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## Interplay of gut microbiota and oxidative stress

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## GRAPHICAL ABSTRACT

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- The diagram illustrates the bidirectional relationship between the gut microbiota and the brain, showing how dysregulation in the gut can lead to brain dysfunction and vice versa.
- Dysregulated Gut Microbiota (Left Side):**
- Stress** leads to a **Western diet/HFD**, which causes **Leaky Gut** and **Obesity**.
  - LPS** (lipopolysaccharides) from **Bacteroides**, **Proteobacteria**, and **Bacterium amylophilus** are present in the gut.
  - Intestinal microbiota dysregulation** and **Gut inflammation that permeabilizes** the gut.
  - Microbiota gut-brain communication** occurs via **Neuroinflammation (Microglia)** and **Neurotransmitters (Serotonin, Dopamine, Norepinephrine, GABA)**.
  - The brain is in a state of **Dysregulated CNS**, showing **Genetics**, **Anxiety**, **Depression**, and **Immune signaling (light, sleep, eating, drinking, circadian rhythms, CNS barriers)**.
  - This leads to **Altered CNS signaling** and **Peripheral oxidative stress**.
- Healthy Gut Microbiota (Right Side):**
- A **Healthy diet** leads to **Probiotics** and **Prebiotics**, which maintain a **Healthy gut**.
  - Neurochemical production** is enhanced, including **Neuroinflammation** (decreased), **Neurogenesis** (increased), **BDNF integrity** (increased), and **Myelination** (increased).
  - High diversity of beneficial commensal microorganisms** is present, including **Bifidobacterium spp.**, **Lactobacillus spp.**, **Polyphenolic metabolites**, **Flavonoids**, **Neurotransmitters**, and **Oleic acids**.
  - Microbiota gut-brain communication** is shown as a central hub connecting the gut and brain states.

## ABSTRACT

**Key Scientific Concepts of Review:** This review is focused on three main key concepts. Firstly, the mounting evidences from clinical and preclinical arenas shows the influence of gut microbiota mediated oxidative

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stress resulting in dysfunctional neurological processes. Therefore, we describe the potential role of gut microbiota influencing the vulnerability of brain to oxidative stress, and a budding causative in Alzheimer's and Parkinson's disease. Secondly, contributing roles of gut microbiota has been observed in attenuating oxidative stress and inflammation via its own metabolites or by producing secondary metabolites and, also modulation in gut microbiota population with antioxidative and anti-inflammatory probiotics have shown promising neuro resilience. Thirdly, high throughput *in silico* tools and databases also gives a correlation of gut microbiome, their metabolites and brain health, thus providing fascinating perspective and promising new avenues for therapeutic options.

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## Introduction

Enteric nervous system (ENS), also known as the second brain of the body acts as a key link in understanding the bidirectional communication between the gastrointestinal (GI) tract and the central nervous system (CNS) [1]. Enteric neurons communicate with the CNS via neuronal (vagus nerve), endocrine, and immune pathways, which are involved in maintaining gut health [2]. However, the modulating factor which can regulate this communication is gut microbiota. Among the gut microbial population (fungi, archaea, virus, bacteria and parasites), particularly gut bacteria constitute equal number to that of human cells in the body [3] and interestingly possess a metabolic potential equivalent to that of human liver [4]. Continuous research in this area shows the immense importance of gut microbiota not only in the functioning of the immune system [5] and regulatory metabolism [6] but even in the development of various organs [7]. Variable environmental factors such as diet [8], drugs [9] and host factors including age and genetics [10] not only alter the composition of gut microbiota but also can cause the change in signaling activity of them. Also, Immunoglobulin A (IgA), which is the most abundant antibody secreted at mucosal surface, coats the commensal bacteria in the gut and maintains diverse and stable gut microbiota community [11,12]. Even, gut microbiota is known to influence the serum protein zonulin, which is required to regulate intestinal and vascular endothelium (blood-brain barrier) tight junctions [13]. Changes in gut microbiota directly affect zonulin pathway resulting in leaky gut [13]. Moreover, gut microbiota is one of the contributing factors controlling gut peristalsis [14]. Among the endocrine factors, elevated levels of cortisol has been observed as contributing factors in gut dysbiosis and is considered a cause of stress and depression [15]. Thus, gut microbiota directly influences human health by sensing, modulating and circulating a vast number of chemical signals coming from the environment.

The relationship between intestinal bacteria and neurological diseases was first hypothesized by Elie Metchnikoff and colleagues in 1900s, which has now been recognized by many research groups. Neurodegenerative diseases (NDDs) were first believed to be caused by defects in the nervous system neglecting the facts that microorganisms in the gut possess the ability to produce and modify various immune, metabolic and neurochemical factors which are known to directly affect the nervous system [16]. NDDs are mainly caused by oxidative damage, increased reactive oxygen species (ROS) production, neuroinflammation and disruptive energy metabolism, which on the other hand also affects the gut microbial population [17]. Surprisingly, gut microbial composition alters with the changes in the metabolism of the body from healthy to diseased state [18,19]. This shows the intersection of gut microbiota between the host and the environment, and its morbid association with various neurological and psychological disorders. Gut dysbiosis and neuroinflammation are consistent factors in the pathophysiology of various neurological disorders. In this review, we emphasized showcasing the role gut microbiota-mediated

oxidative stress in neurodegeneration, including the explanation of mechanisms of ROS production, why the brain is more susceptible to oxidative stress and how gut microbial metabolites influence the oxidative stress-induced damage in the brain with a focus on Alzheimer's disease (AD), Parkinson's disease (PD) and Traumatic brain injury (TBI).

Despite the role of gut microbiota in the pathology of NDDs, unsurprisingly, gut microbiota also has the potential to protect the brain from damage either by releasing the metabolites generated by them from converting dietary fibers, polyphenols or host molecules like bile acids and steroid hormones or their composition in the gut can be modulated by prebiotics in order to promote neuro resilience [20]. Neuroprotective role of gut microbiota is well documented in recent studies, it was observed that *Lactobacillus buchneri* KU200793 isolated from Korean fermented food showed higher antioxidant activity and was able to protect the SH-SY5Y cells from 1-methyl-4-phenylpyridinium (MPP<sup>+</sup>), suggesting its probiotic and neuroprotective effects [21]. Similarly, it was reported that exopolysaccharides isolated from *Lactobacillus delbrueckii* ssp. *bulgaricus* B3 and *Lactobacillus plantarum* GD2 protected SH-SY5Y cells from Aβ(1–42)-induced apoptosis [22], which potentiates their role as a promising natural chemical constituent for the pharmacological therapy of AD. Moreover, treatment of SH-SY5Y and mouse model with heat-killed strain of *Rummicoccus albus* showed the neuroprotective effects, it was found to be very effective in reducing ROS levels and increasing superoxide dismutase (SOD) and glutathione (GSH) levels in hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) treated SH-SY5Y cells and in sodium arsenate treated animal models [23]. Likewise, anti-Alzheimer's actions of *Lactobacillus plantarum* MTCC1325 have been studied in Albino rats with AD induced by D-Galactose (D-Gal) [24]. It has been shown that the *L. plantarum* protects against memory defect in D-Gal and scopolamine-induced AD in mice [25]. Taken together, these studies reflect the promising role of gut microbiota, their antioxidative and subsequently, their neuroprotective roles. Based on these foundational discoveries, we describe the role of gut microbiota, their metabolites, along with anti-inflammatory and antioxidative probiotics in neuroprotection. Also, we have gathered information about the databases and *in silico* strategies utilized to study gut-brain interactions. Altogether, this review will give a deep insight into the dual role of gut microbiota in oxidative stress-induced neurodegeneration and gut microbial metabolites-mediated antioxidative mechanism-based neuroprotection.

## ROS and oxidative stress

Oxidative stress corresponds to the disruption of redox signaling pathway in cells due to an increase of ROS level more than that of antioxidant levels. This state of imbalance results in deleterious effects and is a leading cause of many neurological diseases. Every chemical reaction involved in aerobic metabolism results in the

formation of reactive intermediate products which are unstable and short-lived, known as ROS [26,27].

Biomolecular oxygen ( $O_2$ ) possesses two unpaired electrons which cannot be reduced completely, thus its incomplete reduction results in the formation of highly electrophilic and short-lived ROS like  $H_2O_2$ , superoxide anion, nitric oxide, peroxynitrite anion, hydroxyl and peroxy radicals [28]. Either ROS is generated as an intermediate in normal cellular processes via ROS generating enzymes or in the presence of exogenous factors like drugs, toxins, and radiations [29]. Neuronal tissues due to their high metabolic rate produces a large amount of ROS in comparison to the other organs. Mitochondria is considered as the main cellular site of ROS generation in brain, where during the process of ATP generation (mitochondrial oxidative phosphorylation), anion superoxide is generated as a byproduct, which is then rapidly transformed into  $H_2O_2$  and  $O_2$  by SOD [30]. The greater the amount of  $O_2$ , the greater is the formation of superoxide, which further results in more ROS like  $H_2O_2$  and hydroxyl radicals due to the addition of electrons from leaky electron transport chain (ETC) (complex I and III) [31]. Mitochondrial ROS production also indicates neuronal activity, as intense synaptic transmission boosts superoxide production [32]. Though on one hand mitochondrial ROS can be regulated by intracellular calcium ( $Ca^{2+}$ ) levels [33], moreover, increased mitochondrial ROS production is also associated with the increased mitochondrial membrane potential. Besides inner mitochondrial membrane, mitochondrial matrix enzyme, aconitase also contributes to ROS production by transforming  $H_2O_2$  into hydroxyl radicals facilitated by iron-sulphur cluster in Fenton reaction. Many other enzymes like external NADH dehydrogenase, proline dehydrogenase, dihydroorotate dehydrogenase, and complex IV, also have been reported as contributors in mitochondrial ROS production [34].

Besides inner mitochondrial membrane, monoamine oxidases (MAO) present in outer mitochondrial membrane, present in most of the cell types including neurons and is among the primary source of ROS. MAO catalyzes the oxidative deamination of monoamines, requiring cofactor FAD (flavin adenine dinucleotide), by utilizing molecular  $O_2$  to remove an amine group from the molecule, where  $H_2O_2$  is produced as a byproduct of the reaction [35]. The two isoforms of MAO, namely MAO-A and MAO-B have been known to regulate the redox state of glia and neuronal cells. MAO-A is mainly found in the catecholaminergic neurons and is involved in oxidation of noradrenaline and serotonin, whereas MAO-B is particularly expressed in serotonergic neurons and glial cells and oxidizes  $\beta$ -phenylethylamine [36]. Thirdly, an isoform of nitric oxide synthase (NOS) nNOS present in neurons is also one of the sources of ROS in brain, which is regulated by  $Ca^{2+}$  binding protein calmodulin. NOS catalyzes the oxidation of L-arginine to L-citrulline, producing nitric oxide (NO), utilizing NADPH, tetrahydrobiopterin and  $O_2$  as a cofactor [37]. Though on one hand NO acts as a critical signaling molecule which regulates synaptic transmission, but is also capable of interfering the redox homeostasis by interacting with superoxides to form highly reactive peroxynitrite compounds, which are directly involved in causing nitrosative stress in cells and is associated with apoptotic and necrotic cell death at low concentration and high concentrations, respectively [37].

Besides other enzymes, one of the major endogenous sources of ROS in brain during physiological conditions includes NADPH oxidases (NOX) which catalyze the oxidation of NADPH producing superoxide as its main product. Though, NOX are found to be primarily located in plasma membrane and phagosomes of polymorphonuclear neutrophils, previous immunohistology assessments of mouse and rat tissues showed its abundance in cortex and hippocampus regions of brain [38,39].  $Ca^{2+}$  acts as a prime activator of NOX, leading to the post synaptic localization of the enzyme complex in neurons, thus showing the involvement of NOX in neuronal activity [40]. Seven paralogs of NOX have been

reported, namely NOX (1-5), dual oxidase DUOX (1 and 2), which differ in their size and domain structure but are mainly involved in ROS generation. The proteins get activated, undergo maturation, stabilization and translocation across the membrane on interaction with the other proteins, like NOX (1-3) gets activated by interacting with p22 (phox) transmembrane protein along with G-protein Rac. Similarly, NOX-4 gets activated by interacting with only p22 (phox) transmembrane protein, whereas NOX-5 and DUOX (1 and 2) gets activated by direct binding to  $Ca^{2+}$ . Upon activation NOX (1-3) and NOX-5 mainly catalyzes the production of superoxide and NOX-4, DUOX (1 and 2) are involved in the direct production of  $H_2O_2$  [41]. NOX paralogs are found to be widely distributed in cortex, hippocampus and cerebellum in brain, most prominently NOX-2, NOX-3 and NOX-4. Previous reports also revealed the synergistic relation between mitochondrial ROS and NOX-ROS, thus supporting each other's ROS generation [42]. To date, studies reveal a pivotal role of NOX in mediating the progression of chronic CNS diseases like AD, PD, amyotrophic lateral sclerosis (ALS) and huntington's disease (HD) [41]. Thus, development of isoform selective NOX inhibitor can be a promising therapeutic approach for the treatment of acute and chronic CNS disorders.

Within the cytoplasm, non-heme iron enzymes such as lipoxygenases catalyze the peroxidation of arachidonic acid in the presence of molecular  $O_2$  and generate superoxide and hydroxyl radicals [43]. Many other enzymes in the cytoplasm like xanthine oxidase, cytochrome P450 monooxygenase, cyclooxygenase, D-amino oxidase are also important ROS producers [44]. In concert with mitochondria, organelles like peroxisomes are also the site of ROS production, where beta-oxidation of fatty acids catalyzed by glycolate oxidase and xanthine oxidase results in superoxide and  $H_2O_2$  [27]. Also, increased ROS production occurs in endoplasmic reticulum due to unfolded protein response (UPR) [45].

Oxidative stress results in cellular damage by mediating three main reactions namely lipid peroxidation, oxidation of proteins and nucleic acid damage [46]. In fact, oxidative stress is considered as a part of the normal physiological process during aging, but have been known to be involved in chronic disorders of the brain like AD, PD, HD, ischemic stroke, depression and sclerosis [46]. Moreover, it plays a significant role in lifestyle-related metabolic disorders like Type 2 diabetes (T2D), non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, obesity, cardiovascular diseases and cancer [47].

### Role of ROS in brain under physiological condition

Though ROS at higher levels is considered harmful causing biomolecular damage resulting in a wide range of cellular dysfunctions, whereas at a safe steady level ROS play a useful biological role. Under normal physiological conditions, extracellular ROS helps in mitigating infections by eliciting innate immunity responses. On the other hand, free radicals produced intracellularly helps to stimulate signaling pathways, apoptosis and defense system against oxidative stress. ROS also plays an important role in activating nuclear transcription factor NF- $\kappa$ B, which triggers inflammation leading to oxidative stress. Free radicals like hypochlorous acid (HOCl) are produced in lysosomes by the action of myeloperoxidases, which is used as a strong oxidative agent against pathogens. Thus, ROS act as a strong participant in signal transduction pathways regulating intracellular signaling [27,44].

With respect to CNS, ROS produced as a byproduct in many reactions under the physiological condition not only helps in modulating intracellular signal transduction pathways but also regulates cell proliferation, differentiation, and maturation [48]. Previous reports showed that ROS production and redox balance helps in mediating neuronal differentiation from precursor



neuronal progenitor cells and the axon formation [49], also, it helps in neuronal cell expansion in their niches [50]. Moreover, It has been observed that redox signaling (ROS and oxidative states) also regulates the functioning of transcription factors like (NF- $\kappa$ B), nuclear factor of activated T-cells and the activator protein 1 (AP-1) along with the redox state of tyrosine phosphorylated protein PKC, thus plays an important role in influencing signaling cascades involved in neurogenesis [51]. Also, ROS like  $H_2O_2$  have been observed to modulate the excitability of cortical neurons by enhancing the intracellular  $Ca^{2+}$  signaling [52]. In a similar study it was observed that  $H_2O_2$  increases the phosphorylation of ERK and cAMP-response element-binding protein (CREB) in cortical neurons and PC12 cells [53,54]. This shows that ROS plays a crucial role in influencing signaling cascades in nervous system and can act as a messenger in the signal transduction pathways.

ROS acts as a secondary messenger in various parts of the brain like hippocampus, cerebral cortex, hypothalamus, amygdala and spinal cord, thus helps in maintaining synaptic plasticity [55]. ROS was also found to be necessary for the long term potentiation (LTP) in the hippocampus, which is associated with learning and memory in mammals, thus, showing the involvement of ROS in synaptic enhancement [56,57]. ROS also affects the pain related behavior by its involvement in increasing the excitability of the central nucleus of amygdala, a region of brain responsible for emotional aspect of pain modulation [58]. Likewise, in spinal cord, neuroplasticity processes related to neuropathic and inflammatory pain is also controlled by ROS acting as a signaling molecule [59]. Reports from animal studies showed that NOX mediated direct production of ROS act as an important physiological process which helps in maintaining synaptic plasticity mechanisms particularly in hippocampus and visual cortex [60]. Moreover, dose dependent effect of  $H_2O_2$  was observed to be an obligatory process to bring the redox changes and thus regulating synaptic plasticity [61].

### Why brain is vulnerable to oxidative stress?

Approximately 20% of the basal  $O_2$  is consumed by brain to support the ATP driven activity of  $\sim 86$  billion neurons connected by trillions of synapses, supported by 250–300 billion glia [62]. It was reported that neurons ( $\sim 1.9$  million) and synapses ( $\sim 14$  million) begin to perish every minute when brain is deprived of  $O_2$  [63]. Though  $O_2$  is essential for the brain functioning, but ambiguity always lies in the fact that how oxidative stress causes neurodegeneration.  $O_2$  derived free radical and non-radical species produced during redox signaling equally sustain brain health depicting its potential positive functionality [64]. It has been reported that  $O_2^-$  and  $H_2O_2$  produced by the action of NADPH oxidase (NOX-2) are involved in maintaining the growth of neuronal progenitor cells via PI3K/AKT pathway [49], also deletion of NOX-2 shows its importance in regulating cognitive functions of brain [65]. Recently, it is reported that NOX-2 derived  $H_2O_2$  acts as an endogenous chemo-attractant supporting axonal path finding as well in its regeneration [66]. Thus, diverse reactive species are used by brain to perform signaling functions which make it more susceptible to oxidative stress. There are many other biochemical events which make the brain more vulnerable to oxidative stress that includes:

- a)  $Ca^{2+}$  transients during action potential are required to maintain the bidirectional synaptic plasticity. When high  $Ca^{2+}$  transients across the membrane are disrupted, the free intracellular  $Ca^{2+}$  concentration increases, which then activates neuronal NOS (production of  $NO^\cdot$ ), phospholipase A2 and calpains damaging cytoskeleton. High  $NO^\cdot$  also binds to cytochrome C oxidase, inhibiting mitochondrial respiration.

Further,  $NO^\cdot$  reacts with  $O_2^-$  (from dysfunctional mitochondria) to form  $ONOO^-$ .  $Ca^{2+}$  overloads in mitochondria abolishes the ATP generation by mediating efflux of  $Ca^{2+}$ /  $H_2O_2$  via mitochondrial permeability transition pore (mPTP), this leads to necroptosis. Thus, disruption of  $Ca^{2+}$  homeostasis makes brain susceptible to oxidative stress [67,68].

- b) Glutamate act as an excitotoxic amino acid for neurons and when taken in large amounts, it damages the cell by necrosis. This damage results in the release of large amount of glutamate in the extracellular environment, which also binds to receptors on adjacent neurons leading to a sustained release of  $Ca^{2+}$  and  $Na^+$  in the cell. Reactive species like  $ONOO^-$  inhibits the conversion of glutamate to glutamine by inactivating glutamine synthetase. Also, glutamate inhibits the exchange for intracellular glutamate for intracellular cysteine via  $X_c^-$  transporters, resulting in depletion of GSH, which in turn leads to ferroptosis mediated death of neurons [69,70].
- c) Brain is enriched with redox transition metal ions like  $Fe^{2+}$  and  $Cu^+$  which act as cofactors for many enzymes. Stress factors causing brain damage release metal ions capable of catalyzing free radical reactions. Moreover, the iron released have a prolonged existence because cerebrospinal fluid (CSF) has little or no iron binding capacity [71,72].
- d) Neurotransmitters like dopamine, serotonin and norepinephrine undergo auto-oxidation to generate ROS. Briefly, dopamine reacts with  $O_2$  to produce semiquinone and  $O_2^-$ , which further reacts with  $O_2$  to generate quinone. Quinone so produced is re-oxidized by  $O_2$  to quinol and  $H_2O_2$ , where  $Mn^{2+}$  reacts with  $H_2O_2$  to produce OH. Such auto-oxidation results in mitochondrial and lysosomal dysfunction [73,74].
- e) Brain is also sensitive to oxidative stress induced by glucose. To utilize most of the glucose for pentose phosphate pathway, neurons degrade phosphofructokinase, a rate-limiting glycolytic enzyme. The absence of glycolytic rate results in protein glycation and the formation of advanced glycation end products (AGE). AGE impairs proteins and mitochondrial function by inflammation-induced oxidative stress [75–77].
- f) Brain possesses a high content of polyunsaturated fatty acids particularly docosahexaenoic acid (DHA), which makes it more prone to oxidative stress because of lipid peroxidation and using peroxide lipids by brain to signal. Products of lipid peroxidation like 4-Hydroxynonenal inactivates glutamate transporters by increasing  $Ca^{2+}$  levels, thus are neurotoxic. Lipids peroxides also inactivate alpha-ketoglutarate dehydrogenase, act as vasoconstrictive agent, damages proteasome, and is found to be a consistent factor in NDDs like AD [78,79].
- g) Microglia, the resident immune cells of the brain are important for brain development and function, but during the normal activity of phagocytosis, it produces  $O_2^-$  and other reactive species. Active microglia produce  $O_2^-$  via NOX-2. Thus, microglia activity depends on the total  $O_2$  bioavailability and depicting damage to synapse by consuming more  $O_2$  to produce  $O_2^-$ . Reactive species like  $H_2O_2$  and  $NO^\cdot$  attracts microglia at the site to enforce local inflammation driving neurodegeneration [80].
- h) Brain is prone to disrupted redox homeostasis due to modest antioxidant defense system in comparison to other tissues. Catalase content in neurons is much lower (50 times) than that of hepatocytes. Moreover, their presence in peroxisomes restricts its activity to act on  $H_2O_2$  produced in other subcellular compartments. Similarly, neurons possess very low levels of GSH, which makes them sensitive to ferroptosis and resist them to metabolize electrophiles [81–83].

- i) Hemoglobin is considered as neurotoxic for the brain when its reaction with excess of  $H_2O_2$  results in the release of prooxidant iron ions and heme. Free heme is the strongest promoter of lipid peroxidation. Moreover, its binding with  $NO$  leads to vasoconstriction [84,85].
- j) Though brain contains low levels of cytochromes P450 enzyme, CYP2E1 that makes brain prone to oxidative stress due to leakage of electrons while catalyzing reactions. Study showed that its level might increase due to the consumption of ethanol and smoking [86].
- k) DNA repair enzymes like poly-ADP-ribose polymerase (PARP-1), repairs DNA damage by cleaving  $NAD^+$  and binding ADP ribose to nuclear proteins. But, overactivation of this enzyme leads to depletion of neuroprotective  $NAD^+$ , restricting energy production and opening of transient receptor potential melastatin (TRPM2)  $Ca^{2+}$  channels that results in neuronal cell death [87].
- l) Being single-stranded and non-protected by histone proteins, RNA is more vulnerable to oxidation. Oxidized RNA halts the protein synthesis by ribosomes and might result in unfolded, truncated proteins if left unrepaired. It was reported that oxidized RNA along with redox-active transition metals catalyzes Fenton's reaction. It was also reported that oxidized CuZn-SOD mRNA is a preclinical sign of ALS. However, there is a need to investigate its potent role in neurodegeneration [88].

## Gut microbiota, oxidative stress and neurodegeneration

### Gut-brain axis under physiological condition

Gastrointestinal (GI) tract encompasses trillions of commensal microorganisms and ~1000 of its species which plays an important role in preserving membrane barrier functions [2]. These microorganisms are permanent residents of small intestine and colon, involving the constant flux of molecules within the host organisms, thus regulating a variety of metabolic functions [58]. The microbial community gets stabilized in the host GI tract within two years after birth, but their composition varies among individuals and can change depending upon external factors like age, health, genetics and lifestyle [89]. Luminal side of the GI tract is exposed to dietary components and gut microbiota, moreover, gut tissue is housed by 70% of immune cells and innervated by neurons which connects the gut and brain, involving constant communication between the gut and the brain [2]. Communication between the gut microbiota and brain involves the four main routes; the first important mode includes the activation of vagus nerve which connects the muscular and mucosal layer of GI tract to the brain stem. Recent reports show that enteric pathogens and probiotics regulates the host behaviors like anxiety, feeding, and depression by altering  $\gamma$ -Aminobutyric acid (GABA), oxytocin and brain derived neurotrophic factor (BDNF) signaling in brain via activation of vagal neurons [90,91]. Though, one report showed that indole, a bacterial metabolite obtained from tryptophan, increases anxiety-like behavior in rats via vagus nerve activation, but specific metabolites mediating these effects still need to be identified [92]. The second route of communication influencing brain activity directly or indirectly involves the signaling through serotonin released by enterochromaffin cells (EC) present in gut lining. A study showed the increase in serotonin and serotonin precursor levels in mouse models of depression, when treated with probiotic *Bifidobacterium* spp., improving their depressive state [93]. Similarly, it was reported that metabolites from spore-forming bacteria (*Clostridium* spp.) were able to stimulate serotonin production from EC [94]. Thirdly, gut microbiota plays an essential role in development, maturation and activation of microglia. In a study,

it was reported that germ free (GF) mice carries larger number of immature microglia than conventional mice, moreover when treated with *Bifidobacterium* spp. activates microglial cells through transcriptional activation [95]. Changes in microglia functioning have been observed in behavioral and NDDs, showing the influence of gut microbiota on NDDs mediated via microglia. Gut microbiota also affects the nervous system via systemic immune system i.e., cytokines and chemokines. Study showed that GF mice possess greater blood–brain barrier (BBB) permeability in comparison to conventional mice, thus making brain accessible to microbial products subsequently leads to neuropathological conditions [96]. Last but not the least, gut microbiota communicates by a direct transfer of chemical signals to the brain. For example, fermentation of dietary fiber by intestinal bacteria produces short chain fatty acids (SCFAs) which have been shown to regulate neuroplasticity in CNS, and was also reported to improve the depressive behavior in mice [97]. Furthermore, gut microbiota like *Bacteroides*, *Bifidobacterium*, *Parabacteroides* and *Escherichia* spp. are capable of producing neurotransmitter GABA which implicates that gut microbiota modulates the concentration of neurotransmitters in host organism [98].

### Gut microbiota-mediated oxidative stress and neurodegeneration

Four main phyla of commensal bacteria colonize in human gut which includes Firmicutes, Bacteroidetes, Actinobacteria, and Proteobacteria. Among them, Firmicutes including *Lactobacillus*, *Streptococcus*, *Mycoplasma* and *Clostridium* along with Bacteroidetes encompass 90% of the total. Both commensal and pathogenic bacteria in gut are able to alter the cellular ROS by modulating mitochondrial activity [99]. Commensal bacteria produce formylated peptides which bind to G protein-coupled receptors (GPCRs) on macrophages and neutrophils, which triggers inflammation in epithelial cells. This process results in superoxide production by NOX-1, increasing cellular ROS [100]. Gut *Lactobacilli* and *Bifidobacterium* possess the ability to convert nitrate and nitrites into  $NO$ , making the gut epithelia a rich source of  $NO$ . Similarly, *Streptococcus* and *bacilli* produce  $NO$  from L-arginine using NOS [101].  $NO$  in nanomolar concentration is considered to be neuroprotective and is a neurotransmitter for noradrenergic, noncholinergic enteric neurons. While at a higher concentration, it results in the detrimental effect caused by the production of reactive oxygen and nitrogen species (RONS) like superoxide and  $H_2O_2$ , which further forms highly reactive hydroxyl radicals associating it to neuroinflammation, axonal degeneration and NDDs [18]. Beneficial metabolites like SCFAs produced by gut bacteria help to reduce ROS by influencing mitochondrial activity. This will be discussed more in detail in another section.

Membrane associated molecular pattern (MAMP) maintains structural integrity and basic functions of all classes of microorganisms and are detected even by brain. These are diverse chemical groups including peptides, nucleotides, carbohydrates and lipids [102]. When such molecular patterns are undetected by the host, it may escort acute to chronic inflammation and is found to alter brain development and function. These highly conserved structural motifs bind to pattern recognition receptors (PRR) present on cells of innate immune system, thus inducing mitochondrial ROS production and activation of NF- $\kappa$ B pathway leading to inflammatory responses, causing neuronal stress and cell death [103]. In a recent study, it was reported that bacterial cell-wall component peptidoglycan translocate to the developing brain affecting gene expression and causes a change in social behavior [104]. Similarly, lipopolysaccharide present in Gram-negative bacterial cell-wall was found to impair fetal brain development, acute depression and cognitive impairment in mice [105]. Moreover, acute and chronic exposure of MAMP was observed to be a responsible factor

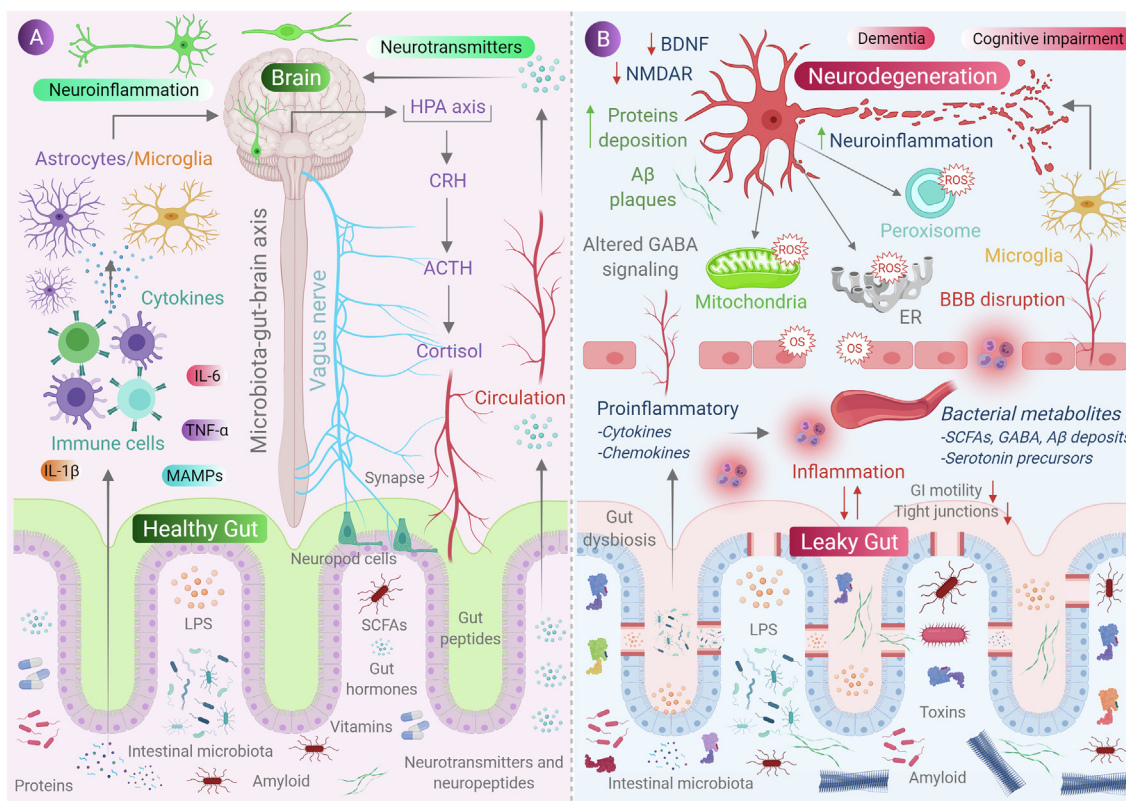
in developing disease symptoms in PD, autism spectrum disorder (ASD) and synucleinopathy models [106]. Apart from MAMPs, bacterial toxins produced by opportunistic pathogens also exert a negative impact on host nervous system. Lethal toxins like toxin B, enterotoxin and epsilon toxin produced by *Clostridium* spp. were discovered to decrease neuronal viability and also inhibit the release of neurotransmitters by reaching the brain via disrupted BBB [107]. Enterotoxins and cereulide produced by *Staphylococcus* spp. and *Bacillus* spp. were found to induce vomiting and sickness behavior by stimulating vagus nerve [108,109]. Pathogenic bacteria like *Salmonella* and *E. coli* are able to degrade sulphur containing amino acids, thus producing hydrogen sulphide ( $H_2S$ ) in the gut. An increase in  $H_2S$  levels imposes change in various metabolic activities like increased lactate and decreased ATP production, inhibition of cyclooxygenase 2 (COX-2) activity [110], decreased consumption of  $O_2$  by mitochondria and an increased expression of pro-inflammatory cytokines [111] and is known to stimulate hypertension and neuroinflammation [112]. Fig. 1 shows the role of gut microbiota-mediated oxidative stress in neurodegeneration.

Etiopathology of NDDs like AD and PD involves the intraneuronal protein misfolding and its aggregation. Moreover, oxidative stress is also considered as one of its pathogenic factors, but the exact underlining mechanism is still unknown. The first evidence showing the relationship of NDD pathology with gut microbiota was shown by Heiko Braak group, where they found the  $\alpha$ -synuclein aggregation in submucosal Meissner's and Myenteric Auerbach's plexuses in the gut of PD patients, suggesting the role

of gut microbiota in initiating the  $\alpha$ -synuclein aggregation in the gut, which is then ascended trans-synaptically to CNS neurons causing neurodegeneration [113]. Interestingly, microbiota-mediated proteinopathy and neuroinflammation is termed as "mapronosis" showing their interim relationship [114]. So far, numerous studies have shown the altered gut microbiota composition in neurological disease state in comparison to healthy individuals, but further work is needed to identify the mechanisms on how bacteria and bacterial factors influence the disease progression. Here, we describe the recent work depicting the link between gut bacteria, oxidative stress and NDDs, focusing on AD, PD and TBI.

#### Gut microbiota-mediated oxidative stress in Alzheimer's disease

Alzheimer's disease (AD) is the leading cause of dementia, affecting over 50 million population worldwide, where its prevalence is higher in older population, with about 80 per 1000 individuals above 85 years of age. Non-symptomatic pathology of AD is thought to begin approx. 20 years before the symptoms like memory loss and cognitive deficits arise [115]. Pathological changes in brain associated with AD include the extracellular accumulation of protein amyloid-beta ( $A\beta$ -amyloid plaques) and the intracellular accumulation of tau proteins (tau tangles) [116]. This abnormal accumulation of proteins leads to activation of microglia for the clearance of  $A\beta$  and tau proteins, but with subsequent aging, chronic inflammation occurs causing neuronal cell death, leading



**Fig. 1.** Role of gut microbiota in neurodegeneration. (A) Communication between gut and the brain involves neural, metabolic, endocrine and immunological pathways. Gut microbial molecules like neurotransmitters, amino acids, short-chain fatty acids (SCFAs), amyloid, lipopolysaccharide (LPS) and microbe-associated molecular patterns (MAMPs) interacts with host immune system via circulation affecting metabolism and the nervous system of the host and, also it affects the brain by direct activation of the vagus nerve via enteric nervous system to the brain. Conditions like stress causes the hypothalamic neurons to secrete corticotrophic releasing hormone (CRH), triggering the release of adrenocorticotrophic releasing hormone (ACTH), subsequently activating the release of cortisol, which affects intestinal barrier integrity affecting gut health. (B) when, there occurs a condition of gut dysbiosis, there is a decrease of anti-inflammatory molecules (like SCFAs,  $H_2$ ) to that of pro-inflammatory molecules (LPS, amyloids) also with an alteration of beneficial bacteria to that of pathogenic in the gut. This results in increase of intestinal and blood brain barrier permeability, subsequently causing increase in peripheral immune responses, thus increasing oxidative stress in central nervous system (CNS). An increased production of reactive oxygen species (ROS) can be observed in cell organelles like mitochondria, endoplasmic reticulum (ER) and peroxisomes in neurons, along with neurotoxin aggregation, resulting in neurodegeneration.



to atrophy [117]. Despite of rare genetic mutation causing A $\beta$  accumulation 20 years before onset, followed by decreased glucose consumption by brain 18 years before and atrophy began 13 years before the development of disease [118], many cross-sectional studies have documented modifiable risk factors as an etiopathology of AD [119]. Among the possible risk factors, the role of oxidative stress and gut microbiota has attracted the scientific community and is considered as an immediate plausible consequence of neurodegenerative processes.

In addition to high energy demands of brain, the link between oxidative stress and AD is reflected in many studies which showed the alteration in antioxidant defense system of the brain i.e. changes in activity and levels of SOD and catalase enzyme [120]. Likewise, oxidative stress biomarkers like malondialdehyde, 4-hydroxynonenal, and F2-isoprostane (lipid oxidative damage); protein carbonyls and 3-nitrotyrosine (products of protein oxidation), 8-hydroxydeoxyguanosine (nucleic acid oxidation) were found at high levels in blood and CSF [120], also their concentration was found proportional to that of cognitive impairment and brain weight [121]. ROS production in AD brain is also characterized by dysfunction in cellular organelles like mitochondria (deficiency of cytochrome C oxidase) [122], endoplasmic reticulum due to UPR [123], accumulation of metal ions in neuritic plaques [124] and due to the hyperactivation of microglia followed by the overexpression of NADPH oxidase [125]. There is also an inter-relationship between A $\beta$  deposition and oxidative stress i.e. A $\beta$  aggregation induces oxidative stress (also in organelles like mitochondria, ER and golgi apparatus) and oxidative stress induces A $\beta$  accumulation [126]. Even, aggregation of tau proteins in neurons leads to decreased NADH-ubiquinone reductase activity resulting in increased ROS production and mitochondrial dysfunction [127].

Recent facts and figures show that AD is not only a result of confined brain inflammation but is also a consequence of peripheral inflammation [128]. This is supported by the fact that gut dysbiosis leads to inflammation which increases with age, disruption of BBB, activation of immune system followed by neurodegeneration, on the other hand, healthy and well-balanced gut helps to decrease detrimental effects produced by ROS [19]. Individuals suffering from AD have been identified with decreased population of commensal bacteria such as *Bifidobacterium* spp. and Firmicutes, and an increased abundance of *Escherichia*, *Shigella* spp. and Bacteroidetes, followed by increased inflammation and A $\beta$  accumulation [129]. Similarly, decline in A $\beta$  plaque formation was seen in APP/PS1 mice model when treated with the combination of broad-spectrum antibiotics [130]. Likewise, 5xFAD mouse model of AD showed shifts in microbiota population towards proinflammatory species along with the changes in amino acid catabolism, and conversely, treatment with antibiotics reversed the effects, suggesting the possible link between severity of disease and transformed gut population [131]. Microbial amyloid protein formed in the gut activates the Toll-like receptors (TLR) and cluster of differentiation 14 (CD14) facilitated immune response leading to overlooked misfolded A $\beta$  with impaired A $\beta$  clearance, subsequently increasing cytokine production resulting in disrupted intestinal and BBB [114]. Also, it was shown that levels of enteric hormones decrease in AD patients, on the contrary, gut microbiota metabolites like H<sub>2</sub>S and trimethylamine increase, enhancing its rigor [132].

Age-related decrease of gut microbial biodiversity is also considered as one cause of dementia. It has been shown that with growing age, there is a decrease in *Bifidobacterium* spp. and an increase in Proteobacteria, where dementia results not because of decrease in SCFA's but due to interference in lipid metabolism. *Bifidobacterium* plays an important role in regulating cholesterol levels directly facilitating its fecal elimination and indirectly by

increasing the serum leptin levels, thus involved in maintaining hippocampal plasticity and memory functions [133,134]. Gut bacteria like *Lactobacilli* and *Bifidobacterium* metabolize an inhibitory neurotransmitter GABA [135]. In a study, it was observed that synaptic plasticity in hippocampus was altered in APPSwe/PSEN1 DeltaE9 bigenic mouse model of AD, where reduced GABA production was found with a concomitant increase in glutamatergic neurotransmission [136,137]. Although, reports show that phylum *Cynobacteria* produces neurotoxins causing cognitive impairment, but no relation has been observed with AD [138].

Another possible connecting link, cerebral amyloid accumulation and gut microbiota involve the mechanism of cross seeding of microbial amyloids in a manner similar to prion propagation, thus different amyloid conformers formed induces toxicity at distinct levels in their cellular targets, hypothesizing the existence of AD phenotypes [139]. In addition to gut microbiota, a link between commensal bacteria in oral cavity and AD was also studied. Interestingly, poor oral hygiene and teeth loss was found to cause an increased risk of early onset of AD [140].

#### Gut microbiota-mediated oxidative stress in Parkinson's disease

Parkinson's disease (PD) is pathologically characterized by progressive degeneration of dopaminergic neurons, aggregation of phosphorylated protein  $\alpha$ -synuclein, excessive ROS production, mitochondrial dysfunction and microglia activation [141]. Symptomatically, it is characterized by inability of the patients to control voluntary movements (tremors, muscle rigidity, difficulty walking and hunched posture) due to damage in substantia nigra and striatum regions of the brain. It is the second most common NDD affecting more than 1% of elderly population worldwide [142]. The first report on relationship between gut and PD was mentioned in an essay on shaking palsy by James Parkinson in 1817 [143]. Braak's hypothesis supported this view showing the initiation of pathology in the gut, then affecting the brain. Accumulating evidences show that gut inflammation, early accumulation of phosphorylated  $\alpha$ -synuclein transcending to the dorsal motor neuron of the vagus nerve, constipation problems and increased intestinal permeability are common in PD patients, suggesting a strong relationship between gut microbiota and PD pathogenesis [144]. Moreover, it was observed that risk of developing PD decreases in those individuals who have gone for vagotomy [145]. In addition, lower levels of GSH, and higher level of iron and H<sub>2</sub>O<sub>2</sub> makes substantia nigra pars compacta (SNc) neurons susceptible to oxidative stress [146]. Also, lipid peroxidation and dopamine oxidation in this region leads to neuronal cell death. Studies also show that mitochondrial respiratory chain dysfunction leads to excessive ROS production. It is supported by the fact that inhibitors of complex 1 induces cytotoxic effects on dopamine neurons [147], also patients with pathology of  $\alpha$ -synuclein, phosphatase and tensin homolog (PTEN)-induced putative kinase 1 (PINK1) and Parkin were detected to have mitochondrial dysfunction with increased oxidative stress [148]. Similar to AD, aggregation of abnormal protein  $\alpha$ -synuclein is interrelated to increased oxidative stress and vice versa. Coming to the role of gut microbiota, some pathogenic spp. release toxins causing mitochondrial dysfunction in cells of the gut and ENS resulting in neurodegeneration [149]. The pathogenic bacteria increase in gut of PD patients and their microbial products are directly involved in PD pathogenesis. In support of this fact, recently it was reported that pathogenic bacteria *Escherichia coli* produces amyloid protein known as curli, which promotes  $\alpha$ -synuclein aggregation in gut and brain and was observed to cause motor deficits in mice [150]. On the other hand, when mice were treated with gut restricted amyloid inhibitor, it has shown the improvements in motor functions along with amelioration of



constipation [151], showing the involvement of gut in etiology of PD symptoms, supporting Braak's hypothesis.

Gut inflammation caused by gut bacteria can be directly correlated with progressive neurodegeneration in PD. Though serum metabolic profile and gut composition are found altered in PD patients, it was observed that in severe PD condition, *Enterobacteriaceae* level enhances in gut with very low level of anti-inflammatory bacteria, also showing its parallel association with gut inflammation in Crohn's disease [152]. This shows that patients with Crohn's disease possess very high risk of developing PD. Similarly, it was observed that *Citrobacter rodentium* infection in mouse model (PTEN induced Kinase 1 (PINK1) knockout mice), aggravated PD symptoms by inducing gut inflammation [153]. In addition to induce inflammation, gut microbiota also exerts metabolic effects, like its metabolites  $\beta$ -glucuronate, tryptophan and SCFA's were found to be altered in case of PD patients [154]. Recently, one striking attribute of gut microbiota was also reported showing that it acquires the ability to reduce the efficacy of anti-PD drugs either by decreasing its bioavailability or by increasing drug inactivation, as observed in the case of standard levodopa treatment [155,156]. Inclusive of these studies, decreased production of  $H_2$  by gut bacteria is also found to be one of the contributing factors in PD [157]. A recent report showed that when 50%  $H_2$  saturated water was given to rat and MPTP mouse model of PD, it was found to be successful in reducing neuronal loss in substantia nigra and also the oxidative stress markers and when double blind randomized trial was performed in humans, an improvement in motor ratings of PD patients was observed [157,158]. Further, towards this notion, recent work on GF mouse model of PD with overexpressed human  $\alpha$ -synuclein gene showed the reduced level of SCFAs along with the decreased microglia activation and improved motor functions which suggests the direct involvement of gut microbiota in enhancing PD. In addition to it, when gut microbiota from PD patients was transplanted into GF  $\alpha$ -synuclein overexpressed mouse model, worsened the motor symptoms, suggesting the role of dysfunctional gut microbiota in PD patients [151]. Similarly, mouse model treated with neurotoxin showed altered gut microbiota composition with increased levels of pathogenic *Enterobacteriaceae* [159]. Furthermore, increased Firmicutes to Bacteroides ratio (condition also in gut inflammation) was observed in mice treated with pesticide rotenone [151]. Strikingly, some specific bacterial species like *Proteus mirabilis* were found to bolster neurodegeneration in mice [160]. Taken together, these studies suggest that gut microbiota exacerbates neuronal dysfunction and neuroinflammation in both human and animal models of PD.

#### Gut microbiome and traumatic brain injury (TBI)

Traumatic Brain Injury (TBI) is one of the most prevalent injury types sustained in the world population with an annual incidence of ~1.4 million cases in the United States, and is among the major cause of death and disability [161]. The disabilities which occur in TBI not only includes a primary mechanical damage of brain but involves post injury secondary damages, which takes place at the cellular and molecular level, and may lead to metabolic anomalies like mitochondrial dysfunction, oxidative stress, inflammation, microglia activation, excitotoxicity, resulting in temporary or life-long cognitive impairments [162]. Moreover, severity of TBI is not only focused on brain but can be a multiorgan damage and is considered as a heterogeneous pathological condition. Due to the heterogeneous nature of brain injury, therapies for TBI-induced neuropathologies are still lacking, pertaining to the consideration of novel therapeutic regimens. Towards this approach gut eubiotic therapeutics have gained much attention, because of

its capability to restore the bifacial relationship between gut dysbiosis and TBI [163,164].

Growing line of evidences reveal that there exists a bi-directional relationship between a gut microbiome and TBI injury. One of the systemic manifestations of TBI has been observed as a disruption of intestinal motility and permeability, mucosal damage, histopathological alterations of intestinal villi, thus indicating the perturbation in the composition of gut microbiome [165–167]. Conversely, it has been observed that gut dysbiosis also influences the pathophysiology of traumatic CNS injury, alterations in BBB permeability and activation of microglia, leading to severe repercussions [168–170]. Recent report showed that a mice exposed to mild and repetitive brain injury for 20 days show a progressive emergence of white matter damage, cognitive deterioration and a mild, transient gut dysbiosis [171]. Similarly, it was observed that depletion of gut microbiota in murine model of TBI prior to and following brain injury resulted in an increased CA1 hippocampal neuronal density, attenuated associative learning deficit and had reduced lesion volume [172]. Recent study also claims that gut dysbiosis takes place after traumatic spinal cord injury which resulted in intraspinal inflammation and lesion pathology [173]. Also, changes in two major order of bacteria in gut Bacteroidales and Clostridiales was observed i.e. ~30% decrease in phylum Bacteroidetes and ~25% increase in phylum Firmicutes. This was accompanied by the consistent changes in minor taxa including Anaeroplasmatales, Turicibacterales and Lactobacillales. Such changes were found to be persistent and lasted for about 4 weeks post injury [174]. A similar modulation in gut microbiome population, but an inverse relation of decrease in Firmicutes and an increase in Bacteroidetes was found to occur 2 h following injury and being persistent for about 7 days in rodent model of moderate TBI [175]. Likewise, recent report showed that their occurs a rapid significant decrease in three species *Lactobacillus gasseri*, *Ruminococcus flavefaciens*, and *Eubacterium ventriosum* and a significant increase in *Eubacterium sulci*, and *Marvinbryantia formatexigens* in human gut microbiome just in 24 h after TBI in mice [176]. Furthermore, a decrease in Bacteroidales, Fusobacteriales, and Verucomicrobiales, along with an increase in Clostridiales and Enterococcus within 72 h were observed in severely injured patients with polytrauma [177]. Gut microbiota also plays a very important role in recovery from TBI, as observed in a recent report where gut dysbiosis induced by a broad spectrum antibiotic before, during and after TBI resulted in an increased neuronal loss, suppressed neurogenesis as well as altered the microglia and peripheral immune response along with the modulation in fear memory response [178]. Thus, the influence of gut microbiota on TBI patients is of paramount clinical significance because TBI patients become susceptible to alterations in gut microbiota due to regular antibiotic administration and prolonged hospitalization. Furthermore, detection of gut microbiota modulation might provide a diagnostic tool for the identification of TBI severity, thus providing targeted therapeutic approaches.

#### CNS antioxidants and neuroprotection

CNS is highly vulnerable to oxidative stress and leads the neurological disorders. High level of ROS is generated during the functioning of CNS due to high  $O_2$  demand and rush of peroxidation-susceptible lipid cells. This oxidative metabolism generates reactive species for transmitting redox signals to regulate critical functions such as synaptic plasticity [29,179]. Antioxidants whether enzymatic or non-enzymatic, endogenous, or exogenous, protects the brain against the oxidative stress by preventing the generation of ROS or by scavenging the free radicals or inactivate the free radical product. The first line of antioxidative

defence mechanism involves the use of endogenous enzymes like SOD, glutathione peroxidase (GPx), glutathione reductase, and catalase [180]. Whereas, second line of antioxidative defence involves the use of endogenous non-enzymatic molecules like thioredoxin, ferritin, transferrin, ceruloplasmin, albumin, and metallothionein. Also, enzyme co-factors, i.e., coenzyme Q and alpha-lipoic acid, and metabolites, i.e., bilirubin, melatonin, and uric acid plays an important role in antioxidative defence mechanism [181,182]. Similarly, natural dietary compounds like vitamins A, E, and C, flavonoids, phenolic acids, and carotenoids are also known to possess a strong possible antioxidative defence against oxidative stress-induced neurodegeneration [182].

The antioxidant enzymes such as SOD decreases the concentration of superoxide anion by catalyzing the dismutation of superoxide to  $O_2$  and  $H_2O_2$ ; GPx reduce  $H_2O_2$  and lipid peroxides; thiol-specific peroxidases such as peroxiredoxins reduce the amount of hydroxyperoxides, and catalase transforms  $H_2O_2$  to  $H_2O$  and ordinary molecular  $O_2$  [29,183]. The free radicals activate the transcription of genes involved in antioxidant pathways and protect the cells from adverse effects. Glutathione is present in low amount in the CNS which reacts with free radicals in its reduced form to convert the  $H_2O_2$  to  $H_2O$  by self-catalyzing to GS-SG and regenerates again to glutathione by a reductase [183]. Insufficiency of glutathione may limit the activity of peroxidases that could make the neurons more susceptible to oxidative stress. *In-vivo* and *in-vitro* studies performed till date showed that the SOD and catalase improves the neuronal survival following the  $A\beta$ -induced neuronal toxicity [184–187]. Likewise, both thioredoxin and thioredoxin reductase are widely expressed in brain and are known to exert neuroprotective effect against oxidative stress models of HD and AD [188,189].

Another very important pathway is Kelch-like ECH-Associating protein 1 nuclear factor erythroid 2 related factor 2-antioxidant response element (Keap1-Nrf2-ARE). Keap1-Nrf2-ARE is highly expressed in neurons and linked with the defense mechanisms against oxidative stress associated with NDDs. It modulates the activity of SOD, thioredoxin, peroxiredoxins, and GPx via transcriptional regulation [190]. The importance of NF- $\kappa$ B is also reported as a redox-sensor in CNS that is activated by ROS. Moderate level of ROS phosphorylates NF- $\kappa$ B inhibitor that results in NF- $\kappa$ B activation. Activated NF- $\kappa$ B regulates the expression of anti-apoptotic and inhibits caspase-dependent cell death pathways. However, high levels of ROS inhibit the binding of NF- $\kappa$ B via inactivating it. This mechanism promotes the apoptosis of cells and halts the pro-survival pathways [29]. The regulation of antioxidant metabolism of the CNS is tightly controlled where the role of gut microbes is highly dynamic.

## Gut microbiota in neuroprotection

Gut microbe-microbe and microbe-host interactions regulate the level of exogenous and endogenous ROS via various metabolites production such as absorbable vitamins, polyphenols, SCFAs, BDNF, diffusible antioxidant and oxidant gases, etc. Gut microbes also control the permeability of metabolites to BBB, tight junction integrity and intestinal barrier, modulate the immune system and impede the intestinal colonization of pathogens [191]. The vagus nerve of the parasympathetic nervous system senses the gut metabolites and communicates to CNS about the gut information to generate specific responses. Under the stress condition, the vagal tone is repressed and shows detrimental effects such as irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD) due to dysbiosis [192].  $A\beta$  proteins involved in the pathogenesis of AD are expressed by gut bacteria such as *Escherichia coli* and *Salmonella enterica* in ENS [183]. Beneficial gut microbes also

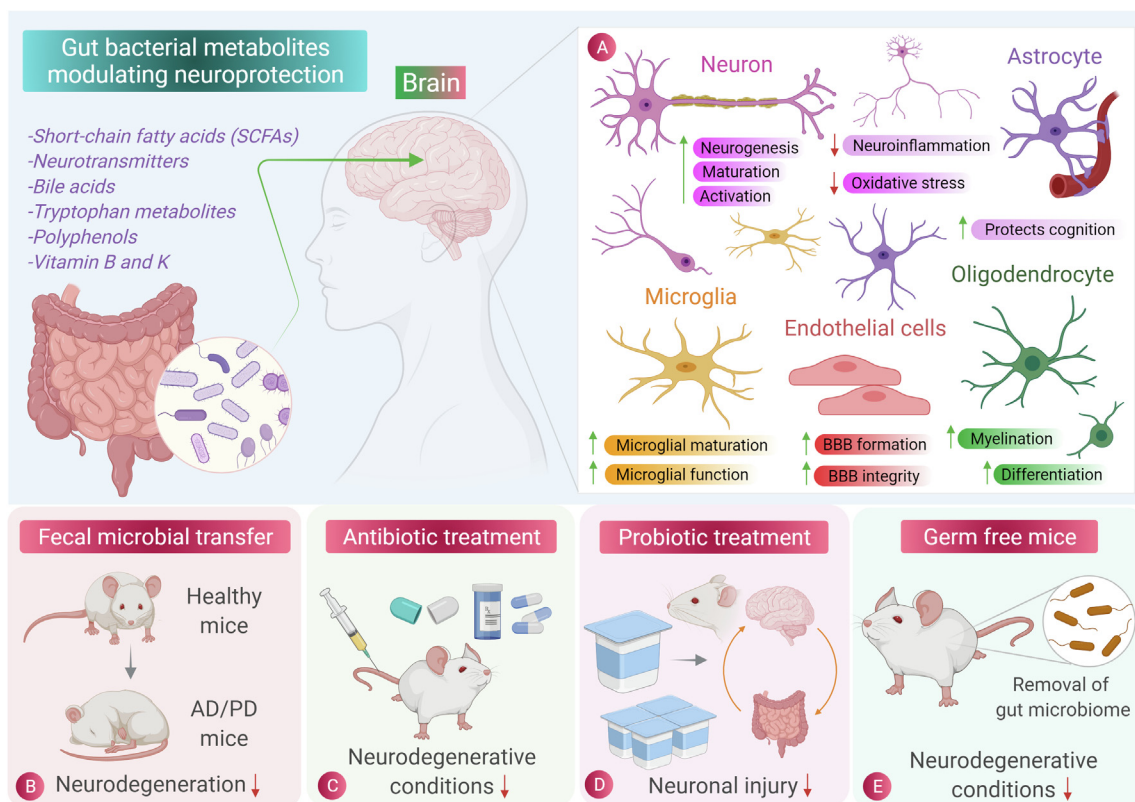
produce dopamine, serotonin, and GABA. These are the CNS neurotransmitters which modulate the ENS activity and may correlate [179]. In some studies, it was revealed that gut microbes manage the activation and maturation of microglia, and activated microglia releases significant amounts of inducible nitric oxide synthase (iNOS) to regulate NO production. Dysbiosis provokes the inflammatory iNOS and causes neuroinflammation [183].

As we have seen the potential role of gut microbiota as well as essential role of oxidative stress in mediating neuronal disorders, in recent years, a growing need and a major scientific focus is on developing antioxidant-based therapies for treating oxidative stress-induced NDDs. Antioxidants are chemical or natural substances capable of counteracting oxidative stress induced by ROS/RNS [193]. Though a potent therapeutic effect of antioxidants has been observed on diseases like diabetes, arthritis, cataract and osteoporosis, antioxidant therapies used for CNS disorders are limited and still requires deep mechanistic understanding [194]. Contrary to the antioxidant therapies, dichotomous role of gut microbiome is observed, which one hand is responsible for the basic underlying mechanism of neurodegeneration (gut dysbiosis and neuroinflammation) and on the other hand, gut microbiome and its metabolites regulate many associated pathways suggesting their neuroprotective therapeutic role. Microbial molecules like protein, vitamins are produced *via* multistep biosynthetic pathway, which may exert beneficial or detrimental effects on the host system [16]. Therefore, a healthy gut microbiome maintained with a proper diet including prebiotics and probiotics is a prerequisite for maintaining neuronal health [195]. Fig. 2 shows the role of gut microbiota metabolites along with the modulation procedures on gut microbiota and their effect on NDDs. Here, we review how bacterial metabolites (their natural, transformed, and dietary metabolites) help to combat oxidative stress-induced neuronal damage. Moreover, we will further discuss about the role of antioxidant and anti-inflammatory probiotics/prebiotics in neuroprotection. Table 1 shows the recent studies on gut microbiota showcasing its neuroprotective role.

## Gut microbiota metabolites in neuroprotection with their cell-specific responses

### Gut microbiota interaction with host molecules

**Bile acids.** Bile acids are produced in liver and are released in the intestinal lumen, primarily involved in the solubilization of lipids and fat-soluble vitamins, signaling in energy metabolism and is also known to play an important role in physiology and pathophysiology of the brain [196]. Bile acid influences neuronal activity in different brain regions and also vagal neuronal activity either by directly binding the receptors in brain crossing BBB, or by indirectly inducing the release of fibroblast growth factor (FGF) and glucagon-like peptide 1 by binding to gut receptors [197]. Bile acids like ursodeoxycholic acid (UDCA) and tauroursodeoxycholic acid (TUDCA) possess neuroprotective properties and lack of cytotoxicity as proved in their phase III clinical trials [198] and in an animal study [199], respectively. Recent data shows that TUDCA helps to attenuate autophagy,  $\alpha$ -synuclein aggregation and protein oxidation in chronic mouse model of PD [200]. Moreover, it helps to prevent neuronal apoptosis in rats affected by subarachnoid hemorrhage *via* Takeda G protein-coupled receptor 5/sirtuin-3 (TGR5/SIRT-3) pathway [201]. Likewise, UDCA showed a neuroprotective effect in charged multivesicular body protein 2B (CHMP2B) Intron 5 models of frontotemporal dementia [202]. Gut microbiota in the intestinal lumen converts primary bile acids (cholic acid and chenodeoxycholic acid) into secondary bile acids by the action of dehydratases, involves deconjugation of amino acids with bile salt hydrolases and other enzymatic processes, which alters their nuclear receptor binding, solubility and



**Fig. 2.** Role of gut microbiota in neuroprotection. (A) Scheme of brain cell specific effects in response to beneficial metabolites released by gut microbiota in reducing inflammation and oxidative stress. (B) Fecal microbial transfer (FMT) which involves the transfer of fecal bacteria from healthy individual to one having pathological condition and was found to be an effective procedure in reducing the pathophysiology of neurodegenerative disorders such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD) and conditions like Multiple sclerosis (MS). (C) and (D) Antibiotic treatment and Probiotic treatment, respectively, which have shown the considerable effectiveness in decreasing the pathogenesis of neurodegenerative diseases. (E) The germ-free mice (mice free from gut microbiota), showed the decrease in neurodegenerative conditions and also used to study the effect of gut microbiota on brain physiology, thus showing the involvement of gut microbiota in neurodegeneration.

circulation [203]. Changes in secondary bile acid levels have been found in human and mouse model of AD [204], PD [205], ASD [206] and multiple sclerosis [207]. Also, bacteria-modified bile acids were found to be neuroprotective in case of ALS and stroke [208]. Modulation of gut microbiota community can cause changes in the level and properties of bile acids, which might be neurodegenerative or neuroprotective. It has also been reported that gut microbiota-mediated increase in deoxycholic acids induces the release of neurotransmitter serotonin in EC in mice [94]. Bile acid metabolites were found to improve demyelination [209] and reducing oxidative stress [210], potentiating its neuroprotective role *via* acting on oligodendrocytes and microglia, respectively. Still, the potential role and effects of microbiota manipulated bile acid is unknown and remains to be defined clearly.

**Steroid hormones.** Signaling by steroid hormones is crucial for brain development and functions (memory, decision making and sexual behavior) [211]. While circulating throughout the body, steroid hormone encounters microbiota in intestinal lumen [212]. Gut bacteria modify steroid hormone in a deconjugation reaction mediated by the action of  $\beta$ -glucuronidases and  $\beta$ -glucosidases, which reactivates the hormone and prevent it from excretion. Thus, gut microbiome influences the level of active and inactive steroid hormones *via* degradation and activation pathways [213]. Androgens and oestrogens are found to be influenced by gut microbiome. A large number of enteric bacteria were found to metabolize oestrogens [214] and oestrogens also undergo oxidation–reduction reactions in faecal samples [215], suggesting the role of gut microbiota. It has been observed that gut microbiota also possesses the ability

to convert testosterone [216] and cholesterol to androgens [217]. Microbial influenced oestrogens were found to be neuroprotective, showing anti-inflammatory effects on microglia [218]. Also, altered gut microbial community was observed to result in low levels of oestrogen, which resulted in chronic inflammation [219] and cognitive impairment [220]. Oestrogenic molecules also affects differentiation and myelination in oligodendrocytes [221]. Recent report also showed that even progesterone treatment in MPTP parkinsonian mouse model showed neuroprotective, anti-inflammatory and immune-modulatory effects, but whether the neuroprotective role begins in gut or brain is still unknown [222].

#### Gut microbiota interaction with dietary molecules

**Amino acids.** Dietary amino acids can also be metabolized by gut microorganisms and their effect on the brain varies depending upon the type and frequency of diet intake [223]. Although, gut microbiota encoded amino acids circulate in the host, but those affecting CNS are dietary amino acids metabolized by gut bacteria [224]. Aromatic amino acids like tyrosine, tryptophan and phenylalanine are metabolized by gut bacteria into SCFAs, indole derivatives, neurotransmitters, organic acids, amines and ammonia [225]. The end product of tyrosine metabolism is the formation of two catecholamines, dopamine and noradrenaline from tyramine intermediate. *In vitro* studies showed that large number of gut bacteria can produce noradrenaline in millimolar range [226]. Recent report showed that non-adrenaline increases the supply of glutathione from astrocytes by stimulating B-3 adrenoceptor, thus protecting neurons from  $H_2O_2$ -induced neuronal death [227]. It is found that tyrosine is also metabolized by gut

**Table 1**

Summary of various reported studies on the role of gut microbiota in neuroprotection.

Microbiota	Neurodegenerative disease	Model	Study outcome	Reference(s)
<i>Lactobacillus buchneri</i> KU200793	PD/AD	SH-SY5Y cells	Treatment with heat killed strain reduced Bax/Bcl-2 ratio and increased BDNF expression	[288]
<i>Lactobacillus delbrueckii</i> ssp. <i>bulgaricus</i> B3 and <i>Lactobacillus plantarum</i>	AD	SH-SY5Y cells	Protected cells from A $\beta$ -induced cytotoxicity	[22]
<i>Lactococcus lactis</i> p62(SQSTM1)-engineered	AD	3xTg-AD mice	Diminished oxidative stress and inflammation, reduced levels of amyloid peptides and improved memory	[289]
<i>Lactocaseibacillus rhamnosus</i> HA-114	ALS/HD	<i>Caenorhabditis elegans</i> and mouse model of ALS	Restores lipid homeostasis and energy balance through mitochondrial $\beta$ oxidation	[290]
<i>Clostridium butyricum</i>	AD	APP/PS1 mouse model of AD	Prevents A $\beta$ deposition, microglia activation, production of TNF- $\alpha$ and IL-1 $\beta$	[291]
<i>Lactobacillus fermentum</i> NCIMB 5221	AD	APPswe and PS1E9 mutant transgenic mice	Ferulic acid produced by bacterium reduces oxidative stress, A $\beta$ fibrillation and improves memory	[292]
<i>Lactobacillus plantarum</i> WCFS1, <i>E.coli</i> Nissle and <i>Bifidobacterium infantis</i> spp.	AD/PD	NA	Proficient in producing butyrate, propionate and acetate	[293]
<i>Lactobacillus plantarum</i> MTCC1325	AD	D-galactose- induced AD mice model	ATPase enzyme levels and Na <sup>+</sup> and K <sup>+</sup> ATPase activity was restored required for potential neural activity	[294,295]
SLAB51 ( <i>Streptococcus thermophilus</i> , <i>Bifidobacterium longum</i> , <i>Bifidobacterium breve</i> , <i>Bifidobacterium infantis</i> , <i>Lactobacillus acidophilus</i> , <i>Lactobacillus plantarum</i> , <i>Lactobacillus paracasei</i> , <i>Lactobacillus delbrueckii</i> subsp. <i>bulgaricus</i> , <i>L. brevis</i> )	AD	3xTg-AD mice	Inhibits A $\beta$ deposition, decreased acylation of p53 protein along with increase in SIRT1 deacetylase activity and ADAM10- $\alpha$ secretase activity	[274]
<i>Rummicoccus albus</i>	NA	Oxidative stress induced Sprague Dawley rats and SH-SY5Y cells	Reduced ROS levels and increased SOD and GSH levels in oxidative stress condition	[23]
<i>Lactobacillus acidophilus</i> and <i>Bifidobacterium infantis</i>	PD	Human PD patients	Reduced symptoms of abdominal pain and bloating	[296]
<i>Lactobacillus acidophilus</i> , <i>Bifidobacterium bifidum</i> , <i>Lactobacillus reuteri</i> , and <i>Lactobacillus fermentum</i>	PD	Human PD patients	Decreased movement disorder society-unified Parkinson's disease rating scale scores	[297]
<i>Lactobacillus casei</i> Shirota	PD	Human PD patients	Improved abdominal symptoms	[298]
<i>Lactobacillus acidophilus</i> , <i>Lactobacillus casei</i> , <i>Bifidobacterium bifidum</i> , and <i>Lactobacillus fermentum</i>	AD	Human AD patients	Decreased C- reactive protein (CRP) levels and insulin resistance and neuronal cell death	[299]
<i>Lactobacillus acidophilus</i> , <i>Bifidobacterium bifidum</i> , <i>Lactobacillus reuteri</i> , and <i>Lactobacillus fermentum</i>	PD	6-OHDA treated male Wister rats	Improved rotational behavior, cognitive function, lipid peroxidation, and neuronal damage	[300]
<i>Lactobacillus acidophilus</i> , <i>Bifidobacterium bifidum</i> and <i>Bifidobacterium longum</i>	AD	Animal model of AD	Improved cognitive performance and restored synaptic plasticity	[301]
<i>L. casei</i> LC122 and <i>B. longum</i> BL986	Age related neurodegeneration	C57BL/6 mice	Attenuated oxidative stress, improved gut barrier function and inhibited hepatic lipid accumulation	[302]
<i>Lactobacillus johnsonii</i>	AD	Germ free mice	Decreased kynurenine and increased serotonin levels	[303]

microbiota in phenols like 4-ethyl phenol, which subsequently get sulphated in host to 4-ethyl phenol sulphate, which is found elevated in a mouse model of ASD, and also a urinary biomarker for children with ASD [228]. Indole derivatives like tryptamine and kynurenine are the products of tryptophan metabolism by gut bacteria, which are neuroactive molecules [92]. Indole propanoic acid, an indole derivative act as an antioxidant reducing neuroinflammation, and is observed to have a potential role in decreasing AD pathology [229]. Kynurenine metabolites were found to affect anxiety, memory and stress-like behavior [230]. It has also been observed that disturbances in kynurenine metabolic pathway promote inflammation, excitotoxic glutamate production, and free radical attack, suggesting the neuroprotective role of balanced kynurenine and its anti-inflammatory role in AD, PD and HD [231]. Tryptophan metabolites help to decrease the inflammatory responses of astrocytes by modulating its aryl hydrocarbon receptor and also affects their interaction with microglia. Likewise, it has also been observed that indoxyl-3-sulphate controls activation of microglia and subsequently its interaction with astrocytes [232]. Amino acid glutamate is also converted by gut bacterial glutamate

decarboxylases to form GABA, an inhibitory neurotransmitter, which is observed to reduce depression and anxiety symptoms in mouse model [90]. In case of amino acid arginine, it is metabolized into four polyamines agmatine, putrescine, spermidine and spermine, which act via glutamate receptors and are involved in maintaining synaptic plasticity and memory formation [233]. Agmatine shows the therapeutic effects in case of CNS disorders while acting as a ligand for  $\alpha$ -2 adrenergic and imidazole receptors in brain [234]. Spermidine also showed its neuroprotective effect in 3-nitropropionic acid 3-NP model of HD [235]. Moreover, agmatine was found to stimulate Nrf-2 signaling pathway, ameliorating ROS production induced by lipopolysaccharide (LPS) [236]. *In vitro* and *in vivo* studies also revealed that agmatine protects astrocytes and microglia from damage induced by oxidative stress [237]. These studies suggest the potential role of gut microbial endocrinology in neuroscience.

**Dietary fibers.** Undigested dietary fibers like complex carbohydrate polysaccharides are acted upon by intestinal microbial enzymes glycoside hydrolases and polysaccharide lyases and are converted



to SCFAs via anaerobic fermentation [238]. Butyrate, acetate, and propionate comprise SCFAs, which act as a source of energy for colonic epithelial cells. Besides this, it also enters systemic circulation, subsequently affecting physiological functions of many organs including neural development and functions directly or indirectly [238]. Reports reveal that when gut microbiota of AD mouse model was modulated by treating with a mixture of probiotics or by using anti-inflammatory SCFAs, it helps to counteract the progression of the disease [239]. Similarly, SCFAs were found effective to exacerbate motor symptoms in GF mouse model of PD [240]. SCFA, acetate crosses the BBB and activates the neurons and modulates the level of neurotransmitters and neurotrophic factors [241]. In a study, it was shown that propionate and butyrate influence the intracellular potassium level in neurons [242]. Butyrate acts as a potent inhibitor of enzyme which regulates epigenetic gene activation (histone deacetylase) and is found to act as a potent anti-inflammatory agent in mouse model of AD, PD, HD, stroke and memory impairment [238]. Interestingly, SCFAs interfere in the interaction between A $\beta$  peptides to form neurotoxic oligomers, thus preventing AD pathology [243]. It was also reported that fecal microbiota transplantation from wild type mice to the animal model of PD along with the butyrate administration remarkably improved the motor symptoms and dopamine deficiency [244]. When we look at the cell-specific responses, butyrate has been shown to reduce neuroinflammation and oxidation in astrocytes *in vitro*, and acetate is used as a source of energy by these cells [245]. In a study, it was observed that SCFAs increases the expression of tight junction proteins by binding to the SCFA receptors on endothelial cells, thus helps in decreasing the permeability of BBB and preventing the LPS-induced seizures and stroke [246]. SCFAs reduce oxidative stress in the brain by decreasing microglial activation [247], thus combating neuroinflammation in AD and PD. Taken together, SCFAs obtained from dietary fibers helps to improve brain health, depending upon the gut health of the individual.

**Polyphenols.** Polyphenols are bioactive molecules present in plants that plays a fundamental role in growth, protection and reproduction in plants [248]. Polyphenols are classified as flavonoids, phenolic acids and tannins. The molecular structure of polyphenols i.e., positions of hydroxyl group and nature of the substitution of aromatic rings affords them the ability to scavenge free radicals [248] and are widely studied as an antioxidative therapy for the treatment of NDDs [249]. Unabsorbed polyphenol is converted into bioavailable and bioactive metabolites [250] in the host by the action of gut microbiota via hydrolysis and esterification, which is further followed by modifications like methylation, sulfation, hydroxylation before they reach the peripheral tissues [251]. Studies on different polyphenols like resveratrol obtained from grapes and wines, curcumin and epigallocatechin-3-gallate from green tea exerts neuroprotective effects by activating protein kinase pathways like Keap1/Nrf-2/ARE, which are major pathways in alleviating both endogenous and exogenous ROS. It has also been reported that bacterial polyphenolic metabolites such as 3-hydroxybenzoic acid and 3-(3'-hydroxyphenyl)propionic acid inhibits amyloid aggregation, thus facilitates to inhibit the progression of AD [252]. Similarly, it has been observed that a flavonoid quercetin act as BACE-1 inhibitor [253]. Moreover, natural flavonoid proanthocyanidins mitigate rotenone-induced oxidative stress in dopaminergic neurons *in vitro* [254]. Also, polyphenols like ferulic acid produced by gut microbiota promote neurogenesis and have shown the neuroprotective role in mouse models of AD [255] and cerebral ischemia [256]. Equol and Enterolactone are also derivatives produced by gut bacteria by metabolizing phytoestrogen, one of the polyphenols [257], which might have an effect on classical neuroprotective pathway mediated by oestrogen recep-

tors. Interestingly, polyphenols can also modulate the composition of gut microbiota [258], which further convert them into anti-inflammatory and neuroprotective metabolites.

### Vitamin B and vitamin K

Gut microbiota also acts as an important source of vitamins particularly vitamin B and K, which are not only essential for the gut microbial metabolism but also show its effects on physiological pathways in the host [259]. Gut bacteria like *Escherichia coli*, *Klebsiella pneumoniae*, *Propionibacterium*, and *Eubacterium* produces vitamin K, B2 (riboflavin) is produced by *Bacillus subtilis* and *E. coli*; B9 (folic acid) by *Bifidobacterium*, *Lactococcus lactis* and *Streptococcus thermophilus*; and B12 (cobalamin) is produced by *Lactobacillus reuteri* and *Propionibacterium freudenreichii* [260]. Though dietary vitamins are absorbed through small intestine, uptake of microbiota-derived vitamins occurs in the colon. To prevent hemorrhagic disease in neonates, prior to the establishment of gut microbiota, vitamin K is administered as an essential agent for the process of thrombosis [261]. Moreover, vitamin B and K are found to be important for brain development and function [262]. In the case of NDDs, many studies have shown the effective role of vitamin B and K in improving neuronal health. Vitamin K deficiency was found to be correlated with the pathogenesis of AD, similarly, increased uptake of dietary vitamin K has helped to improve the memory functions in elderly patients. Recent report shows that vitamin K2 (menaquinone-4) possesses potent antioxidative properties, and was found to significantly inhibit rotenone-induced p38 activation, ROS production and caspase-1 activity and subsequently, restored mitochondrial membrane potential, showing its potential in the treatment of neuroinflammation-induced PD [263]. Similarly, vitamin K2 was found effective to modulate bax and caspase-3 activation in PC12 mouse neuroblastoma cells, protecting it from 6-OHDA induced apoptosis [264]. Notably, one recent report has shown that low levels of vitamin K2 in PD patients are associated with dysregulated inflammatory responses and cascade coagulation signals [265]. Deficiency of vitamin B was also found to be associated with neurological disorders like beriberi, and polyneuropathy [266]. Similarly, folate deficiency was found to be associated with cognitive impairment and progressive dementia in older women [267]. Also, high intake of B6, B9 and B12 decreases the rate of atrophy in the brain region linked with the cognitive decline in AD [268]. Further, more constructive studies will be required to prove the potential link of gut microbiota produced vitamins in neuroprotection.

### Antioxidative and anti-inflammatory effects of probiotics

Free radicals in the form of ROS are byproducts of normal cellular metabolic processes. Free radicals are potentially able to damage the genetic material, enzymes inactivation, depolymerization of complex carbohydrates and lipid peroxidation. This vandalization of intracellular molecules leads to the cell death. To balance the free radicals, the body have specific antioxidants such as glutathione [269]. Some products also started to flow in pharmaceutical markets to tackle oxidative stress such as ferulic acid (FA) due to its antioxidative and anti-inflammatory properties. It helps to proliferate neuronal stem cells by enhancing the production of BDNF and nerve growth factor (NGF) and some neuropeptides having anti-inflammatory properties [270,271]. In 2017, Westfall *et al.* reported that FA is also produced by probiotic bacteria such as *Lactobacillus plantarum* NCIMB 8826, *Lactobacillus fermentum* NCIMB 5221 and *Bifidum animalis* in large quantity by bacterial FA esterase enzymes [272]. Due to its therapeutic effect, it is gaining attention

for its use in AD treatment, pre-treatment with FA has been shown to reduce the A $\beta$  fibrils and to treat the neuroinflammation in AD mice [273]. FA-producing probiotic bacteria inhibits the formation and aggregation of beta-amyloid fibrils through scavenging ROS.

Other probiotic bacterial protein, sirtuin-1 (SIRT1) protein deacetylase has been shown to have antioxidant properties. This protein regulates the genes of antioxidant pathways of host and has been documented to have neuroprotective effects. Recent research probed the capability of a formulation of probiotic bacteria named SLAB51 (*Streptococcus thermophilus*, *Lactobacillus acidophilus*, *L. plantarum*, *L. paracasei*, *L. delbrueckii* subsp. *bulgaricus*, *L. brevis*, *Bifidobacterium longum*, *B. breve*, *B. infantis*) to relieve oxidative stress and discovered the molecular mechanism of its effects [274]. In the treated transgenic 3xTg-AD-mice, the expression and activity of SIRT1 protein in the brain were observed to be retrieved and the formation of A $\beta$  peptide was shown decreased. However, in untreated AD mice, the expression of SIRT1 was found to be substantially decreased. Moreover, the enhanced activity of SIRT1 reduces the p53 protein acetylation and improves the survival of stressed cells by repressing apoptotic pathways. Other studies also showed that probiotic supplements activate the SIRT1 pathway and provoke antioxidative effects. SLAB51 also enhances the activity of GPx and catalase antioxidant enzymes to alleviate oxidative stress-causing impairments. Similar findings were also observed in humans. The concentration of SIRT1 in the brains of AD patients was found significantly reduced which is closely associated with the accumulation of amyloid- $\beta$  and tau in the cerebral cortex of persons with AD [275]. An improved level of SIRT1 has been reported in a human study supplemented with *Lactobacillus casei* 01, a probiotic strain [276].

There is a very fragile relationship between gut microbiota and host immune cells. Immune cells are specialized to peculiarly differentiate the host friendly bacteria from pathogenic bacteria. If this relationship hurts, it can lead to unnecessary immune responses, prompting chronic inflammation [277]. This differentiation is started by intestinal epithelial cells who are responsible for producing the educated macrophage phenotype based on bacterial cell

surface antigens such as LPS, peptidoglycan and flagellin. When epithelial cells become vulnerable to pathogenic attack, the antigens translocate into vasculature and in response, proinflammatory cytokines such as IL (interleukin)-1, IL-6, and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) are produced, which leads to septic shock and inflammation in the gut and brain. Some bacterial toxins can also cross the BBB [269,278]. To gaze at the role of microbiota in amyloidosis, an investigation was conducted through assessing the pro- (CXCL2, CXCL10, IL-1 $\beta$ , IL-6, IL-18, IL-8, inflammasome complex NLRP3, TNF- $\alpha$ ) and anti-inflammatory (IL-4, IL-10, IL-13) cytokine activity of several gut microbiota taxa in cognitively impaired patients and it was observed that the number of *Escherichia/Shigella* increases and *Eubacterium rectale* decreases significantly correlated with changes in concentration of pro- and anti-inflammatory cytokines in cognitively impaired and amyloid positive patients. In concert, an increased level of IL-6, CXCL2, NLRP3, and IL-1 $\beta$  and a decreased level of IL-10 was observed in AD patients. This study suggests that gut microbiota could initiate, worsen or alleviate peripheral inflammation in neurological diseases [279].

### In silico strategies to advance the gut-brain research

With the advancement of technology, knowledge about the brain is increasing exponentially. The neuroscientists have generated plenty of data from molecular biology, molecular genetics, brain imaging, and other new technologies, and have a significant interest in sharing the neuroscience data for various analysis. Neuroimaging is also very helpful in predicting and detecting NDDs and mental disorders. In the interest of neuroscience data collection and analysis, various bioinformatics tools are being developed for the further development of devices based on brain functions. To date, researchers have a rudimentary knowledge of molecular pathways involved in neurodegeneration due to various stress conditions. The integrated databases will be helpful to collect the different types of data related to neurodegeneration diseases from publicly available sources (Table 2).

**Table 2**  
Overview of currently active databases related to neurological data.

Database	Web address	Data type	Reference(s)
PDGene	<a href="http://www.pdgene.org/">http://www.pdgene.org/</a>	Meta-analysis of genome-wide association studies (GWAS)	[304]
MDSGene	<a href="http://www.mdsgene.org/">http://www.mdsgene.org/</a>	Genetic mutations, movement disorder genes related to PD	[305]
Alzforum	<a href="https://www.alzforum.org/mutations">https://www.alzforum.org/mutations</a>	Repository of variants in genes linked to AD	[306]
AlzGene	<a href="http://www.alzgene.org/">http://www.alzgene.org/</a>	Systematic meta-analyses of AD	[307]
Neuroinformatics Database (NiDB)	<a href="https://www.nitrc.org/projects/nidb/">https://www.nitrc.org/projects/nidb/</a>	Imaging	[308]
Neuroscience Information Framework (NIF)	<a href="https://neuinfo.org/">https://neuinfo.org/</a>	Metadata (imaging, genes, omics, function, grants, protocols etc.)	[309]
BrainMaps	<a href="http://brainmaps.org/">http://brainmaps.org/</a>	Brain structure and function	[310]
Hippocampome Portal	<a href="http://www.hippocampome.org/php/index.php">http://www.hippocampome.org/php/index.php</a>	Morphology, molecular marker, membrane biophysics and synaptic physiology	[311]
NeuroElectro	<a href="https://neuroelectro.org/">https://neuroelectro.org/</a>	Electrophysiological properties	[312]
NeuroMorpho	<a href="http://neuromorpho.org/index.jsp">http://neuromorpho.org/index.jsp</a>	Neuromorphology and metadata	[313]
NeuronDB	<a href="https://senselab.med.yale.edu/NeuronDB/">https://senselab.med.yale.edu/NeuronDB/</a>	Voltage gated conductances, neurotransmitter receptors, and neurotransmitter substances	[313]
Collaborative Research in Computational Neuroscience (CRCNS)	<a href="http://crcns.org/">http://crcns.org/</a>	Electrophysiology and behavioral data	[314]
NeuroImaging Tools and Resources Collaboratory (NITRC)	<a href="https://www.nitrc.org/">https://www.nitrc.org/</a>	Neuroimaging, imaging genomics software tools, data, and computational resources	[315]
BigBrain	<a href="https://bigbrainproject.org/">https://bigbrainproject.org/</a>	Ultrahigh-Resolution 3D Human Brain Model	[316]
Brain Transcriptome database (BrainTx)	<a href="http://www.cdtb.brain.riken.jp">http://www.cdtb.brain.riken.jp</a>	Gene expression	[317]
Marmoset Gene Atlas	<a href="https://gene-atlas.brainminds.riken.jp/">https://gene-atlas.brainminds.riken.jp/</a>	Gene expression	[318]
Allen Brain Map	<a href="https://portal.brain-map.org/">https://portal.brain-map.org/</a>	Metadata (gene expression, imaging toolkits etc.)	[319]
BrainCloud	<a href="https://www.libd.org/brain-cloud/">https://www.libd.org/brain-cloud/</a>	Gene expression	[320]
M <sup>2</sup> IA	<a href="http://m2ia.met-bioinformatics.cn/">http://m2ia.met-bioinformatics.cn/</a>	Microbiome and metabolome integrative analysis	[283]
Microbiota-Active Substance Interaction Database (MASI)	<a href="http://www.aiddlab.com/MASI/">http://www.aiddlab.com/MASI/</a>	Effect of bioactive compounds on microbiota and vice versa	[284]

The comprehensive knowledge of microbiome and their importance in human health is increasing at a fast pace with the aggrandizement of high throughput technologies. Microbiota interacts with the host metabolites and converts them to secondary metabolites. Gut microbiota also produces their metabolites which play very important role in human health. Comprehending the interaction of metabolites and gut microbiota, it is important to know the function of microbiota in health and disease status and to develop natural therapies [280]. In the recent past, it has been proved that gut bacteria can alter CNS physiology and dysbiosis could be a potential factor in neuroinflammation [281]. In 2019, Lu and Claud reported that initial colonization and microbiota development affect brain development in preterm infants [282]. To manage and facilitate this exponentially increasing information, microbiota databases are being developed for in-depth understanding of the role of microbiota in human health. To establish the correlation between microbiota and metabolites, new pipelines are being developed such as M<sup>2</sup>IA, an automated microbiome and metabolome integrative analysis pipeline [283]. Other microbiota databases provide useful information about disease-associated microbes, modulation of drugs by microbiota, the effect of diet on gut microbes. To distribute the knowledge about the alteration of active substances such as therapeutic drugs, dietary components, herbal products, probiotics and environmental chemicals by microbiota and alteration of microbiota by active substances, Microbiota-Active Substance Interactions (MASI) database is developed [284]. These databases will be very helpful to establish the correlation between bacterial metabolites and neuronal health and pathogenesis. It has been reported that in clinical trials, the outcome of L-dopa treatment for PD varies between the recruiting subjects. This variation is because of their microbiota. L-dopa is metabolized by Tyrosine decarboxylase (TDC) and dopamine dehydroxylase (Dadh) of different gut bacterial species namely *Enterococcus faecalis* and *Eggerthella lenta* A2 [285]. For the inactivation of bacterial L-dopa decarboxylase, a drug, (S)- $\alpha$ -fluoromethyltyrosine (AFMT) was discovered. The combination of L-dopa and AFMT is being used for Parkinson's treatment. Zhuang *et al.* showed that gut microbiota is altered in patients with AD compared to healthy individuals at taxonomic levels, such as Bacteroides, Actinobacteria, Ruminococcus, Lachnospiraceae, and Selenomonadales [286]. Metagenomic data/16S RNA sequencing data support firm association between dysbiosis and AD. Bacterial products such as LPS and SCFAs are associated with amyloid pathology [287]. The main objective of the development of these databases is to organize data in a set of structured records that can be helpful to retrieve the information for different analysis by analyst to provide the solutions to different unsolved mysteries related to neurodegeneration.

## Conclusion

Interconnection of gut microbiota and brain has led to transformative advances in neuroscience research. To date, most of the studies found are related to gut bacterial neuroscience research, but the gut microbiome is vast and requires the attention of scientists to identify and characterize the role of gut micro-organisms and their communities, affecting gut-brain signaling routes. There is a need for additional understanding of pathways employed by gut microbiota in mediating communication between the gut and brain in the process of neurodegeneration and neuroprotection, which may open the way to new hypotheses in pathology and treatment of the disease. New treatment regimens like fecal microbial transfer and probiotics, though have helped in improving brain health to some extent, but lacking empiric pieces of evidence in commercial probiotic strains provokes the need to study particular probiotics for the treatment of particular NDDs. Further, the

growing potential of *in-silico* strategies will help to gain a deep understanding of microbial effector molecules in neurodegeneration and neuroprotection, but unfortunately, these studies are very limited. Bioinformatic tools are the need of the hour, which could potentiate the designing of such drugs that can target the specific bacterial enzymes mediating the production of harmful metabolites. Neuroprotective and neurodegenerative roles of gut microbial metabolites are continued to be uncovered, providing opportunities to develop novel therapeutic modalities.

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All authors have read the final version of the manuscript and have given their consent for publication.

## CRediT authorship contribution statement

**Shruti Shandilya:** Conceptualization, Writing – original draft, Writing – review & editing, Artwork & schemes, Visualization. **San-deep Kumar:** Writing – original draft, Writing – review & editing, Software. **Niraj Kumar Jha:** Formal analysis, Editing, Artwork & schemes. **Kavindra Kumar Kesari:** Supervision, Writing – review & editing, Validation. **Janne Ruokolainen:** Supervision, Validation, Data curation, Funding acquisition.

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The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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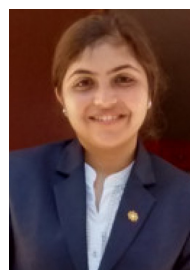


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