in the probiotic therapy group vs. control group - n.s. differences in gene expression for VEGF, or LDLR, or in biomarkers of inflammation or oxidative stress (NO, GSH)	- no examination of the influence of the therapy on microbiota
Tamtaji et al., 2018 [98] RCT, double-blind, placebo controlled	- Control group 30 PD patients; age 66.7 ± 10.2 - Therapy group 30 PD patients; age 68.2 ± 7.8	- Mixture of *Lactobacillus acidophillus, Bifidobacterium bifidum, Lactobacillus.reuteri si Lactobacillus fermentum*, 2 × 10^9 CFU/g each - 1 capsule/day for 12 weeks	- ↓ MDS-UPDRS score, hc-CRP level, MDA, insulin level, HOMA-IR and ↑ GSH and QUICK, marginally significant ↓ in triglyceride and cholesterol levels in the probiotic group vs. control	- no examination of the influence of the therapy on microbiota
Ibrahim et al., 2020 [99] RCT, double-blind, placebo controlled	- Control gorup 28 PD patients (17 m,10 f); age 70.5 (62 –70.3) - Therapy group 27 PD patients (16 m, 9 f); age 69 (64–74) 68.2 ± 7.8	- Probiotic mixture (Hexbio®) with orange flavor containing microbial cells (MCP®BCMC®) at 30 × 10^9 UFC, 2% fructo-oligosaccharides (FOS) and lactose. Composition: *Lactobacillus: L. acidophilus* (BCMC® 12130)– 107 mg, *L. casei* (BCMC® 12313) –107 mg, *L. lactis* (BCMC® 12451)-107 mg, (BCMC® 02290) –107 mg, *Bifidobacterium: B. infantis* (BCMC® 02129) 107 mg, *B. longum* (BCMC® 02120)-107 mg. Placebo: granulated milk similar in appearance to probiotics, containing lactose without fructo-oligosaccharides or microbial cells, orange-flavored. - one sachet mixed in a glass of water twice a day, before or after meals, for 8 weeks.	- improvement of constipation by increasing the number of stools and of intestinal transit time in the therapy group compared to the control group	Lack of dietary control in terms of fiber intake, which could influence the results
Lu et al., 2021 [100] Open-label study	- 25 PD patients (17m/6 f); age 61.84 ± 5.74	- Capsule with *Lactobacillus plantarum* PS128, 30 × 10^9 UFC	- improvement of the UPDRS score for motor activities, ↑ duration of "ON" states and	- no control group, no evaluation of changes in microbiome composition

Table 3 (*continued*)

Study/Study design	Sample features –number, sex (m/f), age	Therapy – product used, dose, frequency, duration	Main results	Limitations
		- 2 capsules each night for 12 weeks	improvement of quality of life post- vs. pre-treatment	
Segal et al., 2021 [101] Series of cases	- 6 PD patients (3 m, 3 f); age 47–73	- Fecal microbiota transplant - 300 ml of fecal matter suspension from healthy donors, administered in 3 samples - 100 ml at the level of the terminal ileum, 100 ml at the level of the cecum, 100 ml in the rest of the colon, by colonoscopy	- improvement of motor and non-motor symptoms, relief of constipation 6 months after treatment, 1 patient - short-term adverse reaction	- small number of patients
Hall et al., 2023 [102] Open-label, non-randomised	- 10 PD patients medically naive (5m, 5 f); age 62.90 ± 6.89 - 10 PD patients under allopatic treatment (6 m, 4 f); age 65.70 ± 9.3	- Fiber mixture - 30% potato starch, 30% malto-dextrin (Nutrirose™), 30% rice bran, 10% inulin from agave, incorporated in a bar - 1 bar with prebiotics/day for 10 days	- Beneficial changes in microbiota, -↓ of abundance of pro-inflammatory bacteria, ↑ of those producing SCFA, changes in the functionality of some genomic pathways - ↑ total SCFA plasma concentration - improvement of the integrity of the intestinal barrier (↓ zonulin and plasma calprotectin) - ↓ of neurodegeneration (NfL↓) - ns changes in BDNF or other inflammation markers (IFNγ, IL-6, IL-8, IL-10, TNF-α, CRP) or of the inflammatory response to LPS (LPB)	- small number of patients, but comprehensive evaluation, the amplitude of the response to the treatment differs between the group with allopathic treatment and the medically naive
Tan et al., 2021 [103] RCT duble-blind	- 34 PD patients 70.9 ± 6.6 - 38 healthy controls 68.6 ± 6.7	- capsule with 10×10^9 CFU containing eight bacterial strains (*Lactobacillus: L. acidophilus, L. reuteri, L. gasseri, L. rhamnosus, Bifidobacterium: B. bifidum, B. longum, Enterococcus: E. faecalis, E faecium*); placebo-capsule with maltodextrin - 1 capsule/day for 4 weeks	- significant increase of the number of stools/week in the therapy compared to control group, amelioration of constipation and stool consistency - improvement in the quality of life	- patients can use laxatives during the intervention - short duration of treatment
Georgescu et al., 2016 [104] Clinical trial	- 40 PD patients (17m/23f) 69.8 ± 5.64	- 60 mg Probiotic/capsule *Lactobacillus acidophilus* and *Bifidobacterium infantis* - 2 capsules/day for 3 months	- diminished discomfort/ abdominal pain post-treatment	- does not mention the quantity of each bacterial strain
Hegelmaier et al., 2020 [105] Proof of concept study	- 16 PD patients (6 m, 10 f)	- Strict, balanced ovo-lacto-vegetarian diet, 3 main meals, 45% of the dishes served contained ghee with up to 30% butyric acid - Diet containing butyric acid for 14 days - 8 patients also performed 1 enema with oil, electrolytes, and a laxative, for 8 days	- ↓ UPDRS-III post-therapy (diet + enema) - a correlation was found between UPDRS and the frequency of Ruminococcaceae - > possible future intervention	- small group, the butyric acid administration was not quantified
Du Y et al., 2022 [106], RCT – placebo controlled	- 46 PD patients with constipation - 23 (69.6% m, 30.4 % f) probiotics group age (68.39 ± 7.55) - 23 controls (43.5% m, 56.5% f), age 66.65 ± 8.66	- *Bacillus licheniformis* (2.5×10^9 CFU/capsule, 2 capsules each time, three times daily), *Lactobacillus acidophilus, Bifidobacterium longum, Enterococcus faecalis* (BIFICO, 1.0×10^7 CFU per strain), 4 capsules each time, twice daily, for 12 weeks.	- ↑ number of bowel movements/week, improvement of stool quality, of symptoms and quality of life related to constipation posttreatment - changes in the microbiota composition post-compared to pre-treatment (↑ in Lachnospirales, ↓ in Prevotellaceae)	- no other clinical measures, or biochemical parameters evaluation
Cassani et al., 2011 [107] Pilot study	- 40 PD patients with constipation cf. Rome III criteria	- dietary therapy in the first week, followed by 5 weeks with ingestion of probiotics from fermented milk, with 6.5×10^9 CFU of *Lactobacillus casei* Shirota - 65 ml fermented milk/day, for 5 weeks	- ↑ number of normal stools/ week post-treatment - Reduced frequency of digestive symptoms (bloating, abdominal pain, feeling of incomplete emptying)	- small number of patients
Sun et al., 2023 [131] RCT double-blind placebo controlled	- 48 PD patients in the probiotic/Benserazide, dopamine agonists	- 2 g of Probio-M8 powder (3×10^8 CFU of *Bifidobacterium animalis* subsp. *Lactis*)/day for 3 months	- ↓ depression (HADM-17), anxiety levels (HAMA), and cognitive dys-function	

(*continued on next page*)

Table 3 (*continued*)

Study/Study design	Sample features –number, sex (m/f), age	Therapy – product used, dose, frequency, duration	Main results	Limitations
	- 34 PD patients in placebo + Benserazide, dopamine agonists		(MMSE), improved sleep (PDSS score), alleviated constipation-related symptoms (PAC-QCL score) - ↑ SCFA concentration, ↓ neuro-inflammation- related pathogens and increased SCFA-producing bacteria - changes in bacterial metabolytes spectrum - ↑ serum level of DOPA and acethic acid - improved lipid metabolism in probiotic group	
Alexoudi et al., 2023 [132] Retrospective study	- 32 medical records of patients with PD (18 f, 14 m) and chronic constipation cf. Rome III criteria - age 73.4 ± 7.34 years	- postbiotic containing supplement: butyrate triglyceride 302.86 mg, *Crocus sativus* L 30 mg and vitamin D 100 mcg administered at least 3 months - data acquired at baseline and after 3 months of treatment	- improved motor disability and quality of life, increased defecation frequency post-treatment	- the study can not distinguish the effects of the post-biotic from the effects of other supplement ingredients (vitamin D, or Saffron); small sample
Ghalandari et al., 2023 [133] Triple-blind RCT	- PD patients with constipation -14 patients probiotic lot (6 f/8m), age 68.07 ± 6.68 -13 patients placebo lot (6 f/7 m), age 68.54 ± 6.92	- Comflor® (Fara Daroo Fanavar Mehr Co) capsules containing a total of 4.5×10^{11} CFU of *Lactobacillus: L. plantarum, L. casei, L. acidophilus, L.bulgaricus, Bifidobacterium: B.infantis, B. Longum,B. breve,* and *Streptococcus thermophilus* (each genus accounting for 1.5×10^{11} CFU), 1 capsule/day for 8 weeks	- enhanced bowel movement frequency, consistency and sense of complete evacuation - ns differences in motor function	- small sample and short duration of treatment, no analysis of therapy effects in other domains evaluated with UPDRS
Yang et al., 2023 [134] RCT double-blind	- probiotic group - 65 PD patients (31m/34f),age 67.22 ± 6.46 - placebo group – 63 PD patients (42 m, 21 f); age 69.64 ± 6.41	- Fermented milk (100 ml), containing 1×10^{10} living cells of *Lacticaseibacillus paracasei* strain Shirota (LcS) or a placebo (acidified milk with no LcS) daily at breakfast for 12 weeks	- improvement in constipation & non-motor symptoms (NMSS score),in quality of life (PaC-QCL score) - ↓ depression level (HADM-17score) - ns changes in cognition (MoCA test) - changes in fecal microbiota, -↑ of Lacticaseibacillus ↓ of fecal- & ↑ of plasma L Tyrosine in the treatment group	- 11 patients terminated experiment at 10 weeks and an intention to treat analysis was done; dietary style differences between the two lots were not documented

Legend: NMSQ- Non-motor Symptoms Questionnaire; BDI- Beck depression inventory (Beck AT et al., Archives of Gen Psychiatry,1961; GHQ – General Health Questionnaire (Goldberg DP et al., Psychol Medicine, 1979); DASS- Depression Anxiety and Stress Scale (Crawford JR, Brit J of Clin Psychol. 2004); , NMSQ- Non-motor Symptoms Questionnaire; BSS-Bristol Stool Scale; MDA-malondialdehide; HOMA-IR-homeostasis model for assessment estimated level of insulin resistance; HOMA-B- homeostasis model assessment for B-cell function; QUICKI- quantitative insulin sensitivity check index; VEGF-vascular endothelial growth factor; LDLR-low density lipoprotein receptor (receptor LDL); MDS-UPDRS-Movement Disorders Society-Unified Parkinson's Disease Rating Scale; PDQ-39- Parkinson's disease Questionnaire (39 items), PGI-C- Patient Global Impression Change; HAMA-Hamilton Anxiety Scale; HADM-17 – Hamilton Depression Scale-17; PDSS – Parkinson's Disease Sleep Scale; ADL – Activities of Daily Living; PAC-QCL-Patient's Assessment of Constipation Quality of Life; NfL-neurofilament light chain; LPB- lipopolysaccharide (LPS) binding protein; SCFA-short chain fatty acids; ↑-increase; ↓ - decrease; ns - non-significant.

Table 4
Studies examining microbiota modulation in ALS patients.

Study/Study design	Sample features –number, sex (m/f), age	Therapy – product used, dose, frequency, duration	Main results	Limitations
Walk et al., 2023 [108] RCT placebo controlled	- therapy lot 14 ALS patients (4m/10f); age 60 ± 9.9 - control lot 9 ALS patients (5m, 4 f); age 56.4 ± 10	Inozine (metabolite of microbiome) -3 g inozine/day for 20 weeks	-2 patients had complications - kidney damage and nephrolithiasis; - increase in serum urate level	- no symptoms improvement

patients treated with Sodium oligomannate, a prebiotic obtained from brown algae.

4.4. Parkinson's disease (PD)

Most therapeutic interventions on the microbiota have been reported in PD, given that it is accompanied by digestive symptoms (with constipation in almost 80% of patients) and probiotics have been traditionally used in digestive disorders treatment. Digestive symptoms, including constipation, precede by many years motor symptoms. These early manifestations may be caused by neurohumoral factors, abnormal aggregation of synuclein-α which can lead to degeneration of the vagus nerve and enteric nervous system (ENS), which can further cause imbalances in the secretion and regulation of some neurotransmitters [94]. Many studies in PD to date focus on microbiota modulation in treating gastrointestinal (GI) complications (constipation, bloating, abdominal pain) and the level of quality of life in relation to these complications [95,99,103,104,106,107,131–133]. Amelioration of ENS function is expected to favorably influence neuropsychiatric symptoms, fatigue and other autonomic dysfunctions [94,110]. In fact, bacterial species that relieve constipation (e.g. *Lactobacillus acidophilus*, *Bifidobacterium lactis*) are also components of probiotic mixtures with beneficial effects on depression, on clinical picture, or on some systemic inflammatory biomarkers, Table 3.

In Parkinson's disease, there is more diversity in the therapeutic approach, both in terms of the active product administered (e.g. probiotics, prebiotics – fibres/fructo-oligosaccharides, symbiotics, postbiotics), and in route of administration (orally as capsules, drinks, bars, or rectally through fecal transplant). Most studies used mixtures of multiple bacterial species and strains; three studies used single strains in the therapeutic intervention, namely *Lactobacillus Plantarum* PS128, with beneficial effects on both motor activity and quality of life [100], *Bifidobacterium lactis* [131], or *Lacticaseibacillus paracasei* strain Shirota (LcS) [134], with beneficial effects on mental health and GI symptoms. LcS administration increased serum L-tyrosine, a precursor of neurotrasmitters dopamine and norepinephrine, which might contribute to the observed reduction in GI symptoms and mood. Of note is the effect of a prebiotic (SymbioIntest), which administered for eight weeks, reduced the severity of depression, of non-motor symptoms, as well as the concentration of calprotectin (biomarker of intestinal inflammation) and increased butyrate (postbiotic), which has a protective role in nervous tissue [96].

4.5. Motor neuron diseases

4.5.1. Amyotrophic lateral sclerosis

There were no studies identified on the effect of probiotic administration in ALS patients, although alteration of the microbiota in ALS is documented [109]. Only one study [108], examined the tolerability and safety of administering a postbiotic-inosine (which is also a metabolite of the microbiome) and its effect on serum urate levels (Table 4). Urate (salt of uric acid) is considered an important protective agent against oxidative stress, with an essential role in preventing and diminishing the manifestations of neurodegenerative diseases. In particular in ALS, increased serum urate concentration is a predictive factor for extending the life span of the patients. The administration of inosine is a way to increase serum urate. The intake of 3g inosine/day for 20 weeks however did not bring any changes in the clinical picture of the patients, despite the increased urate levels reached. Moreover, 2 patients (out of 14) experienced renal complications and nephrolithiasis.

No published articles on probiotic-based therapeutic interventions in patients with other motor neuron diseases were identified.

5. Discussion

This study reviews the results published so far related to administration of probiotics (psychobiotics), as well as pre- and postbiotics in patients with the most prevalent neurodegenerative diseases that are not caused by genetic defects. In general, human studies on this topic are few compared to animal studies. Of the 31 studies identified, about half are randomised, double-blind, placebo-controlled clinical trials and with one exception [93], involve a relatively small number of participants. This limits the detection of post-interventional changes in clinically relevant markers or parameters, as well as the generalizability of results.

The assessment of therapy effects entails a heterogeneous spectrum of outcomes and evaluation instruments, which raises some challenges in comparing the results across the studies.

A more promising intervention in terms of efficacy and durability of effects compared to probiotics appears to be the administration of certain prebiotics or postbiotics. Ingestion of butyrate (a metabolite of intestinal bacterial flora) in an ovo-lacto-vegetarian diet rich in ghee for only 14 days, accompanied by daily enema for 8 days, had beneficial clinical effects in PD patients, correlated with changes of the relative abundance in the gut microbiota [105]. Also, administration of a prebiotic bar [102] for only 10 days, induced changes in gut bacterial flora, with decreased proinflammatory- and increased SCFA-producing bacterial populations, improved gut barrier integrity and reduced neurodegeneration markers like neurofilament light chain (NfL).

The largest published study [93] to date involving nonmedicated AD patients treated with the prebiotic GV-971, a mixture of linear acidic oligosaccharides obtained from brown algae [111], reported a positive effect on cognition, (as measured with ADAS-Cog12), especially in the moderate compared to mild cases. The study does not report the sustainability of the effect though, despite mentioning an evaluation of the patients 4 weeks post-treatment, nor does it report an analysis of potential brain structural or functional changes in the subset of patients that undertook MRI and PET exams.

The experiments involve a relatively short-term treatment (4–24 weeks, with one study for 36 weeks) compared to the evolution and duration of neurodegenerative diseases and, with three exceptions [80,92,101], investigated the effects immediately after the end of therapy, without exploring their sustainability long-term. This aspect is important, as maintaining the observed beneficial effects would require long term administration of pre-/pro-/postbiotics, with studies of tolerability and possible adverse effects, as well as comprehensive assessments of effects on microbiota composition, disease-specific symptomatology, cognitive, digestive, motor and immunological functions. For example, Tankou and co-workers [80,81] observed after three months a return to the pre-treatment level of microbiota composition and fading of effects on the immune system and expression of certain genes studied. In contrast to the administration of probiotic mixtures prepared or obtained by fermentation (e.g. kefir), the fecal microbiota transplant demonstrated a persistence of beneficial effects even 6 months post-treatment [92,101].

A critical factor in the sustainability of the probiotic-based treatment effects is their capacity to correct disregulated cellular signaling through their products, including gaseous mediators like nitric oxide (NO), carbon monoxide (CO), or hydrogen sulfide (H_2S). H_2S emerged as an important neuromodulator [136,137]; it is generated in the brain and in the colon through transsulfuration pathways [138], but also by gut bacteria like *Helicobater pylori, Clostridium difficile*, certain species of *Klebsiella, Proteus, Escherichia*, opportunistic pathogens like *Prevotella, Corynebacterium_1*, and *Porfyromonas* or sulfate-reducing bacteria from the genera *Desulfvibrio, Desulfobacter,* or *Desulfobulbus* [139]. Like NO, H_2S has a hormetic effect. In normal physiologic concentrations it exerts neuroprotective effects, stimulating mitochondrial bioenergetics, whereas at high concentrations it becomes cytotoxic, by releasing cytochrome *c* protein from the mitochondrial membrane [139]. It is well documented that mitochondrial dysfunction is involved in neuronal destruction and in the pathophysiology of ND [140]. Overgrowth of H_2S producing bacteria is often detected in PD, where the elevated concentration of H_2S increases the ferrous iron levels in the cytosol, favoring excessive reactive oxygen species (ROS) production and accumulation of alfa synuclein oligomers and

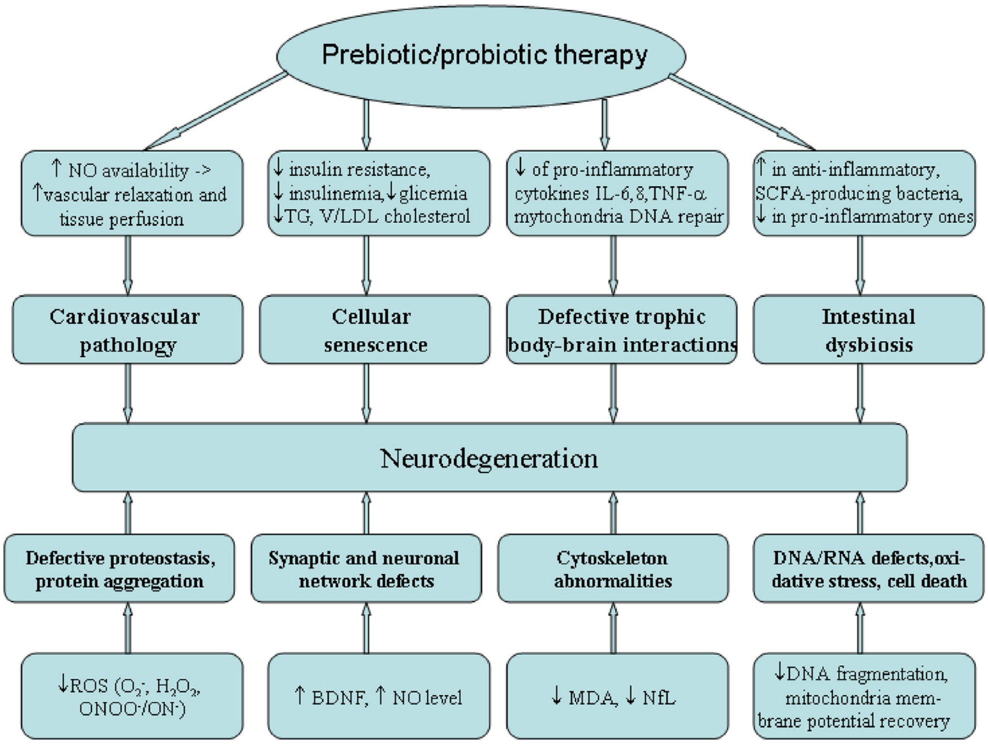

Fig. 3. Effects of intestinal microbiome modulation through pre-/probiotics therapy on the pathogenetic mechanisms of the neurodegenerative diseases [18] and on the morpho-functional alterations at the subcellular/molecular level [59]. NO-nitric oxide, TG-triglyceride, V/LDL-very /low density lipoprotein, SCFA – short chain fatty acids, IL-6-interleukin-6, TNF-α - tumor necrosis factor α, ROS- reactive oxygen species, BDNF- brain-derived neurotrophic factor, MDA –malonic dialdehyde, NfL-neurofilament light chain.

fibrils; furthermore, by affecting bacterial species like *Blautia, Fecalibacterium Prausnitzii*, or *Roseburia faecis*, it inhibits the butyrate synthesis, a key neuroprotective agent [139]. In AD, on the other hand, a reduced level of H_2S compared to normal was reported, correlated with disease severity [138]. Specific probiotic-based interventions that also target normalization of H_2S production, might improve the efficiency and sustainability of the treatment, a direction worthwhile to explore.

The reviewed studies generally use combinations of bacterial strains, mainly from *Lactobacillus, Bifidobacterium, Streptococcus, Enterococcus* species, which have been previously tested on animals, or on healthy humans, with beneficial effects observed. One study used kefir-fermented milk [90], with positive effects on preserving cognitive function and DNA in Parkinson's patients and decreasing oxidative and inflammatory stress.

5.1. *Effects of probiotics-based therapies on the pathogenetic mechanisms of ND*

Microbiome regulation through pro-/pre-/postbiotic administration has an impact on the main pathogenetic mechanisms of the NDs, Fig. 3.

a) Pathological processes at the cardiovascular level

An increased availability of NO was reported in MS [79] and in AD [90] patients. NO is a vasoactive agent that induces endothelial relaxation and regulates cerebral blood flow (CBF); it also acts as a neurotransmitter in regulating vascular smooth muscle tension and is involved in maintaining learning and memory functions. However in large concentrations NO can cause neurovascular dysfunction and becomes neurotoxic [121]. The concentration and bioavailability of NO are influenced by the interplay between nitric oxide synthase (NOS) variants: endothelial, neuronal and inducible NOS (eNOS, nNOS, and iNOS). eNOS and nNOS, produced in the vascular endothelial cells and in nervous systems cells, respectively, contribute to maintaining neurovascular unit integrity and brain homeostasis. eNOS activity decreases with age and with oxidative stress, the latter also activating iNOS leading to overproduction of NO, with deleterious cellular effects. Insights into the specific action of probiotics on NOS variants would be obtained by measuring their concentration. However, the post-treatment decrease in the level of the oxidative stress markers and increase in NO in AD patients [90], together with the improvements in cognitive functions, suggest a restauration of the eNOS activity and reduction of iNOS, which may exert positive effects on cerebrovascular endothelial cells and on nervous tissue. Some studies did not find significant differences post-treatment [87,91]. This may be due to the small sample size, to difference in disease severity, or in therapy specificity. Given the important role NO plays in the health and pathology of nervous tissue, elucidating which and how different bacterial strains and metabolites affect the balance in NOS/NO pathways could lead to potentially efficient therapies in ND.

b) Cellular senescence

Senescent cells in the central nervous system are characterized by DNA damage and disabled repair, dysfunctional mitochondria, perturbed metabolism and compromised structure and function. Moreover, they exhibit abnormal proteostasis and usually an increased secretion of pro-inflammatory cytokines like interleukin-6 (IL-6), IL-1β, IL-8, interferon gamma (IFNγ) tumor necrosis factor α (TNF-α), various extracellular proteolytic enzymes (metalloproteinases like MMP-3, MMP-10), bioactive lipids, chemokines and reactive metabolites. Perturbations in dynamic regulation of protein synthesis, folding, and degradation (proteostasis) is an

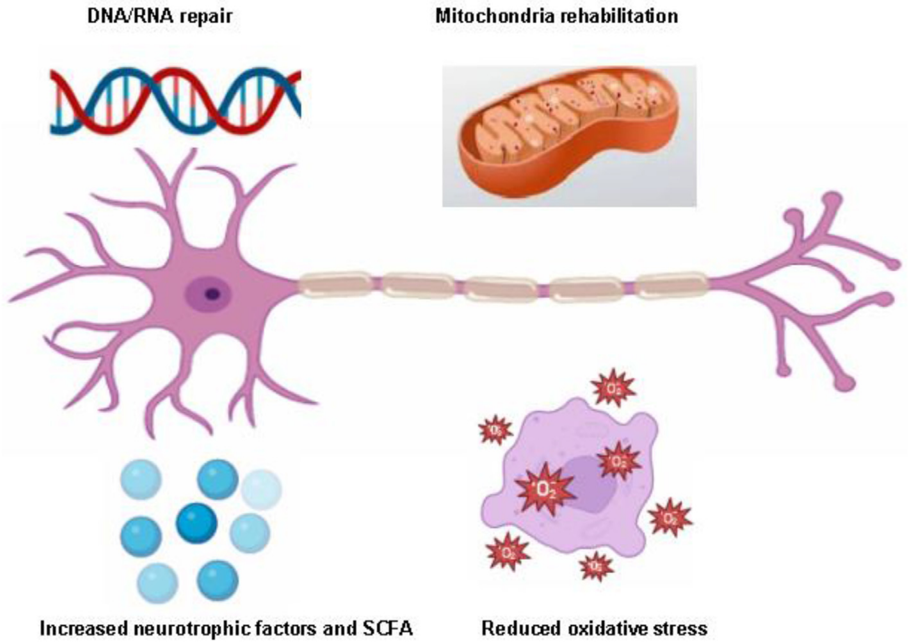

Fig. 4. Neuronal restoration effects through probiotics-based interventions.

important cause for protein aggregation (amyloid beta and neurofibrilary tangles in AD, or synuclein in PD). Probiotic-based interventions downregulated expression of inflammation-related genes or markers like hs-CRP, IL-6, IL-8, IL-1β, TNF-α and this was associated with improved mental health in MS [79,82,83], AD [89,91], and PD [96,98]. Adminstration of kefir daily for 90 days in AD [90] decreased serum levels of some reactive oxygen species (O_2^-, H_2O_2, and $ONOO^-/OH^-$) and had positive effects on cellular structural and functional integrity, inducing the recovery of compromised mitochondrial membrane potential and the decrease of apoptosis and DNA fragmentation (increase of p53 protein content with an important role in the control of cell apoptosis). These results suggest that probiotic-based interventions can inhibit pathways involved in the induction and maintenance of the senescence-associated secretory phenotype, acting as senomorphics and reducing tissues destruction [122].

c) Defective trophic body—brain interactions

Microbiome regulation through probiotic intervention also improves glucidic and lipidic metabolism, resulting in decreased glycemia and insulinemia in MS [79], improved insulin sensitivity and insulinemia in AD [89,91,98] and PD [98]. Insulin resistance reflects the incapacity of the cells to properly respond to insulin signaling, leading to reduced glucose uptake, compromised function and ultimately cell death. Chronic hyperglycemia can cause brain toxicity through neuronal lipid peroxidation, oxidative stress, inflammation, and DNA damage, leading to neuronal death through apoptosis [123]. There is an established link between diabetes and dementia, AD being called “type 3 diabetes”. Likewise, obesity induces a low grade inflammation in the body and in the brain, facilitating leucocytes infiltration through the blood—brain barrier and pervasion of adipocyte-secreted inflammatory cytokines, affecting synaptic transmission, neuronal metabolism and nervous tissue structure and function [124]. Studies exploring effects of probiotic-based therapies on lipidic profile revealed a decrease in LDL cholesterol and triglyceride levels in AD [89,91] and in PD [98] and an anti-infamatory peripheral immune response in MS [80,81]. Collectively, these results indicate that probiotic-based interventions can improve altered trophic body—brain interactions.

d) Intestinal dysbiosis

All the studies involving microbial community profiling following pro-/pre-/postbiotics therapies reported changes in gut flora. These are associated with improved anti-inflammatory peripheral immune response in MS [80,81], improved gut barrier function as reflected by decreased zonulin, and increased concentration of butyrate-producing bacteria like *Faecalibacterium prausnitzii* [125], *Ruminococcus* and *Clostridium* [135] in AD [88,130], or increase in other SCFA producing bacteria (i.e. *Lachnospirales*) and decrease in pro-inflammatory ones in PD [102,106,131]. Clearly more extensive studies are necessary to explore microbiota changes and correlation with other clinical and metabolic parameters following treatment.

5.2. Probiotic-based therapy in repairing subcellular morphofunctional alterations

Probiotic-based therapies in ND induced structure and function restoring processes at the cellular and subcellular level, Fig. 4. In MS patients [79] a decrease in concentration of serum malonic dialdehyde (MDA) was observed. MDA is considered a biomarker of the degree of peroxidation of lipids - the major constituents of cell membranes and neuronal myelin sheath [85]. Moreover, an increased level of BDNF was detected, with amelioration of depression and fatigue in MS patients [82], or with a trend towards nondeterioration in AD [130]. BDNF is an important factor in dendritogenesis, synaptogenesis and synaptic plasticity, in neuronal signaling and survival, as well as in the control and stimulation of neurogenesis [126,127]. Generally, in ND a BDNF depletion is observed and associated with pathological protein aggregation in the CNS. Therefore, BDNF is a potential biomarker and therapeutic agent in ND. Pro-/prebiotics appear to increase BDNF expression through modulation of kynurenine and SCFA metabolization pathways [128], effects that can be exploited in the development of novel ND therapeutic protocols. Prebiotics therapy for 10 days in PD patients reduced the neurofilament light chain (NfL) [102], a polypeptide that is part of the neuronal cytoskeleton and is a biomarker for neuroaxonal degeneration [129]. Together with the repairing of mitochondrial DNA damage and inhibiting apoptosis effects reported in AD, patients [90], these results show the protective and restorative effects of pro-/prebiotics on the structure and function of the neural tissue cells. A better understanding of the mechanisms of action involved, could lead to more targeted interventions to modulate pathways that are critical to neuronal survival and homeostasis.

5.3. Factors that impact the effects of probiotic-based therapies

a) Disease specific symptom modifying medication (DSMM)

A different magnitude of response was observed in the PD patients on disease-specific drug therapy compared to the non-medicated group, the latter showing a bigger reduction in the markers of neurodegeneration, like NfL [102]. This observation raises an important issue to consider, namely the interaction between microbiota, medication, and pro-/pre-/postbiotics, a less investigated issue in ND patients, but very important for treatment optimization. Many studies do not specify the medication taken by the enrolled patients, although experiments in vitro and in vivo - both in animal models and humans [112–114] show that non-antibiotic, disease specific symptom modifying medication induces changes in gut microbiome, its metabolites and related functional pathways. For instance in the studies by Tankou et al. [80,81], most MS patients were on glatiramer acetate, which has been shown to modify the microbiome (including some metabolic pathways and cellular-umoral immune response balance) compared to non-medicated patients [115]. In PD patients certain commensal bacteria species like *Enterococcus* and *Lactobacillus* can metabolize levodopa, reducing the drug availability to the brain [116,117]. AD (and other dementias) first-line treatment includes acetylcholinesterase inhibitors like galantamine, donepezil and rivastigmine, which increase the synaptic availability of acetylcholine. These drugs often have gastrointestinal side effects like loss of appetite, diarrhea, nausea, vomit, weight loss, which very likely influence gut ecology. A mouse model of AD [118] revealed that treatment with donepezil hydrochloride induced alterations in gut flora, with an increase in *Akkermansia* species.

With advanced age, often patients with ND have comorbidities (diabetes, cardiovascular disorders, autoimmune diseases, chronic pain, etc.) and take other disease-specific medications, many of which being shown to impact gut flora [114]. How various non-antibiotic drugs used in ND affect microflora and its response to pro-/pre-/postbiotics therapy is much less investigated in humans, but essential for individualized optimal treatment. To this end, multicentric studies on large cohorts and stratification analysis in examination of gut microbiota changes are needed.

b) Severity of ND

Two studies show that probiotic therapy did not improve cognitive performance in patients with advanced AD after 12 weeks of probiotic treatment [87], or after fecal microbiota transplantation [92]. However, another study reported improvement of the intestinal barrier, reflected by decreased zonulin concentration, after four weeks of probiotic therapy [88]. It might be the case that the subtle structural effects at the gut level require a longer period of time (and therapy) to sensibly influence the cognitive functions, an aspect interesting to explore. Other factors like the dose of probiotics strains used and the diagnostic tests ("Test you memory", versus MMSE, with different reliability and validity) might have contributed to the different results. A more objective evaluation should include extensive standardized clinical, cognitive, behavioral, and quality of life evaluation.

6. Conclusions, limitations, and future directions

The beneficial effects on mental health, specific symptoms and quality of life, on metabolic parameters, inflammatory and oxidative stress, and on reducing neural cells deterioration, recommend probiotic/prebiotic/symbiotic/postbiotic therapy as an important component in the treatment of ND, complementing conventional therapy. This is all the more so, as it is (based on current results) generally well tolerated and without the side effects often present in allopathic therapy. It is to be noted that a limitation of this review is that it included only articles in English and it is possible that relevant results were published in other languages.

To optimize therapeutic outcomes, however, there is a need to understand the biochemical processes/pathways that are affected by various probiotic strains and combinations, or by components of different types of pre-/postbiotics and to understand their interaction with other factors that influence microbiome (diet, lifestyle, stressors, etc.). In this respect, long term studies on large cohorts are needed, with comprehensive clinical, biochemical, genetic and neuroimaging evaluation. Brain imaging methods (e.g. nuclear magnetic resonance or positron emission tomography) [119,120] can offer relevant information on therapy-induced brain structural and functional changes by quantifying parameters such as grey/white matter volume, fractional anisotropy, cortical thicknes, metabolic maps or structural and functional connectivity. Few studies have used imaging methods in evaluating the therapeutic effect of probiotics, especially in healthy subjects, where changes in grey matter volume and functional connectivity have been observed post-intervention [e.g. 119]. These explorations would be of particular importance in neurodegenerative diseases.

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Authors' contribution

Adina Mincic - study conception, data collection, analysis and interpretation of the results, writing original draft of the manuscript; Miklos Antal, Lorena Filip and Doina Miere: writing-reviewing and editing.

Conflict of interest

The authors declare that they have no competing interests.

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