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Editor's Comment: There is growing recognition of the importance of the multitude of organisms (100 trillion of them!!) that reside in our intestinal tract, labeled the gut microbiota, not only with regard to their impact on gut function but on many other aspects of human function and behavior. In this timely review, Parashar and Udayabanu provide a thorough and thought-provoking tour through the fascinating landscape provided by the intersection between the gut microbiota and Parkinson's disease and the possible role the gut microbiota may play, not only in producing clinical symptoms in individuals with Parkinson's disease, but also with regard to the possible genesis of the disease itself. I believe readers will find this review tremendously interesting, informative, and enlightening.

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Review article

Gut microbiota: Implications in Parkinson's disease



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ABSTRACT

Gut microbiota (GM) can influence various neurological outcomes, like cognition, learning, and memory. Commensal GM modulates brain development and behavior and has been implicated in several neurological disorders like Alzheimer's disease, multiple sclerosis, amyotrophic lateral sclerosis, anxiety, stress and much more. A recent study has shown that Parkinson's disease patients suffer from GM dysbiosis, but whether it is a cause or an effect is yet to be understood. In this review, we try to connect the dots between GM and PD pathology using direct and indirect evidence.

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1. Introduction

Gut microbiota (GM), referred to as “forgotten organ” is home to 100 trillion bacteria (and some fungi, archaea, and viruses), 10 times greater the number of cells present in human body. In addition to this, the total genome of gut microbiota (gut microbiome) has around 3 million genes, 150 times more than the human genome. Interestingly, one-third of our GM is common to most people, while two-thirds is specific to each individual, like an identity card. Recently, a study revealed that every individual possesses a unique microbial fingerprint that distinguishes him from others [1]. Identification and characterization of the

remarkably diverse population of gut microbes is just the dawn as a shocking 50–60% of the microbes have never been cultured, possibly because of their resilient spores which are meant for host-to-host transmission [2,3]. Researchers are now intrigued by the hypothesis that such a big population of microbes with a huge genome can significantly modulate human behavior, physiology, and biology. The existence of a bidirectional network often known as the “gut microbiota-brain axis (GMBA)”, has now achieved global acceptance and its dysregulation has now been linked to numerous diseases, igniting the need for deeper insights and new treatment strategies [4]. GMBA can influence brain neurochemistry (altered levels of neurotransmitters, their receptors, and various neurotrophic factors) and behavior [5–9].

Parkinson's disease (PD) is a multifocal neurodegenerative disorder characterized by akinesia, muscular rigidity, tremor, slowness of movement, difficulty in walking and gait. Besides these motor traits, other symptoms include dementia, depression, sensory and autonomic dysfunction. Other than the commonly known

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dopaminergic loss in substantia nigra pars compacta (SNpc), PD is characterized by synucleinopathy i.e. deposition of insoluble polymers of α -synuclein in the neuronal body, forming round lamellated eosinophilic cytoplasmic inclusions, the Lewy bodies. These Lewy bodies are responsible for neurodegeneration and neuronal death [10,11]. Interestingly, substantia nigra is not the induction site of PD and there is co-existence of considerable extranigral pathology. PD triggering occurs outside the basal ganglia with the formation of the very first Lewy bodies in non-dopaminergic neurons of the glossopharyngeal-vagal complex, coeruleus-subcoeruleus complex, caudal raphe nuclei, gigantocellular reticular nucleus and olfactory pathways [12].

Interestingly, the brain is not the only organ bearing the burden of PD pathology and there exists an extra neurological perspective too. PD patients often have comorbid gastrointestinal dysfunction, with approximately 80% of PD patients suffer from constipation [13]. Additionally, the relationship between idiopathic constipation and PD is well established [14,15]. In PD, constipation is associated with α -synuclein accumulation and neurodegeneration in the enteric nervous system [16], with increased local inflammation, oxidative stress and intestinal permeability [17,18]. These pathophysiological changes can be observed even in initial stages of PD, and in some cases years before the motor hallmarks appear, conferring support to the hypothesis that PD pathogenesis might act primarily via the gut [15,19–22].

One of the most extensively studied examples of microbial association of PD is that of *Helicobacter pylori*. The prevalence of *H. Pylori* infection is high among PD patients and causes motor impairments by hindering the absorption of levodopa, a primary drug for PD management (reviewed in Ref. [23]). Similarly, small intestinal bacterial overgrowth (SIBO), a disorder of excessive bacterial growth in the small intestine has been associated with PD too. SIBO affects nearly one-quarter of PD patients and was found to be significantly higher than in controls. SIBO was associated with motor impairments and its eradication resulted in improvement in motor fluctuations [24,25]. Recently, GM dysbiosis was found to be associated with PD as observed by a significant reduction of *Prevotellaceae* in stools of PD patients as compared to controls. Additionally, a direct correlation was found existing between the abundance of *Enterobacteriaceae* and severity of postural instability & gait difficulty [26]. In another study, PD patients suffered from increased mucosal permeability and systemic endotoxin exposure of coliform bacteria [17]. Similarly, bacteria belonging to the genus *Blautia*, *Coprococcus*, and *Roseburia* were significantly reduced in feces of PD patients as compared to controls. And bacteria belonging to the genus *Faecalibacterium* were significantly reduced and that of genus *Ralstonia* were significantly increased in the mucosa of PD subjects. At the genetic level, significant dysregulation in genes involved in lipopolysaccharide biosynthesis and secretion system were observed in the PD fecal microbiome [27]. Another study reported that no change in *Bifidobacteria* level was found in PD patients [28]. Gut microbial intervention in PD can be appreciated from the fact that DA synthesis in the brain is induced by DA producing enzymes, whose synthesis/inhibition is controlled by GM via the “GMBA” [29]. In addition, gut microbes like *Bacillus* spp. are known to produce DA [5] and GM accounts for almost half of the of body's DA production [30,31].

Diverse strategies have been implied to explore the influence of the GM on brain viz germ-free/gnotobiotic animals, oral antibiotics, probiotics, fecal microbiota transplantation and gastrointestinal infection studies. Table 1 encompasses the various strategies used to study the effect of GM on brain & behavior and how they can possibly underline PD etiology. The current review focuses on various other evidence that gives rise to the hypothesis of GM's possible mediatory role in PD pathology.

1.1. Germ-free/gnotobiotic animals

Germ-free (GF) mice often referred to as axenic, are mice that are free of all microorganisms. Gnotobiotic mice are axenic mice that are inoculated with a cocktail of one or more known non-pathogenic microorganisms. The fetus inside the mother is sterile and gains microbiota during birth from mother's vagina; therefore to produce GF animals surgical procedures like hysterectomy rederivation are employed. GF mice are maintained in isolators under very strict handling procedures to keep them germ-free.

Catecholamine (DA, NA, and 5-HT) levels when measured in different brain regions like frontal cortex, striatum, and hippocampus of GF and control mice, showed significant alterations. GF mice exhibited significant higher turnover rates of DA, NA and 5-HT in the striatum as compared to control counterparts [7]. In a similar study, DA level in the brain was found to be roughly twice in GF than in control mice [32]. This finding was consistent with those in which GF mice displayed increased locomotor activity compared to control counterparts [7,33]. In contrast, a study reported that the DA, NA, and 5-HT turnover rates were increased in the brainstem, striatum, and medial prefrontal cortex of control mice than in the GF mice, suggesting an increased monoaminergic neurotransmission in the normal mice as compared to the GF mice [34]. Similarly, GF rats exhibited a decreased DA turnover rate in the striatum, hippocampus, and frontal cortex compared to control rats [35]. Interestingly, enzymes responsible for the conversion of tyrosine to DA i.e. tyrosine hydroxylase and DOPA decarboxylase, their synthesis or inhibition is controlled by GMBA [36]. Therefore it is plausible that commensal microbes control brain DA levels, which is depleted in PD. Further, brain tyrosine level is controlled by GM as GF mice had lower tyrosine than normal mice [32].

DA is known to be critical in regulating motor and cognitive functions [37]. In GF mice, D1 DA receptor gene expression was significantly elevated in the hippocampus, while reduced in the striatum and nucleus accumbens, compared with control mice. Gene expression of NGFI-A, a protein essential for synaptic plasticity, was significantly reduced in prefrontal cortex and striatum of GF mice indicating decreased synaptic plasticity in the striatum of GF mice. Expression levels of proteins involved in synaptogenesis (synaptophysin and PSD-95) in the striatum were remarkably increased in GF mice as compared to control mice. However, no such dissimilarities were found in frontal cortex and hippocampus. Further, microarray analysis revealed significant differential expression profiles of 23 genes in the striatum of GF mice as compared to normal mice. This significant control of GM over striatal synaptogenesis and gene expression could have a role in PD pathology [7].

Using a transgenic (α -synuclein over-expressing [ASO]) mice model of PD, GF condition lead to reduced microglia activation, α -synuclein inclusions, and motor deficits compared to animals with a normal GM. Treatment with GM produced short chain fatty acids (SCFAs), all major features of the disease in GF mice were restored [38]. This indicates that GM produced mediators can play a protective role in PD pathology.

Since striatum and DA are involved in various activities like locomotion, reward, mood, cognition and in PD pathology, it is possible that GM mediates PD by influencing these two benchmarks.

1.2. Antibiotics

Minocycline, a broad-spectrum tetracycline antibiotic besides having an impact on GM is a caspase and inducible nitric oxide synthase inhibitor, enzymes that are essential for apoptosis. Numerous reports now suggest the neuroprotective activity of

Table 1
Various strategies used to study GM and how it might mediate PD pathology.

S.No.	Strategy	Description
1	Germ-free	<ul style="list-style-type: none"> ↑ Or ↓ turnover rates of DA in the striatum, brainstem & medial prefrontal cortex of GF mice [7,32,34]. ↓ Dopaminergic turnover rate in the striatum, hippocampus & frontal cortex of GF rats [35]. ↓ Brain tyrosine (DA precursor) levels of GF mice [36]. ↑ D1 DA receptor in the hippocampus [7]. ↓ D1 DA receptor striatum & nucleus accumbens [7]. ↓ Synaptic plasticity in the striatum of GF mice [7]. ↓ Striatal gene expression [7]. ↓ microglia activation, ↑ α-synuclein inclusions and ↑ motor deficits [38].
2	Antibiotics	<p>Minocycline:</p> <ul style="list-style-type: none"> ↓ <i>Firmicutes/Bacteroidetes</i> ratio [48]. Prevented nigrostriatal dopaminergic neurodegeneration [39]. ↓ DA depletion in striatum & nucleus accumbens [39]. Dopaminergic neuroprotection against rotenone toxicity [40]. Antioxidant & anti-inflammatory properties and conferred potent dopaminergic neuroprotection [41,42]. Amplified MPTP-induced damage to DA neurons [44]. Deleterious effects in PD [45]. <p>Ampicillin:</p> <ul style="list-style-type: none"> Prevented motor & behavioral impairments in mice exposed to GAS antigen [49]. ↑ tyrosine hydroxylase, D1 & D2 receptors in striatum [49]. <p>Others:</p> <ul style="list-style-type: none"> Ceftriaxone ↓ locomotor activation controlled by striatum [50]. Neomycin, metronidazole and polymyxin B cocktail ↓ locomotor activity, ↓ <i>Firmicutes</i> and ↑ <i>Bacteroides</i>, <i>Proteobacteria</i> and <i>Actinobacteria</i> [51].
3	Probiotics	<ul style="list-style-type: none"> ↑ production of L-DOPA by <i>Bacillus</i> sp. <i>JPJ</i> [53]. ↑ production of antioxidant vitamins, preventing oxidative damage in PD [54,55,67]. ↓ constipation in PD patients by <i>Lactobacillus casei</i> Shirota [71].
4	Fecal transplant	<ul style="list-style-type: none"> ↓ GI pathology in neurodegenerative disorders [52,75,78–80]. ↑ motor impairment, ↓ <i>Lachnospiraceae</i> and <i>Ruminococceae</i> by fecal transplantation from PD patients [38].
5	Infection	<ul style="list-style-type: none"> ↓ L-dopa absorption & ↑ clinical disability in PD patients with <i>H. pylori</i> infection [86,87]. ↑ infectious burden of cytomegalovirus, Epstein-Barr virus, herpes simplex virus type-1, <i>B. burgdorferi</i>, <i>C. pneumoniae</i> and <i>H. pylori</i> [101].

minocycline in PD. Minocycline prevented neurodegeneration of nigrostriatal dopaminergic neurons and also blocked DA depletion in the striatum and nucleus accumbens in MPTP mouse model of PD [39]. In-vitro, minocycline conferred neuroprotection against the tyrosine hydroxylase immunoreactive neurons using rotenone-induced toxicity in primary dopaminergic cultures [40]. Using fruit fly as a model for PD several studies have reported that minocycline has anti-inflammatory and antioxidant properties and that it conferred potent dopaminergic neuroprotection [41,42]. Clinically, minocycline was assessed as a potential drug candidate for PD in Phase II trials and is being considered for Phase III trials [43].

In few contradictory studies, minocycline was found to augment MPTP-induced cellular insult to DA neurons, although it inhibited microglial activation [44]. Minocycline contributed to PD pathology as it caused a severe loss of putaminal dopaminergic nerve endings in MPTP-intoxicated monkeys [45]. Overall, minocycline has shown to significantly improve disease conditions like rheumatoid arthritis and vascular complications, suggesting that the commensal bacteria contribute at some level to disease development [46–48]. Minocycline has the ability to rebalance the dysbiotic GM by reducing the *Firmicutes/Bacteroidetes* ratio [48]. Knowing the neuroprotective potential of minocycline in PD and its impact on GM, it seems reasonable to assume that commensal GM has a role in PD pathogenesis. Although a study directly correlating the effect of minocycline on GM in PD patients or animal models is yet to be pursued.

Ampicillin (amp) has also shown some neuroprotective potential in PD. Amp treatment prevented motor and behavioral impairments in mice exposed to Group A streptococci (GAS) antigen, which is responsible for the dysfunction of the central dopaminergic system. Amp increased the level of tyrosine hydroxylase, D1 and D2 receptors in the striatum, without any reduction in the levels of anti-GAS antibodies [49]. Since the central dopaminergic system is highly dysregulated in PD it could be possible that amp could exert its effect via modulating GM and GMBA.

Cocaine addiction is related to increased central dopaminergic activity in reward seeking mechanisms. Cocaine causes locomotor activation and behavioral sensitization. Ceftriaxone (CTX), a cephalosporin antibiotic, decreased locomotor activation (controlled by striatum and is involved in PD pathology) and attenuated behavioral sensitization development induced by frequent cocaine exposure. Reward-seeking circuitry too is impaired in PD and the ability of CTX to modify the motor control and behavior could have a significance in PD [50].

Similarly, a cocktail of antibiotics viz Neomycin, metronidazole and polymyxin B was associated with reduced locomotor activity. This cocktail reduced *firmicutes*, increased *Bacteroides*, *Proteobacteria*, and *Actinobacteria*. This means that antibiotics exert their action on locomotion (possibly via GMBA) which is impaired in PD [51]. Another case study reported an unexpected and sharp decline in PD symptoms when treated with antibiotics like vancomycin, metronidazole, and colchicines [52].

1.3. Probiotics

Probiotics are the living and often referred to as “the good” microorganisms (mainly bacteria and yeasts), which when administered in adequate amounts, confer health benefits to the host by restoring the body’s “good” vs. “bad” microbial balance. Probiotic bacterium *Bacillus* sp. *JPJ* can produce L-DOPA from L-tyrosine *in-vitro* which is then converted to DA with the aid of DOPA decarboxylase [53].

Oxidative stress is considered to be the common underlying mechanism for cellular insult and apoptosis of dopaminergic neurons whether it is idiopathic or genetic cases of PD [54,55]. GM and probiotics potential of producing vitamins with antioxidant properties is another interesting research venue which has now been demonstrated to be beneficial for PD pathology. For example; Higher consumption of Vitamin E was associated with a lower risk of PD [56,57]. It also protected dopaminergic neurons in the SNpc,

prevented DA loss and showed protection against paraquat toxicity [58,59]. Vitamin D3 supplementation prevented the deterioration of the Hoehn & Yahr stage in PD patients [60] and Vitamin D was beneficial in animal (*in-vivo*) and cell culture (*in-vitro*) models of PD [61–63]. Prolonged administration (6 months) of riboflavin show improved motor capacity in PD patients [64]. Low intake of vitamin B6 was associated with an increased risk of PD [65]. Human GM has the potential to synthesize vitamin K and most of the water-soluble B vitamins, such as biotin, cobalamin, folates, pantothenic acid, nicotinic acid, pyridoxine, riboflavin and thiamine [66]. Particularly, probiotic strains like *Lactobacilli* and *Bifidobacteria* are highly capable of producing potential antioxidants, vitamins, and bioactive molecules [reviewed in Ref. [67]] [68–70], hence are capable of limiting excessive amounts of free radicals, leading to attenuation of several diseases associated with oxidative stress and may be PD too. Recently, a clinical pilot study has shown that a regular intake of fermented milk beverage containing *Lactobacillus casei Shirota* can significantly improve constipation and bowel movement in PD patients. Since gastrointestinal dysfunction, like constipation, directly contributes to the morbidity of PD patients and exacerbates the clinical scenario, use of probiotic might offer relief from the complications [71].

1.4. Fecal microbiota transplant

Fecal microbiota transplantation (FMT) or fecal bacteriotherapy is a technique whereby fecal matter from a healthy donor is delivered into the GI tract of a patient. FMT aims at restoring healthy gut flora. The process involves screening for pathogens followed by homogenization, filtration and resuspension of stool sample and then delivered either by nasogastric tube, enema, or colonoscopy into the recipient [72].

Patients with neurodegenerative disorders often suffer from altered gastrointestinal tract motility. For example, chronic and idiopathic constipation are commonly co-morbid in PD patients and can be associated with colonic and anorectal dysmotility [73]. Several case reports suggest the beneficial role of FMT in treating constipation in addition to marked improvement in non-GI symptoms in patients with neurological disorders [74]. Such reports have tweaked the interest of researchers in investigating and identifying the underlying mechanisms as to how GM connects to the pathogenesis of PD. Proposed mechanisms behind FMT benefits include direct communication via the vagus nerve, changes in neurotransmitter metabolism, immune activation, production of neuroactive metabolites and neurotoxins [5,74–76]. Since most of the PD patients have gastrointestinal dysfunction, innervation of the gut by the autonomic nervous system (ANS) has provided a novel investigation tool. The ANS connects the gut and the brain, and vagus nerve serves as a major pathway for relaying the signals in GMBA. This autonomic input from the gut is connected to the limbic system of the brain, which includes the hippocampus, the amygdala, and the limbic cortex. Limbic cortex is of importance since it regulates motor functions, which are impaired in PD. The connection between the limbic system and ANS is a critical factor underlying between gut health and brain & behavior [77]. Recently, it was found that fecal transplant from PD patients exacerbated motor impairment with reduction in *Lachnospiraceae* and *Ruminococceae* in recipient mice model of PD. Interestingly, same genera were significantly reduced in fecal samples from PD patients [27].

Several case reports of patients with PD, multiple sclerosis, myoclonus dystonia, Alzheimer's disease, chronic fatigue syndrome, and autism have shown that FMT and/or antibiotic regimen was helpful in treating GIT symptoms like constipation, ulcerative colitis, and bowel disorders. Further, the therapy was helpful in relieving several non-GIT symptoms too [52,75,78–80].

1.5. Infection

Exposure to infections, toxins and brain injury in early stages of life might trigger a PD clock by initiating a cyclic inflammatory process (oxidative damage, excitotoxicity, mitochondrial & proteolysis dysfunction) ultimately leading to neuronal death [81–84].

One of the best examples of chronic infection in PD is that of *H. pylori* in the GIT where it reduces the absorption of L-dopa and hence worsens the clinical symptoms [85]. Antibiotic treatment of *H. pylori* infection resulted in reduced cachexia [86], increased L-dopa absorption and reduced clinical disability in PD patients undergoing L-dopa treatment [87]. *H. pylori* has also been proven to reduce DA levels in the areas of the brain controlling locomotion [88]. It is possible that *H. pylori* might not have a direct involvement in PD pathogenesis, but its presence in GIT and systemic circulation could affect the advancement and treatment strategies of PD, likely by initiating inflammation and autoimmune responses [89–91]. Working on similar mechanism other infectious agents like a virus (encephalitis, AIDS, coronavirus) [92–94] and bacteria [95–97], have been found in PD patients and could have a causal link.

Additionally, *in-vivo* models of PD have been designed using viral and bacterial infections to initiate and mimic the pathogenic process (inflammation and autoimmunity) in the brain [98,99]. Another study showed that common soil bacteria like *Streptomyces venezuelae* could also act as a source of toxicity and contributor to dopaminergic neurodegeneration [100]. Most recently, a study analyzed the antibody titers against some common infectious pathogens in the serum of PD patients and normal controls. They found that the infectious burden of cytomegalovirus, Epstein-Barr virus, herpes simplex virus type-1, *Borrelia burgdorferi*, *Chlamydo-phila pneumoniae* and *H. pylori* were associated with PD. Both bacterial burden and viral burden were independently associated with PD. The study provided strong evidence to the hypothesis of microbial underlining of PD etiology [101].

1.6. Others

1.6.1. Microbial toxins

Epoxomicin, a natural proteasome inhibitor, is a toxin produced by actinomycetes bacteria. Systemic exposure of epoxomicin in rats led to neurodegeneration in the SNpc and other regions in a pattern similar to that found in PD. Additionally, neurodegeneration was accompanied by the intracytoplasmic Lewy body-like inclusions which were positive for α -synuclein and ubiquitin [102]. Using fish as a model, epoxomicin caused a reduction in spontaneous movement, selective loss of dopaminergic and noradrenergic neurons, and formation of Lewy bodies in the CNS, a pattern similar to PD [103]. These findings demonstrate that epoxomicin is an effective dopaminergic neurotoxin as it can induce the pathological features of PD.

Similarly, Lipopolysaccharide (LPS), an endotoxin from Gram-negative bacteria has been implied in PD pathology [104]. Since PD patients have a disturbed GIT physiology, the intestinal LPS can enter the systemic circulation. LPS acts by stimulating microglia and has been used to study the inflammatory process in the pathogenesis of PD (reviewed in Ref. [105]). Another neurotoxin, β -N-methylamino-L-alanine (BMAA), generated by *Cyanobacteria* of the GM, was found to be elevated in the brains of patients with ALS, PD and AD [106,107].

1.6.2. Lifestyle

Emerging evidence suggests that lifestyle factors can contribute to PD pathology. Recently it was established that smoking and coffee were associated with reduced risk of PD and it was hypothesized that these effects were mediated via GM (reviewed in Ref. [108]).

2. Conclusion

Human GM has now been accepted as a potential modulator of human biology. Although new to the world of science, GM's impact on brain & behavior has drawn great attention around the globe. Studies have now proven that gut microbiota can directly or indirectly modify brain neurochemistry via various mechanisms like neural, immune and endocrine.

As reviewed in this article, GM has the ability to target various benchmarks of PD (Table 1). It can influence DA turnover, DAergic receptor expression, striatal gene expression, locomotion, synaptic plasticity, oxidative stress and many more factors in different brain regions. Recent findings too suggest that the GM's composition is altered in PD and that this dysbiosis is related to motor fluctuations. These changes could be exploited as a biomarker for PD pathogenesis. Although we still need to establish a cause and effect relationship between GM and PD, such a study may provide novel approaches for prevention and treatment of neurological disorders such as PD.

Current approaches mentioned in this review have laid the groundwork for identifying the mechanisms underlying the ability of the GM to influence host's brain & behavior. Deeper insights into the gut microbiota brain axis could connect the dots between GM and PD etiology. It could help in preventing or early diagnosis of PD possibly through some peripheral biomarkers. If this hypothesis is valid and that GM is involved in PD etiology, we might be looking at a new therapeutic and treatment regimen probably focused on dietary and pharmacological interventions to maintain healthy GM.

Conflict of interest

Authors declare no conflict of interests.

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