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Review article

Gut microbiota in neurodegenerative disorders

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ABSTRACT

Gut dysbiosis, a primary factor behind various gastrointestinal disorders may also augment lipopolysaccharides, pro-inflammatory cytokines, T helper cells and monocytes causing increased intestinal and BBB permeability via microbiota-gut-brain axis. Consequentially, accumulation of misfolded proteins, axonal damage and neuronal demyelination sets in, thus facilitating the pathogenesis of neurodegenerative disorders like Parkinson's disease, Alzheimer's disease, multiple sclerosis and amyotrophic lateral sclerosis. Studies revealed that intake of probiotics may help in the integrity of intestinal and BBB thus ameliorating the above neurodegenerative disorders. This review summarizes the current understanding of the role of gut microbiota in neurodegenerative disorders and possible intervention strategies.

1. Introduction

Gut microbiota refers to the symbiotic microorganisms like bacteria, archae, viruses and fungi present in human gut (Guarner and Malagelada, 2003; Quigley, 2013). These diverse groups of microorganisms play multiple roles in humans like fermenting undigested carbohydrates, producing short-chain fatty acids (SCFA), synthesizing Vitamin B and K, metabolizing essential substances (bile acids, sterols and drugs) and protecting against outside pathogens. (Quigley, 2013) Generation of microbiota in human gut is itself a unique phenomenon. At birth, the human foetal gut is sterile and devoid of any microorganism. As the child develops, the actual colonization of microbes and its diversity take place (Sekirov et al., 2010). Factors which influence the composition of microbiota are gestational age, mode of delivery, diet, level of sanitation and exposure to antibiotics (Fouhy et al., 2012; Marques et al., 2010). The two most prominent phyla of gut microbiota present in human are *Firmicutes* and *Bacteroides* (Bäckhed, 2011; Eckburg et al., 2005; Qin et al., 2010). The gut flora in human has been differentiated as, essential or beneficial flora (considered as housekeepers of gut) and opportunistic bacteria (which causes infection). *Lactobacteria* species (*L. rhamnosus*, *L. acidophilus*, *L. plantarum* etc), *Bifidobacterium* (*B. bifidum*), *Enterococci, Propionobacteria and Peptostreptococci* belongs to the first group. The second group comprises of *Bacteriodes, Bacilli, Clostridia, Enterobacteria, Actenobacteria, Peptococci, Staphylococci, Streptococci* and *Yeasts* etc. (Joshi et al., 2018). Imbalance between these two groups causes dysbiosis which leads to gastrointestinal disorders like irritable bowel syndrome, ulcerative colitis, crohn's disease, colorectal cancer and metabolic disorders (Frank et al., 2007; Guinane and Cotter, 2013; Ley et al., 2006). Gut has an intimate bidirectional relationship with the central nervous system (CNS). While, gut communicates with CNS via sympathetic and parasympathetic nervous system (termed as Gut-Brain Axis), CNS communicate via both afferent and efferent autonomic pathways (ANS) with muscle and mucosal layer of gut. Thereby brain modulates gut motility, immunity, permeability and secretion of mucus. In parallel gut also communicates with Hypothalamic–pituitary–adrenal axis (HPA axis) (Belmaker and Agam, 2008; Collins and Bercik, 2009; Forsythe et al., 2009). HPA axis can be activated in response to environmental factors, such as emotion or stress leading to the production of corticotrophin releasing hormone (CRH) from hypothalamus (Belmaker and Agam, 2008). CRH circulates through bloodstream, reaches the anterior pituitary and stimulates the release of adrenocorticotrophic hormone which leads to cortisol secretion from the adrenal glands. The cortisol acts on intestinal targets and disrupts intestinal permeability (Collins and Bercik, 2009; Forsythe et al., 2009; Forsythe et al., 2014; Stilling et al., 2014). Moreover, microbes present in gut effect the growth and regulation of the immune system and therefore may modulate the immune system CNS communication (Belkaid and Hand, 2014). Gut bacteria may also be involved in the synthesis of neuroactive molecules and metabolites which may modulate the pathogenesis of various neurodegenerative disorders like Parkinson's disease, Alzheimer's disease, multiple sclerosis and amyotrophic lateral sclerosis (Girolamo et al., 2017; Lei et al., 2016; Pryde et al., 2002; Quigley, 2017; Vital et al., 2014; Zhang and Davies, 2016).

In this review we present an outline of gut microbiota and its interaction with central nervous system. Also the role of gut microbiota in pathogenesis of various neurodegenerative disorders has been portrayed. Further, we have presented probiotics as potential therapeutic interventions against the above neurodegenerative disorders.

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1.1. Parkinson's disease (PD)

PD is a multicentric neurodegenerative disorder due to progressive alpha-synucleinopathy i.e. deposition of alpha-synuclein (α-syn) in the neuronal cell body. This results in the formation of Lewy bodies which are round lamellated eosinophilic cytoplasmic inclusions (Braak et al., 2003). It causes loss of dopaminergic neurons in the substantia nigra present in the midbrain (Dickson et al., 2009). The motor symptoms include akinesia, muscular rigidity, resting tremor, difficulty in walking and gait disorder (Braak et al., 2003). The loss of dopaminergic neurons and motor symptoms are interrelated (Dickson et al., 2009). Non-motor symptoms include dementia (Tsuang et al., 2013), depression (Parashar and Udayabanu, 2017), loss of smell (Cersosimo et al., 2013) and gastrointestinal (GI) dysfunction such as nausea, dysphagia, abnormal salivation, constipation and defecatory dysfunction (Edwards et al., 1992; Mulak and Bonaz, 2015).

Progression of PD has been frequently associated with the dysbiosis of gut microbiota. Studies have shown that imbalance in gut microbiota plays an important role in aggravating PD (Braak et al., 2006; Kieburtz and Wunderle, 2013; Savica et al., 2009; Shannon et al., 2012). One such study found lower abundance of *Prevotellaceace* species compared to relative abundance of *Enterobacteriaceae* in the stool of PD patients (Scheperjans et al., 2015). *Prevotellaceace* family members are commensals and involved in production of mucin and short chain fatty acids (SCFAs) through the fermentation of dietary fibers (Arumugam et al., 2011). Reduction in *Prevotellaceae* population leads to increase in gut permeability and systemic exposure of bacterial endotoxins which initiates or retains excessive α-syn expression in colon and even supports its misfolding (Forsyth et al., 2011; Niehaus and Lange, 2003). The relative abundance of Enterobacteriaceae has been positively related with the severity of postural instability and gait difficulty (Scheperjans et al., 2015). Increase in *Enterobacteriaceae* rises serum lipopolysaccharide (LPS) which is derived from cell wall of these gram negative bacteria (Forsyth et al., 2011). PD patients showed high levels of LPS binding protein in the blood due to high absorption of LPS (Dutta et al., 2008; Tufekci et al., 2011). LPS and other neurotoxins cross the intestinal wall enter into the blood stream and results in disruption of intestinal epithelial barrier (Guo et al., 2013). LPS in the blood stream may induce systemic inflammation by the production of inflammatory cytokines via toll like receptor (TLR) 4 and nuclear factor-kappa B (NF-κB) pathway (Guo et al., 2013; Tufekci et al., 2011). LPS and inflammatory cytokines like tumour necrosis factor (TNF-α), interleukin (IL)-1β and IL-6 disrupts blood brain barrier (BBB) and promotes α-synuclein deposition (Block et al., 2007; Chen et al., 2007; Dobbs et al., 1999; Reale et al., 2009; Sui et al., 2014). BBB breakdown has been reported to result in the destruction of dopaminegic neurons in the substantia nigra (Rite et al., 2007). Therefore relative increase of *Enterobacteriaceae* and increase in LPS has been correlated with the progression of PD (Mulak and Bonaz, 2015; Nair et al., 2018). Tight junction proteins like occludins are a necessary for the structural maintenance of intestinal barrier (Forster, 2008). Dysbiosis may decrease occludins and cause increase in intestinal permeability (Clairembault et al., 2015; Forsyth et al., 2011). (Fig. 1) Another study showed increase of pro-inflammatory cytokine producing bacteria such as *Ralstonia, Proteobacteria, Enteococcaceae* concentration in mucosa of PD patients. A decrease in the butyrate producing bacteria such as *Blautia*, *Coprococcus* and *Roseburia* and *Faecalibacterium* which are considered as anti-inflammatory, have been reported in the stool samples of PD patients. In addition significant increase in LPS biosynthesis gene was reported in the PD fecal microbiome (Keshavazian et al., 2015). Excessive bacterial growth in small intestine termed as small intestinal bacterial overgrowth (SIBO), has been associated with motor impairment and PD (Fasano et al., 2013; Tan et al., 2014). *Helicobacter pylori* infection has also been considered as a triggering factor in PD pathogenesis (Çamcı and Oğuz, 2016).

According to FAO/WHO Probiotics are defined as "Live microorganisms which, when administered/ingested in adequate amounts, confer a health benefit to the host." Probiotics containing *bifidobacteria* and *lactobacilli* has been reported to reverse PD like condition (Pompei et al., 2007). The regular intake of fermented milk beverage containing the probiotic *Lactobacillus casei shirota* have been shown to improve the bowel movement by decreasing the number of fecal *staphylococci* in PD patients (Cassani et al., 2011). Probiotic bacterium *Bacillus* spp. may convert L-tyrosine to L-DOPA which is converted to dopamine in the presence of DOPA decarboxylase (Surwase and Jadhav, 2011).

1.2. Alzheimer's disease (AD)

AD is a neurodegenerative disorder leading to progressive cognitive dysfunction. It is accompanied by the cerebral accumulation of misfolded amyloid-β peptide in senile plaques, a cleavage product of the amyloid-β precursor protein (AβPP) (Alzheimer's Disease Fact Sheet National Institute on Aging and U.S. Department of Health and Human Services, 2013). It is also associated with tau hyperphosphorylation formation of neurofibrillary tangles and loss of cholinergic neurons (Hu et al., 2016; Jiang et al., 2017).

Gut dysbiosis which has been associated with increased gut permeability and inflammation may also results in an increase in circulating levels of microbes like *spirochaete*, *Herpes simplex* virus type 1 (HSV-1), *Chlamydia pneumoniae* and also gut micobiota derived products like β-*N*-methylamino-L-alanine (BMAA), LPS and microbial amyloids (Heneka et al., 2015; Itzhaki et al., 2016; Ransohoff, 2016). BMAA is one of the neurotoxin produced by gut cyanobacteria (Brenner, 2013) which causes neurodegeneration, cognitive impairment, astrogliosis and accumulation of neurofibrillary tangles in adult rats after neonatal exposure (Karlsson et al., 2011). LPS induces the formation of Aβ fibrils (Asti and Gioglio, 2014) which is a potent inducer of NF-κB, known to be involved in neuroinflammation in the AD brain (Lukiw, 2016). Microglia contain Toll-like receptor (TLR) 4 with LPS as its ligand (Lien et al., 2000). TLR4 function depends on the co-receptor CD 14. Abundance of CD 14 has been reported in microglia of AD brain (Doens and Fernández, 2014) (The role of TLR4 and CD14 in AD has been discussed in further details by Liu et al., 2005). Gut microbiota derived amyloid may enhance inflammation in response to cerebral $A\beta_{42}$ by acting upon innate immune system (Friedland, 2015). Moreover aging also causes overstimulation of innate and adaptive immune systems resulting into low-grade, chronic state of inflammation termed as inflammaging (For further details please refer Franceschi et al., 2000; Franceschi, 2007). Inflammaging increases gut and BBB permeability which influences the production of Aβ in the brain (Elahy et al., 2015; Pistollato et al., 2016; Ulluwishewa et al., 2011; Zhao et al., 2015). Gut microbes, micobiota derived products and inflammatory mediators reach brain, trigger neuroinflammation and also enhance the amyloid accumulation. Relative abundance of *proteobacteria* and decrease in butyrate producing bacteria may result in high level of plasma pro-inflammatory cytokines like IL-6 and IL-8 (Biagi et al., 2010). A study showed an increase in concentration of *Escherischia/ shigella* spp. which are characterized as pro-inflammatory and decrease in concentration of *Eubacterium rectal*e spp., characterized as anti-inflammatory, in fecal microbiome of AD patients. This dysbiosis may also increase brain amyloid deposition along with peripheral inflammation (Cattaneo et al., 2017). (Fig. 1).

Various animal studies have been carried out to define the role of probiotics on cognitive behavior. Treatment with the combination of probiotics *Lactobacillus rhamnosus* (R0011) and *Lactobacillus helventicus* (R0052) restored the stress-induced memory impairment by dysbiosis caused by *Citrobacter rodentium* infection in mice (Gareau et al., 2011). Another study showed learning and memory improvement in anxious mice by the administration of *Bifidobacterium longum* 1714 (Savignac et al., 2015). A probiotic strain *Lactobacillus fermentum* NS9 improved spatial memory impairment caused by ampicillin associated dysbiosis

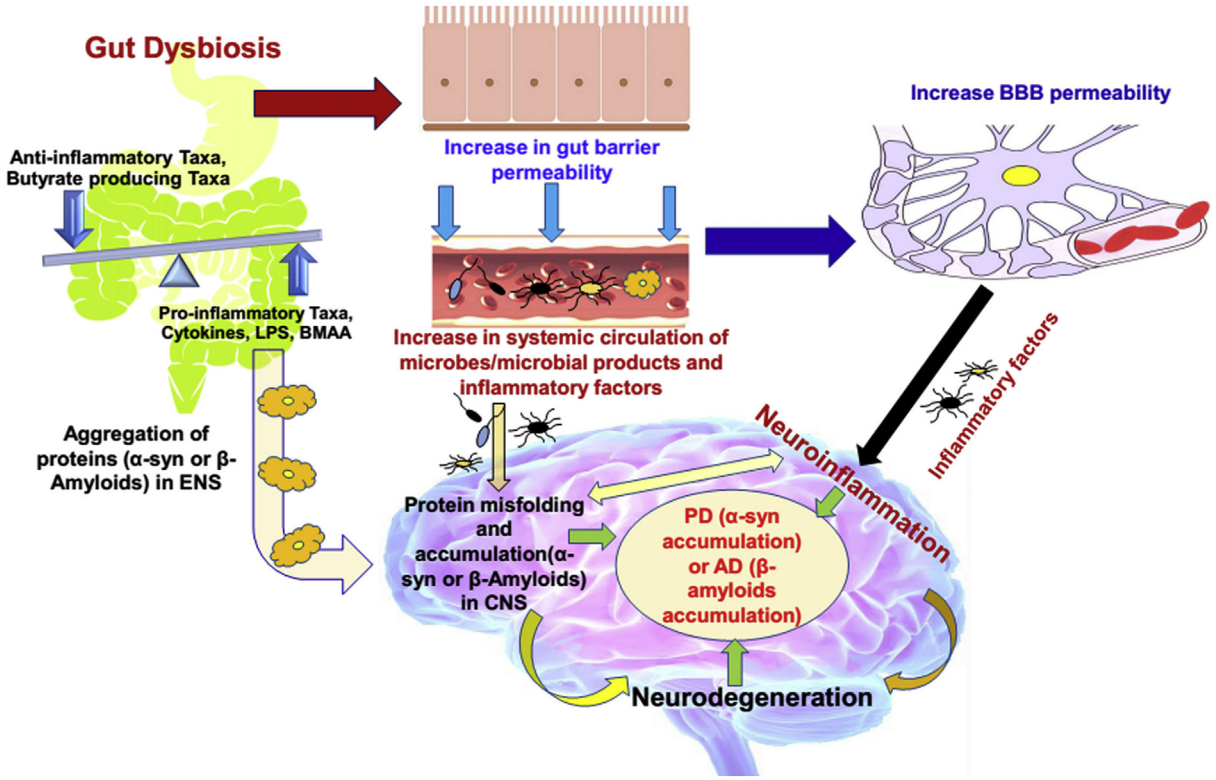

Fig. 1. Gut dysbiosis leading to the pathogenesis of PD and AD.
Imbalance ingroup of micro-organism producing anti-inflammatory cytokines (Anti-inflammatory Taxa) and micro-organisms producing pro-inflammatory cytokines (Pro-inflammatory Taxa) in gut termed as Gut dysbiosis. Gut dysbiosis generates pro-inflammatory cytokines, LPS and BMAA which in turn leads to disruption of gut permeability and increases systemic circulation of microbes, microbial products, and inflammatory factors. The inflammatory factors disrupt BBB and cause neuroinflammation and neurodegeneration. In addition, aggregation of proteins such as α-syn or β-amyloids in ENS is enhanced due to gut dysbiosis. This results in the accumulation of proteins in CNS which further results neuroinflammation and neurodegeneration. Also, the microbes and microbial products present in systemic circulation enhance accumulation of proteins in CNS. Accumulation of α-syn in CNS causes PD and accumulation of β-amyloids in CNS causes AD.
LPS- Lipopolysaccharide, BMAA- β-N-methylamino-L-alanine, α-Syn-α-Synuclein, BBB-Blood Brain Barrier, ENS-Enteric Nervous System, CNS- Central Nervous System.

(Wang et al., 2015a). One more study reported the improvement of spatial memory due to chronic restraint stress by restoring BDNF levels in hippocampus by the treatment of *Lactobacillus helventicus* NS8 (Liang et al., 2015). VSL#3 restored neurogenesis and increased the Ly6Chi monocyte proportions in the brain, resulting in improved cognition (Möhle et al., 2016). A randomized, double blind controlled clinical trial reported positive effect of *Lactobacillus acidophilus*, *Lactobacillus casei*, *Lactobacillus bifidum*, *Lactobacillus fermentum* probiotic combination on cognitive function in AD patients (Akbari et al., 2016). The administration of *Bifidobacterium* species results in abundance of *Bifidobacterium* in the gut microbiota of elderly leading to lower serum levels of pro-inflammatory cytokines TNF-α, IL-5, IL-6, IL-1β and IL-8 (Ouwehand et al., 2008; Wang et al., 2015b).

1.3. Multiple sclerosis (MS)

MS is an immune mediated chronic neurological disorder. The neuropathological hallmarks of MS are demyelination, axonal damage and neurodegeneration. The clinical manifestations include vertigo, vision loss, dizziness, pain, motor dysfunction, impaired coordination, fatigue, numbness, bladder and bowel dysfunction, depression and cognitive impairment. MS is primarily divided into i) Progressive-relapsing MS (PRMS), ii) Primary Progressive MS (PPMS), iii) Secondary Progressive MS (SPMS), iv) Relapsing-Remitting MS (RRMS) (Noseworthy et al., 2000). The pathogenesis of MS depends upon various genetic and environmental factors (Compston and Coles, 2008).

Gut dysbiosis is considered to be an important environmental factor responsible for the neuropathogenesis of MS (Bhargava and Mowry, 2014; Compston and Coles, 2008; Mowry and Glenn, 2018). RRMS is characterized by decrease in bacteria responsible for producing anti-inflammatory responses by immune cells like T regulatory cells (T_{regs}), $CD4^+$ T cells which produces IL-10, regulatory B cells, tolerogenic dendritic cells and suppressive macrophages and abundance of bacteria responsible for pro-inflammatory reactions produced by $CD4^+$ T cells dendritic cells, monocytes or B cells (Shahi et al., 2017) (For details in inflammatory and regulatory cells please refer Chung and Kasper, 2010). The presence of *Clostridium, Bacteroidetes,* (Ríos-Covián et al., 2016) *Prevotella, Parabacteroides* and *Lactobacillus* in gut microbiota can induce production of SCFAs (El Kaoutari et al., 2013; Sivieri et al., 2013) and helps in the maintenance of immune cells which produces anti-inflammatory response (Freedman et al., 2018; Shahi et al., 2017). In RRMS patients, decreased abundance of *Parabacteriodes distasonis* (Cekanaviciute et al., 2016) and *Prevotella copri* (Miyake et al., 2015) were reported when compared with healthy controls. Within *Firmicutes* spp., concentration of *Dorea* and *Blautia* were increased (Chen et al., 2016) and in few studies depletion of *Clostridium* (Miyake et al., 2015) and *Faecalibacterium* (Cantarel et al., 2015) were observed. However, increased colonization of *Firmicutes* has been reported in pediatric MS patients (Tremlett et al., 2016). Another study reported decrease in relative abundance of *Faecalibacterium* in fecal samples of MS patients (Mowry et al., 2012). *Faecalibacterium* is an important butyrate producing bacteria while butyrate production may increase T_{regs} (Arpaia et al., 2013). The human gut colonization by *Clostridium perfringens* type B has been reported in MS patients (Rumah et al., 2013) resulting in increased levels of epsilon toxin (Mete et al., 2013). This toxin degrades BBB, leading to neuronal and oligodendrocyte damage and triggers

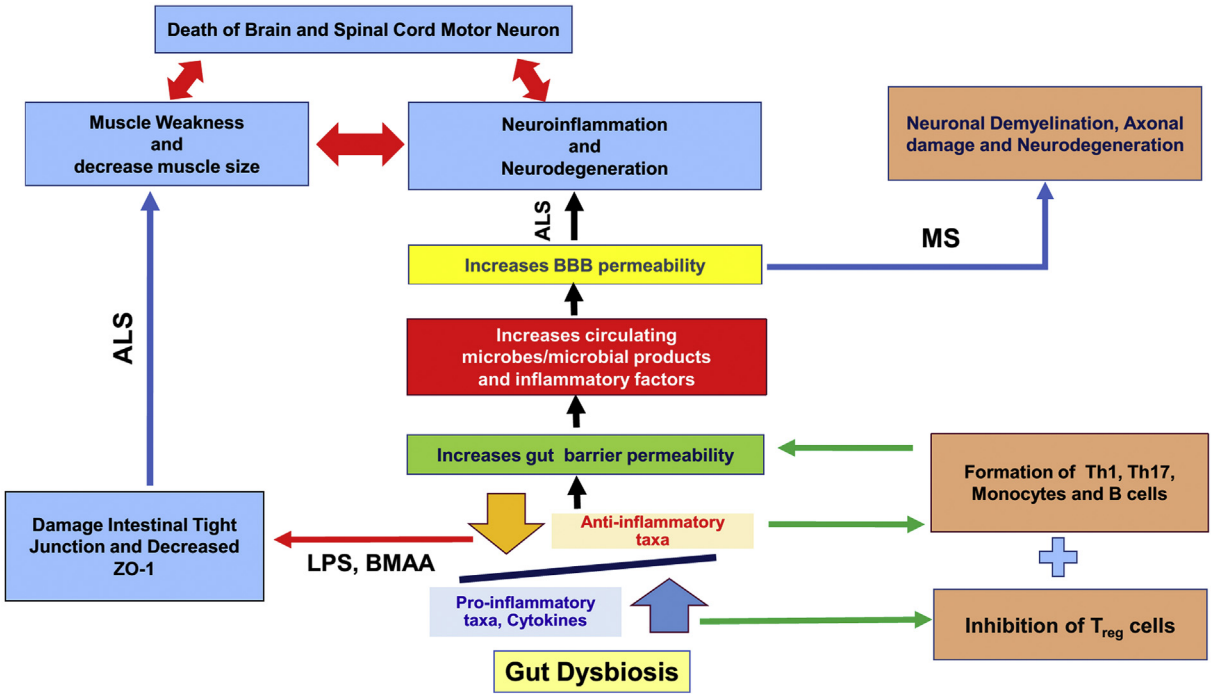

Fig. 2. Gut dysbiosis leading to the pathogenesis of MS and ALS.
In ALS, the pro-inflammatory cytokines produced during dysbiosis leads to disruption of gut permeability and increases systemic circulation of microbes, microbial products, and inflammatory factors. The inflammatory factors disrupt BBB and cause neuroinflammation and neurodegeneration. The dysbiosis product, LPS and BMAA damage intestinal tight junction and junction protein (ZO-1) leads to muscle weakness and decrease muscle size which resultant neuroinflammation, neurodegeneration, and death of brain and spinal cord motor neuron. While in MS, dysbiosis generates Th1, Th17, Monocytes and B cells, and inhibition of T_{reg} cells. These factors disrupt gut permeability and increase systemic circulation of microbes, microbial products, and inflammatory factors. The inflammatory factors disrupt BBB barrier and cause neuronal demyelination, axonal damage, and neurodegeneration.
T_{reg}- T regulatory cells, LPS- Lipopolysaccharide, BMAA-β-N-methylamino-L-alanine, ZO- ZonulaOccludens, Th1- T helper cells, BBB-Blood Brain Barrier, ENS-Enteric Nervous System.

autoimmune demyelinating events (Dorca-Arévalo et al., 2008; Finnie et al., 1999; Lonchamp et al., 2010). Few species of *Dorea* may stimulate IFNγ (Schirmer et al., 2016), metabolize sialic acids and degrade mucin (Hughes et al., 2003). *Dorea* produces gases which are used by *Blautia* resulting in an increased abundance of *Blautia*. (Schirmer et al., 2016) Increased abundance of *Akkermansia* has been reported among MS patients. *Akkermansia mucinphila. Blautia* may degrade mucin and enhance the production of pro-inflammatory cytokines (Cekanaviciute et al., 2016; Jangi et al., 2016). A study reported decreased concentration of *Adlercreutzia equolifaciens* and *Collinsella* (Chen et al., 2016) whereas another study reported decrease in the concentrations of *Collinsella* and *Slackia* but no change in *Adlercreutzia equolifaciens* in MS patients (Jangi et al., 2016). Higher abundance of Proteobacteria species like *Mycoplana*, *Pseudomonas*, (Chen et al., 2016) *Bilophila* (Miyake et al., 2015), *Acinetobacter calcoaceticus* (Cekanaviciute et al., 2016) and lower abundance of *Sutterella (Proteobacteria)* were also observed in MS (Jangi et al., 2016). *Acinetobacter calcoaceticus* can stimulate pro-inflammatory Th1 cytokines and depress regulatory CD4 T cells thereby aggravating MS (Cekanaviciute et al., 2016) (Fig. 2).

Different probiotics have been tested in Experimental Autoimmune Encephalomyelitis (EAE) animal model of MS. Oral administration of *Bifidobacterium animalis* to these animals may reduce in EAE symptoms (Ezendam et al., 2008). Lactobacillus species enhanced regulatory T cells, producing increased IL-10 and decreased IL-17 and improved EAE clinical score in these animals (Lavasani et al., 2010; Maassen and Claassen, 2008; Takata et al., 2011). Regular oral administration of various combinations of probiotic like *Streptococcus thermophiles*, *Bifidobacterium bifidum and Lactobacillus* spp. in both mouse and rat models may improve EAE clinical score, reduce Th1 and Th17 cells along with enhancement of T_{regs} (Kwon et al., 2013).

1.4. Amyotrophic lateral sclerosis (ALS)

ALS is a progressive neurodegenerative disorder pertaining to death of brain, spinal cord and motor neuron. The symptoms include muscle weakness, cramping, problems with coordination, stiff muscles, muscle spasms and muscle twitching. This gradually leads to difficulty in speaking, swallowing and breathing. There are two types of ALS: i) Sporadic ALS, which is the most common form with unknown aetiology and ii) Familial ALS, which is caused by changes to gene (Toepfer et al., 1997).

ALS mouse model which is a G93A SOD1 (superoxide dismutase) transgenic mice are used to study the role of gut microbiota in the disease. The course of ALS in an animal model can be divided into three stages: a) pre-onset- 60 to 70 days, b) onset- 90 to 100 days and c) progressive- 120-130 days (Zhou et al., 2015). During the pre-onset stage the transgenic mice show increased gut permeability and disrupted BBB. Damaged intestinal wall due to decreased zonula occludens (ZO)-1 and E-cadherin has been reported. The SOD1G93A mice feces showed reduced levels of butyrate-producing bacteria like *Butyrivibrio fibrosolvens* and *peptostreptococcus* resulting in elevated level of serum and intestinal pro-inflammatory cytokine IL-17 (Fang, 2015; Wu et al., 2015). Another study reported the delay in ALS progression by administration of 2% Butyrate in drinking water to SOD1 transgenic mice. This may be due to the improvement of intestinal barrier function by relative abundance of *B. fibrosolvens* (Zhang et al., 2017). ALS patients' feces have reduced levels of butyrate producing bacteria like *Oscillibacter*, *Anaerostipes*, and *Lachnospira* and enhanced levels of different species of *Dorea*. *Dorea* may synthesize ethanol as an end product of glucose metabolism and thus considered harmful (Fang et al., 2016). Alterations of LPS and BMAA in plasma levels of ALS individuals have also been reported. These molecules if present in circulation may reach

CNS and contribute to the pathogenesis of ALS through neuroinflammation and deterioration of the BBB function (Bengmark, 2013; Catanzaro et al., 2015; Wright et al., 2018). While, BBB disruption is common in both human and animals with ALS (Garbuzova-Davis and Sanberg, 2014) (Fig. 2). The therapeutic role of probiotics in the improvement of ALS like conditions is yet to be explored.

2. Conclusion

The human intestinal tract contain a huge, active and complex community of micro-organism. The intestinal microbiota plays a vital role in the digestion of food, immunopotentiation, stimulation of development of microvilli, fermentation of dietary fibers and prevention of colonization of the gastrointestinal tract by harmful pathogens. Various observational and animal studies suggest that gut microbiota play a significant role in neuropathogenesis of CNS disorders by altering in Gut-Brain-Axis function. Dysbiosis may increase inflammatory cytokines and bacterial metabolites which may alter the gut and BBB permeability and cause neuroinflammation. This may facilitate the pathogenesis of various neurodegenerative disorders like PD, AD, MS and ALS. Probiotics, by preventing gut dysbiosis may provide protection from the above neurodegenerative disorders.

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