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REVIEW ARTICLE

Dysregulation of the Gut-Brain Axis, Dysbiosis and Influence of Numerous Factors on Gut Microbiota Associated Parkinson's Disease

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Abstract: ***Background*:** Parkinson's disease (PD) has been one of the substantial social, medical concerns and, burdens of the present time. PD is a gradually devastating neurodegenerative disorder of the neurological function marked with α-synucleinopathy affecting numerous regions of the brain-gut axis, as well as the central, enteric, and autonomic nervous system. Its etiology is a widely disputed topic.

***Objective*:** This review emphasizes to find out the correlation among the microbial composition and the observable disturbances in the metabolites of the microbial species and its impact on the immune response, which may have a concrete implication on the occurrence, persistence and, pathophysiology of PD *via* the gut-brain axis.

***Methods*:** An in-depth research and the database was developed from the available peer-reviewed articles to date (March 2020) utilizing numerous search engines like PubMed, MEDLINE and, other internet sources.

***Results*:** Progressively increasing shreds of evidence have proved the fact that dysbiosis in the gut microbiome plays a central role in many neurological disorders, such as PD. Indeed, a disordered microbiome-gut-brain axis in PD could be focused on gastrointestinal afflictions that manifest primarily several years prior to the diagnosis, authenticating a concept wherein the pathological pathway progresses from the intestine reaching the brain.

***Conclusion*:** The microbiota greatly affects the bidirectional interaction between the brain and the gut *via* synchronized neurological, immunological, and neuroendocrine mechanisms. It can be concluded that a multitude of factors discussed in this review steadily induce the onset of dysbacteriosis that may exacerbate the etiologic mechanism of Parkinson's disease.

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1. INTRODUCTION

Parkinson's disease (PD) is a gradually developing neuroinflammatory syndrome and is chronically progressive in nature that affects about 107-108 persons per population of 1, 00,000. The occurrence of PD varies with age from 0.3% at ages 55-65 years to 1% at 85-89 years and gradually increases with the age and could double by 2030 [1, 2]. The key players detected in patients with PD are dopaminergic neuronal loss and α-synuclein aggregation in the lewy bodies that invade the substantia nigra pars compacta [3]. The experimental evidences suggest that the progression and pathogenesis of PD are associated with inflammation of the immune system, α-synuclein aggregation, and dysfunction of the mitochondria, oxidative stress and alterations within the gut microbiota/microbiome (GM) [4]. The key aspect of GM in the pathogenesis of Parkinson's disease *via* the gut-brain axis has emerged as a primary spotlight in these recent years and it has opened up novel opportunities for the intervention of PD and its therapy. In some incredible review studies, the strength of this evidence encouraging and supporting the concept has been extensively explored and debated [5-9].

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This review entails light upon the regulation and influence of the gut microbiome on the gut-brain axis *via* various immunological mechanisms. It was hypothesized that the pathology of α-synuclein extends from the enteric nervous system (ENS) to the central nervous system (CNS), which is correlated with the identification of α-synuclein tangles in the appendix and colonic tissue before PD begins [10-12]. Recently, pathogenic misfolded α-synuclein accumulations have been shown to migrate in a mouse model from the gut and reaching the brain, confirming Braak's theory of idiopathic PD etiology [13]. Increasing evidences also confirm the immune system participation in the overall outcome of PD. Chronic inflammation in the gastrointestinal tract (GIT) occurs as the function of pathogen entry and other environmental factors, making up a connection with the brain *via* various mechanisms discussed below that might be susceptible for certain individuals to exacerbate the existing PD condition [14-16]. Houser and Tansey suggested a PD pathogenesis model which was derived from the part of the gut in which an apparent inflammatory stimulus may contribute to minimal-grade inflammation, cause transformation in the composition of microflora, and increase the permeability of the intestine, thereby enabling the bacteria to leak the subsequent inflammatory metabolites. Therefore, leakage and intrusion in the gut system will raise blood-brain barrier (BBB) permeability and aggregation of α-synuclein, resulting in neuroinflammation and neurodegeneration [14, 17]. Changes in the microbial composition can contribute to a transition in the distribution of bacterial mediated metabolites, which may entail low-grade inflammation, a significant cause for the occurrence of the PD [14, 18]. The communication between the brain and intestine is regulated by various pathways. The most obvious route is through the vagus nerve, which originates in the medulla *via* the dorsal motor nerve and spreads to the viscera *via* the abdomen. The predominant parasympathetic modulation of basic intestinal functions is provided by the vagus nerve, with the plentiful nerve supply to the small intestine, appendix and the stomach that declines proximally and further distally [14]. Response and stimuli arising within the intestine may activate vagal afferent signalling, a vital element of the reflex of neuroimmune inflammatory process networks leading to the regulation of the tonic peripheral immune system. There is also evidence to show that the vagus nerve can serve as a specific and direct portal through which substances from the intestine will move towards the brain [14, 19, 20]. It has been shown that variations in the composition and distribution of intestinal microflora might change the concentrations of these molecules together with growth factor levels and protein signaling in the brain, thereby increasing the possibility for major functional shifts [21, 22]. The prolonged anti-parkinsonian therapy usually following a few years of dopaminergic therapy, PD patients suffer from dopa-resistant motor symptoms and non motor symptoms. Existing chronic drug therapy serves various side effects such as constipation, neurasthenia, hypotension, episodes of akinetic freezing, hallucinations, and rhinitis. The treatment with the anti-parkinsonian drugs is less directed towards diminishing the cause of PD. Thus, this review emphasizes to understand the various other interrelated mechanisms and targets that exacerbate the etiology of the PD [23, 24].

2. THE GUT MICROBIOTA: THE BASIC CONCEPTS AND ITS UNSEEN FUNCTIONS

One amongst the greatest domains (250–400 m^2) of the antigens, host, and the environmental components throughout the body of a human is the human gastrointestinal tract (GIT). In an average life span, nearly 60 tons of food migrates *via* human GIT, together with an excess of environmental microbes that present a major danger to the health of the gut. The set of archaea, eukarya, and bacteria colonizing the GIT are considered as the 'Gut microbiota.' Over thousands of years of human evolution, it has co-evolved with the host to establish a mutually beneficial and intimate relationship. It has been reported that the amount of microbes invading the GI tract reaches 1014, which is 10 times [25]. With extremely sophisticated methods of profiling and characterizing ecosystems being established, a task for the microbiota has become regularly evident in the significant number of diseases that may be extra-intestinal and intestinal [30, 31]. Moreover, it was affirmed that the human is the "meta-organism" comprising 10 to 100 times more the bacterial cells than the cells of humans itself, that immunologically and metabolically combine and interact with each other. The Gut microbiota improves the metabolic state, endocrine signalling, and resistance to infections and is affected by gender, age, ethnicity, medication (particularly antibiotics), stress, diet, gastrointestinal infections, smoking , *etc*. Within every individual, if calculated at various periods, there are substantial differences in the composition of GM. While the definition of healthy microbiota cannot be established these days, and it is not known that microbiota's richness and complexity are measures of its safety [32]. The creation of the microbiota starts in the womb as the eventual birth represents the child's first significant colonization, with results finding substantial variations in Gut Microbiome in vaginally delivered infants relative to those conceived by caesarean (C-section surgery). The microbiota of vaginally born children is defined by the *Lactobacillus* and *Prevotella* taxa, whereas the other infants born by C-section are monopolized and inhabited by the species *Streptococcus* and *Staphylococcus*. Infants delivered *via* C-section bear *Enterobacter* and *Kliebsella* more often. Furthermore, in children born by C-section [33-36], colonization with Bacteroides and *Bifidobacteria* is deferred. Such distinctions tend to have impacts that continue in adulthood with vaginally born infants at reduced harm of developing asthma, obesity, and allergies, relative to the other raised by the C-section [33]. Throughout the beginning and up to 3 years of development, the microflora is continually evolving but remains stable thereafter throughout the lifespan [35].

2.1. Feasible Consequences of the GM Composition in the Periphery: Crosstalks between Periphery and Brain

The microbiome benefits the host for several advantages across distinctive physiological functions, such as preserving the stability of the gut and colon or defining the intestinal epithelium, fighting against pathogens, maintaining host immunity, and collecting energy [26-29]. Nevertheless, owing to an abnormal microbial composition and makeup, known as dysbiosis, there is scope for the failure of these pathways and may be a result of the influence of factors such

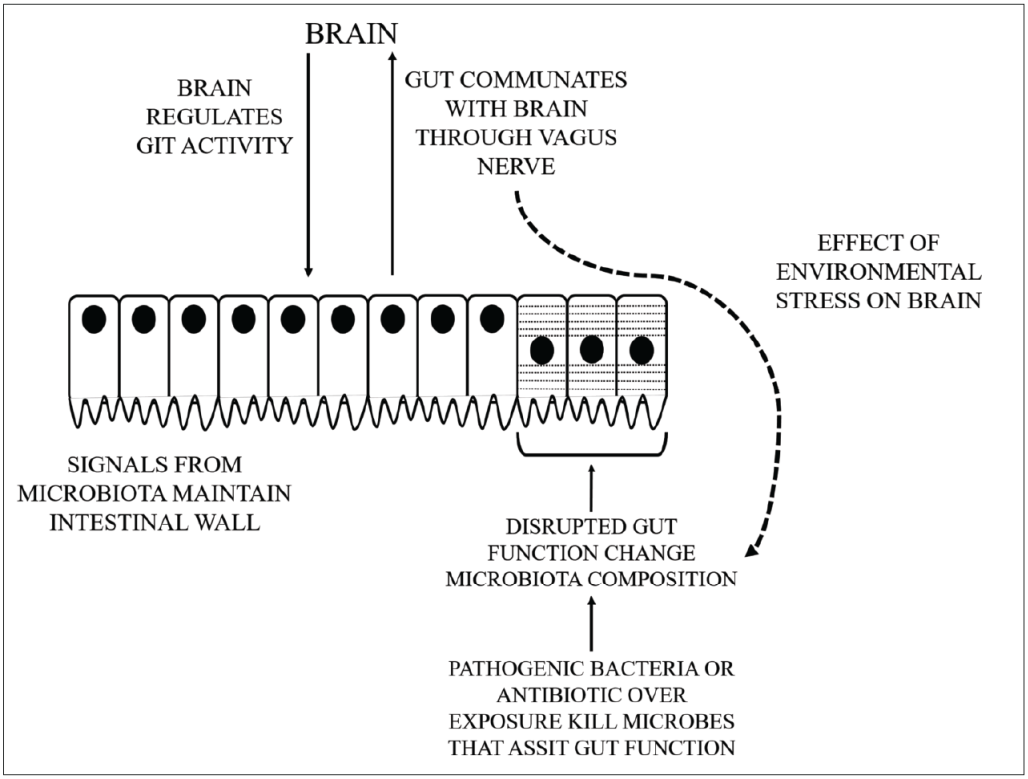

Fig. (1). The complicated crosstalks between GM and brain. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

as genetics, environmental factors, diet, stress, neurotransmitters and metabolites [30, 31].

A number of mechanisms may occur that result in the peripheral-central crosstalks in the microbiota-gut-brain-axis, as shown in Fig. **1**:

- Generation of various bioactive peptides by the gut microbes that involve secondary bile acids, short-chain fatty acids (SCFAs), neurotransmitters, and gut hormones. SCFAs may reach the circulatory system and it is probable that they are likely to transmit to the brain through this mechanism [37, 38].
- The HPA complex activation by stress tends to secrete cortisol. This can affect intestinal motility, integrity and mucus production, owing to such a shift in gut microbiota composition that the immune cells and vagus nerves mediated by the LPS on the gram negative bacteria may influence the brain [39].
- Cross-reaction of the bacterial proteins with human antigens to induce the dysfunctional stimuli to the adaptive immunity [40, 41].
- Microbes possess microbe-associated molecular patterns that can be identified in the ENS by toll-like receptors. In addition, immune signaling is an essential route by which microbiota-gut-brain signaling takes place. Pro-inflammatory cytokines and chemokine synthesis affected by the intestinal microbiota may send signals to the brain through the circulatory system [40-42].
- The vagus nerve is a significant part of the sensory route and the main modes of contact between the intestine and the brain, which is strongly engaged in communicating the microbiota-good-brain axis, regulation of the brain and behavior [43].

The modulation of the barrier integrity in the CNS or peripheral structures due to various pathological events leads to the essential physiological dysregulation and opening of tightly controlled interaction pathways triggering unwanted crosstalks and the movement of cells or noxious substances that sensitize or aggravate established conditions. Internal neuroinflammatory processes may be potentiated by the leakage encouraging peripheral cells to become infiltrated into the brain parenchyma. It may also be precipitated by the neuroinflammation itself. In the regulation of the immune system, peripheral inflammatory markers such as cytokines and chemokines are vital signaling factors that may influence both central and peripheral systems. Through the saturable transport, the chemokines and cytokines are actively transported through the BBB and any changes in blood expression concentrations may have a direct or indirect influence on the function of the CNS. Peripheral inflammation may be a significant contributor to both PD etiology and disease progression [44, 45].

2.2. Role of Gut Microbiota in the Pathogenesis of Parkinson's Disease

The intricacy of the pathogenic pathways influencing neurodegenerative diseases such as PD is owing to multifactorial shifts taking place at the molecular stage that is af-

fected by environmental and genetic factors. However, the causes and triggers for the basic pathogenesis of PD need to be elucidated. Meanwhile, evolving research rapidly affirm the role of imbalances in the composition of the GM population structures as a pathophysiological component that exacerbates the PD progression [46, 47]. The association between intestinal microflora and enteric neurons has been established as a result of recent findings [55, 43] and their ability for the regulation of the hypothalamus-pituitary-adrenal (HPA) axis, accompanied by further synthesis of mediators involved in optimal functioning of the brain [55-58].

Chronic stress in rotenone models triggers a deregulation of the HPA axis that may ultimately result in dysbacteriosis, marked by a noticeable decline in the microbial counting relating the bifidobacterium family leading to the damage of *E.coli*. Extended exposure results in intestinal permeability that generates a "leaky intestine," colitis, and dysosmia by triggering significant neurochemical and neuroanatomical changes [59-63]. An imbalance in the microbiota (dysbacteriosis) of the host may result in the production of cellular degeneration, low- inflammation, and cellular energy imbalance accompanied by enhanced oxidative stress [64]. Overactivity of differentiation clusters can impair immune cell responses at the periphery that will disrupt the integrity of the barriers and its function against the lipopolysaccharides (LPS) of the bacteria as well as other toxins [65-68]. Dysbiosis can trigger various diseases, and one of the specific effects of intestinal flora upon the BBB is shown by the *E. faecalis* and *E. lenta* species, which are capable of metabolizing levodopa, the key medication given to patients with PD. It has been demonstrated that the L-dopa does not enter the Brain barrier for the dopamine exudation, culminating in a very narrower path due to these micro-organisms [69]. As per the evidence, tyrosine decarboxylase of microbe has the potential to limit dopamine exudation, hence limiting levodopa's effect during PD [70]. Another study reported that the occurrence of *H. pylori* infection among all patients of PD was associated with the inhibition of the absorption of the levodopa, leading to increased motor impairment [71]. Likewise, overgrowth of small intestinal bacteria influences about 54-67 % of patients with PD [72]. In a research carried out by Fasano *et al*., all the incidences of overgrowth of the small intestinal microbe in PD were shown to be substantially elevated than in the control subjects, that correlate not only with impairments of motor centers but further weaken the motor fluctuations[73]. Altered composition of the microbiome has also been identified in chemical-induced PD models, such as exposure to rotenone or to MPTP. In samples taken from feces of MPTP-induced Parkinson mice, that were compatible with clinical results, decreased amounts of *Firmicutes clostridales* and *Firmicutes* together with elevated values of the *Turicibacterales, Enterobacteriales,* and *Proteobacteria* have been found [74]. Equivalently essential in the rotenone-treated model of PD mice, an overall decline in microbial diversity and major alterations in microbiota composition were observed, as shown in Table **1** [5, 62]. A new analysis of Sprague-Dawley rats treated with rotenone has observed an enhanced abundance *of Lactobacillus, Sutterella, Bifidobacterium* and *Turicibacterales* and less abundance of the S24-7, *Oscillospira* and *Prevotella* in the colon and the small intestine [75]. Using fecal microbiota transplants and α-synuclein overexpression mice, they found that invasion of animals (mice) with the microflora of patients suffering with PD, culminated in a serious phenotypic character relative to the mice obtaining a transplant of microbe from safe subjects [76, 77]. While the causal association between gut microbiota and PD has not been established, it is noteworthy that microbiota is needed for α-synuclein aggregation and PD-typical phenotype. Interestingly, a significant shift in the GM in the prodromal period of the PD, *i.e.*, REM behavior disorder of sleep, indicates the shifts in the GM are not at all secondary action caused by the therapy with the dopamine [78]. In six separate studies [50, 51, 79], *Lactobacillaceae* sp. were shown to be the more prevalent within the stool of patients with Parkinson, and lower in the other two studies [51, 83]. Mihaila *et al*. also observed a greater abundance of *Lactobacillaceae* in PD patient's saliva relative to controls [84]. Erysipelotrichaceae family, a bacterial family, was reported to have increased in 3 separate studies in PD stools [78, 83], while others reported to have lesser or stayed unaltered relative to stable control subjects [53, 81, 83]. It has been documented that the butyrate forming *Faecalibacterium* [50, 58, 54, 86], *Roseburia* [58, 82, 83] *Dorea* [54, 58, 83], and *Blautia* [58, 81-83] are less prevalent in stools of PD patients.

3. THE GUT-BRAIN AXIS AND ITS RELEVANCE IN PD

The gut microbiota, microbes in the digestive tract of people, contains both pathogenic and commensal organisms. The microbial composition may differ considerably in accordance with the host under physiological conditions as per the mutualistic and climate functions. Gut microbiota influences permeability, intestinal immunity, secretion, motility as well as bidirectional coordination between both these enteric (ENS) and central nervous system (CNS) *via* processes of neuroendocrine, immunology and neurology. Observations in animal PD models have shown the obvious abnormalities in the network of the nigrostriatal pathway have contributed to distorted colonic pathophysiology, whereas colon inflammatory response induces nigrostriatal equilibrium disruption [86]. Both elemental factors of the brain-gut axis are now accepted as being engaged in PD, however, the deregulated microbiota-gut-brain axis (GBA) may focus on gastrointestinal impairment, the most frequently identified non-motor symptoms in Parkinson. Such GI symptoms involve malnutrition, constipation, impaired gastrointestinal emptying, dysphasia and issues with defecation [87, 88]. Clinical studies have already demonstrated that dysregulation of the gut precedes Parkinson's disease through diagnosing at least a decade before. An early study proved that persistent, inflammation of the gut would speed up the age of occurrence of disease, exacerbate α-synuclein pathology that further triggers neuroinflammation in α-synuclein mutated PD model of mice [89]. Sudo *et al*. initially suggested the notion of GBA when they found an abnormal output to stress in the mice free from germs. The GBA is a bidirectional interface between these ENS and the CNS that links their mental and cognitive regions of the brain with the distant intestinal processes of the immune systems, endocrine, the GM and

Table 1. Distinctions in Bacterial Composition in patients suffering from Parkinson's (PD) relative to healthy subjects (HS).

Decrease in Levels	Increase in Levels	Method Adopted	PD	HS	Refs.
Prevotella, Puniceicoccaceae family, Blautia, Roseburia, Clostridium XIVa	*Lactobacillaceae, Bifidobacterium, Lactobacilli, Rikenellaceae*	16S rRNA	64	64	[48]
Prevotella copri, Eubacterium bioforme	*Firmicutes, Akkermansia muciniphila*	shotgun	193	113	[49]
Corpobacillaceae, Lachnospiraceace, Faecalibacterium,	*Oxalobacteraceae, Ralstonia*	16S rRNA	38	34	[50]
Clostridium coccoides, prevotell, Clostridium leptum, Bacteriodes fragilas	*Lactobacillus sp.*	Targeted qPCR	45	32	[51]
Prevotell sp., Bacteriods sp., Dorea, Faecalibacterium species	*Lactobacilli, Oscillospira , Christenesenella, Eubactereace sp., Catabacter, Bifidobacterium*	16S rRNA	89	66	[52]
Clostridales incertae sedis IVsp., Prevotellaceae family	*Lactobacilli, Bradyrhizobiaceae species, Enterobacteriaceae family*	16S rRNA	72	72	[53]
Sediminibacterium sp, Lactobacillus sp.	*Aquabacterium, Anaerotruncus, Clostridium XVIII, Sphingomonas, Butyricicoccus species, Anaerotruncus species*	16S rRNA	45	45	[54]

the intestinal epithelium. This comprises many parts of the nervous system, which include the brain and spinal cord, the ENS, ANS and the HPA axis. The ANS, including the limbs of the sympathetic and parasympathetic areas, controls the lumen signals(afferent) that are transmitted to the CNS through spinal, enteric, and vagal channels and the signals(efferent) from the CNS to the enteric system and the distant intestinal border [9, 90]. Innervations of the vagus nerve with the whole of the intestinal region through the colonic flexure located left regarded the microflora metabolite transmitter and send the information to the brain. The HPA is the component of our limbic network, engaging in emotional, memory actions and acts as central tension efferent nerve managing reactions to stressors of some type. Systemic pro-inflammatory signals and environmental stress may trigger the limbic system through secreting the hypothalamus corticotrophin releasing factor (CRF) and, in effect, activates the secretion of adrenocorticotropic hormone exudates on stimuli from the pituitary gland and eventually contributes to the releasing action of cortisol from the adrenal gland. The cortisol is a significant hormone for stress implicated in various metabolic and physiological processes, particularly in the brain. The ENS is a multidisciplinary neural meshwork with 2 ganglionated-plexuses, submucosal and myenteric, consisting of enteric glial cells (EGCs) and neurons. EGCs have been proposed for reflecting the ENS alternative of CNS astrocytes, as they are immunohistochemically and morphologically similar to astrocytes. The humoral elements of the GBA are the enteroendocrine pathway, the mucosal immune system and the metabolites produced from the microbiota [9]. Enteroendocrine cells (EECs) release hormones such as hydroxytryptamine (5-HT) and ghrelin that have a wider range of effects on the functions of the brain and gut [91]. The intestinal epithelium creates a controlled barrier between the intestinal lumen and the circulating blood products, regarded as the intestinal epithelium barrier (IEB), and acts to avoid the transport of toxic external toxins to consume and release the numerous nutrients [92]. Among these frameworks of the IEB, the rigid epithelial and close pathways are significant because they connect *via* adjacent enterocytes just to ascertain the permeability of paracellular cells *via* the intercellular space laterally and are made up with the transmembrane substances, *i.e.*, occludins and claudins that bound to the cytoskeleton of the actin by proteins of high molecular weight termed as zone occludens [93]. These complexes are beneath the control of the GM as well as its metabolites that serve a crucial role in the reversible communication pathway between the gut and the brain. Each element of the gut-brain axis mentioned above can be influenced individually by the pathology of PD to varying degrees [94].

3.1. Interactions of the Gut-Brain Axis Relating to the Emotional and Behavioral Symptoms of PD

The intestinal gut has the tendency to interact in either manner: individually or in relation to the brain. The brain relation (gut-brain axis) is a two-way process that travels from the brain region to the intestinal area, and conversely. It has known for a long time that certain mood shifts, psychiatric problems, impact on the intestinal stage, such as emotions, depression, and lack of appetite, or rise of appetite. The serotonin acts in the intestine, as neurotransmitter in the suppression of sleep, anger, agitation, mood, body temperature, appetite, and vomiting and holds the responsibility of equilibrium within its place (its distinctive amounts in our system are associated with depressed mindset). More than 50 per cent of dopamine production exists here, a neurotransmitter controlling the levels of satisfaction in the human brain among its functions. Its secretion takes place in circumstances with pleasure and enables one to look for the practice of fun jobs. This implies that in some regions in the brain, such as the preferentially located cortex and the nucleus accumbens, sex, food, and different medications are also stimulants for the production and release of dopamine [95].

3.1.1. Well-being

Although 90% of the serotonin, the "prosperity hormone," is generated and processed there, the mood is rooted in the stomach.

3.1.2. Stress

The brain receives energy and fuel from the bowel in an emergency, and the guts give out indications such as stomach distress.

3.1.3. Memory

The burning of body fat by certain proteins is responsible and accountable for memory, explaining why these obese individuals are far better liable to the problem of dementia.

3.1.4. Sleep

The neurons of the stomach develop benzodiazepines (BZDs) that can calm and trigger sleeping property as we relieve the gut.

3.1.5. Fear

Panic is forcing the brain to alarm and terrify the large intestine. This does not have time to consume liquid enough, thus causes diarrhea

3.1.6. Gluttony

Billions of microbes in the intestine want their own foods to survive, so they are even greedier than us.

There is little research into the relationship between the brain, emotional state, and the microflora.

The findings are rather tentative. At the clinical stage, understanding precisely whether it will have an effect is hard to pin down. These findings point towards the possibility of utilizing probiotics as the alternative therapy to medications that cure anxiety as well as psychiatric issues, because they can actually intensify the results, although that is also provisional. Probiotics or foods high in beneficial bacteria, such as fermented milk and yogurts, showed a good effect on one's behavior: *Lactobacilli* and *Bifidobacterium* are able to produce γ-amino butyric acid, a brain neurotransmitter that controls multiple neurological functions and whose deficiency is linked to depression and anxiety [51].

3.2. Dysregulation of the Gut-Brain Axis, Increased Intestinal Permeability, and α-synucleinopathy in PD

Many people with PD typically suffer from GI dysfunctions, which may include dysphasia, diarrhea, slowing of gastric emptying, constipation, hyper salivation and abnormal bowel habits. Raised permeability of the membrane (mucosal), gut constipation and the relating inflammation of the GIT are conditions directly linked to the makeup of the gastrointestinal microbiota and the metabolites obtained from microbials. Increased permeability of the intestine, a disorder regarded as a leaky intestinal syndrome, was found in the early phases of PD correlating the enteric issues. Elevated permeability of intestine due to an impaired intestinal barrier mechanism, promotes the translocation of microbes that, in effect, can induce inflammation and cause oxidative stress, resulting in ENS synucleinopathy [63]. In addition, elevated values of LPS might damage the BBB's integrity, causing neuroinflammation and SNc damage [96]. The dysbiosis in the gut and overgrowth of the small intestinal raises translocation and intestinal permeability of bacteria, assessing over-response of an immune system and consequent inflammation of the systemic as well as CNS, as summarized in Fig. **2**. EBCs are capable of producing various neuroactive compounds, including catecholamines, serotonin, glutamate-amino butyric acid and SCFAs [97-99]. It has been hypothesized that the number of microorganism-produced neurotransmitters, neurohormones, and neuromodulators, however, provides the severe intricacy of this network. It remains uncertain whether these microbial neurosubstances are produced to an acceptable level for host processing to exert some sort of influence, or might be transmitted *via* systemic circulation to central neurocircuits [97-100].

The peripheral innervations of the tract are diverse, organized into 3 grades of the plexus activities of the ENS including vaso-regulation, bowel motility and management of permeability and the secretion of other gastroenteropancreatic hormones [101]. Furthermore, compared to what happens in the BBB, there are multiple remnants of astrocytes at the boundary of the intestinal barrier that provide a possible route to contact the nervous system. We have around 100 million neurons in the stomach, which is greater than what the spinal cord contains [102]. The plethora of neurons inside the ENS helps one to sense our gut's inner world as well as its contents. Most of this neural strength is reflected in the intricate everyday cycle of metabolism, through decaying food and nutrient absorption. Expelling waste involves contractions of the mechanical, chemical, and rhythmic muscle to push everything to the bottom. Hence it may regulate the gut actions independently to the brain, equipped with its own senses [103]. Proinflammatory immune function and disorders resulting in elevated amounts of α-synuclein in the intestine and brain have been shown [14, 104]. Overexpression of the α-synuclein will then cause its accumulation [14]. Over-expressed and accumulated α-synuclein, in effect, will induce proinflammatory stimuli within these immune cells, generating a +ve feedback which would facilitate the spreading of α-synuclein to various parts [105, 106]. The pathology of α-synuclein in the periphery could be transmitted to the brain. Although chronic systemic inflammation alone could serve to pathologically altered α-synuclein throughout the CNS, peripheral inflammation may be necessary [107]. Moreover, it has recently been shown that human α-synuclein, inserted into the gastrointestinal tract of the rats, may relocate the vagus nerve dorsally to the motor region of the nucleus within brainstem. The migration was induced by a micro-tubular coordinated transport process in neurons that demonstrated similarly for the oligomeric, monomeric, and other fibrillar types of α-synuclein [20]. This proof analysis indicates improvements in α-synuclein can impact directly the brain through the vagus nerve. α-syn stimulates microglia in the brain that could already be prepared by the systemic immune and α-syn in the CNS, raising the risk of neurodegeneration and expanding the period by which, indicating α-syn inclusions and resulting into neurodegeneration [105, 106, 108, 109]. Heiko Braak *et al*. suggested a first step staging method for the advancement of the pathology of PD *via* brain with the DMV

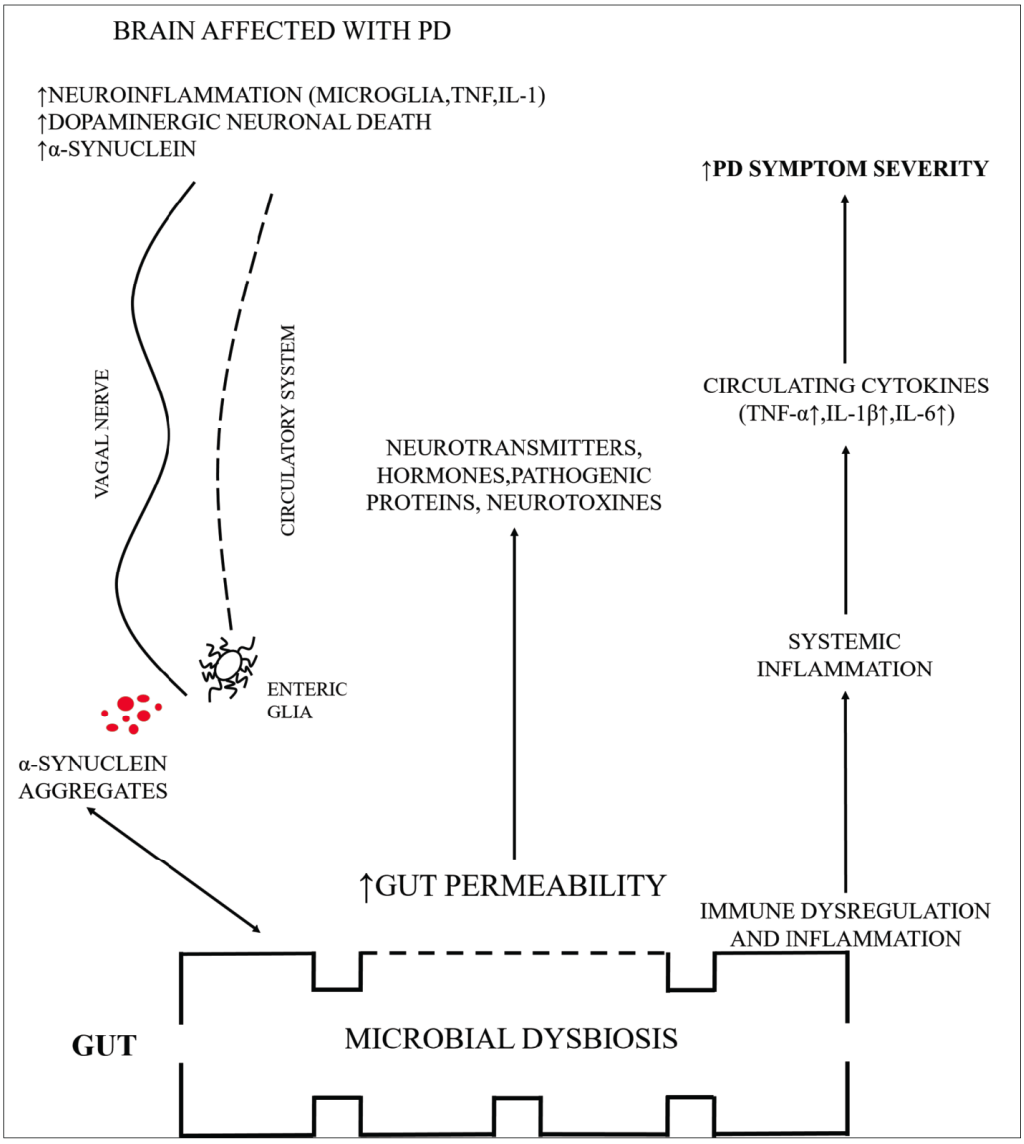

Fig. (2). A summarized form of possible mechanisms through which altered microbiota sends signals to the brain affected with PD. . (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

participation. Questions were presented about Braak's staging scheme and his research methodology [14]. Nevertheless, despite most of Braak's staging, several reports also offered evidence and research intended to contradict his suggestion have also shown that the plurality of cases with PD(~54-81,7%) sticks entirely and only a slight fraction (~7.1-8.3%) does not exhibit disease in the DMV while it is located somewhere else in brain regions. Hence numerous PD cases exhibit a type of disease that progresses the pathological condition and DMV is severely affected [14].

3.3. Importance of Perturbed BBB and Gut Permeability Relating to the Role of GM and their Metabolites in PD

Established for regulating the physiological functions within the human body, the CNS is also dynamically mediated by both the physiological and pathological conditions of the body. Such circumstances alter quite often and sometimes constitute modifications made into the GM that directly modify the CNS through the crosstalk, as revealed by numerous studies. The BBB is a dynamic physical barrier comprises mainly of tight and adhere endothelial junctions with limited paracellular permeability that prohibits huge and possibly harmful substances from reaching the brain, thereby regulating molecular traffic between the cerebrospinal fluid and circulatory system. The information may transmit *via* the BBB by numerous mechanisms between the GI tract and CNS. BBB-permeable substances typically have minimal or no charge with low molecular weight and posses lipid-soluble characteristics. It has been shown by various studies that intestinal metabolic products manifest these features, which allow easy entry to modify brain physiology *via* the BBB [110-114]. Modulations in the BBB and intestinal permeability, microbial dysbiosis, and intestinal epithelial barrier permeability or dysfunction were reported as essential mechanisms for PD progression. The importance of the BBB in the development of neurodegenerative disorders such as

PD is widely recognized, proposing that disturbed blood-brain communication is the vital process that renders neuronal dysfunction. BBB perturbation could further be affected by various factors such as oxidative and psychosocial stress [111]. The GM transforms dietary materials, like micro- and macronutrients, polyphenols, and fibers into a variety of metabolites including trimethylamines, short-chain fatty acids, vitamins and derivatives of amino acids. Such metabolites derived from microbial flora and dietary components have vital signaling and metabolic roles that can modify host homeostasis, particularly brain function and integrity of the BBB. Microbiota taxonomic assessment has defined different linkages for both specific neuroinflammation and commensal bacteria and microbial metabolites in PD patients along with the alteration in population groups of beneficial bacteria (such as genus *Prevotella*) and pathogenic bacteria (*Enterobacteriaceae* family). Specific studies demonstrating the influence of microbial metabolites on the BBB permeability and brain are summarized below. In the amino acid catabolism, GM plays a vital role and the amino acid products may significantly affect the equilibrium between the development of inhibitory and excitatory neurotransmitters crucial for the proper functioning of the brain. *Lactobacillus* and *Bifidobacterium* species metabolize glutamate, the most abundant excitatory neurotransmitter in the brain to generate the main inhibitory neurotransmitter π- aminobutyric acid (GABA). Short chain fatty acids (SCFAs) promote upper-gut motility and colonic blood flow and the BBB access *via* the bloodstream and influence the direct function of its integrity. For example, a decrease in BBB permeability is observed in germ-free mice after butyrate colonization along with producer *Clostridium* by up-regulating tight junctional proteins. It is also possible that modifying SCFA levels may be helpful in avoiding or managing neural loss. The microglial cell maturation controls BBB integrity, neurogenesis, and neuroinflammation, and is modulated by SCFA in the germ-free mice, in which the lowered microglia number, morphology and function can be saved by 4-week SCFA delivery. Vitamin K is produced by *Kliebsella pneumoniae, Escherichia coli, Eubacterium* and *Propionibacterium* and has been demonstrated to have a beneficial effect in the modification of the α-synuclein fibrillization linked with PD. Furthermore, systemic immune activation can cause perturbed BBB integrity and response due to variability of the BBB in these models prevents the generalizability of most preclinical researches to human microbiome interactions [115].

4 TOLL-LIKE RECEPTOR (TLR): UNRAVELING ITS ROLE IN THE INFLAMMATORY SIGNALS REACHING THE BRAIN

Among the multiple Pattern recognition receptors (PRRs) in extracellular and intracellular conditions, TLRs perhaps the most important class of receptors in the mammalians, discovered in 1988 in *Drosophila melanogaster* [116]. Thirteen TLRs have been now discovered in mammals, including humans, out of which, 10 have been described completely in human cells, corresponding not to the epithelial tissue and immune cells but also to the PNS, CNS, neurons and EGCs. The spread of these immune sensors illustrates neural cells' potential for sustaining immune stimulus and their critical emphasis in maintaining the homeostasis [116, 56, 118, 119]. Besides sustaining gut homeostasis and other important physiological functions of the host, gut flora is the source with a variety of TLR ligand that, under some circumstances, may recognize harmful stimuli and respond by exerting proinflammatory influence such as a cytokine, chemokine

Table 2. Potential modulators of the Microbiome-Gut-Brain Axis targeting toll-like receptors are summarized.

Modulator	Impact on Microbiome-Gut-Brain Axis	Target	Refs.
Prebiotics			
Galacto oligosaccharides	Villus surface enhancement in the small intestine	TLR1-TLR13	[110, 134]
Fructo oligosaccharides	Raised expression of BDNF in the hippocampus	TLR2, TLR4	[110, 135]
Short-chain fatty acids (SCFA)	Colonic epithelium probity maintenance	TLR4	[110, 136]
Probiotics			
L.rhamnosus	GABA-A receptor modulation	TLR1, TLR2, TLR6	[110,137]
Lactobacillus reuteri	Increased frequency of evacuation and enhanced bowel movement	TLR1, TLR2, TLR6	[113, 138]
Lactobacillus casei shirota	Diminishing bloating of viscera and pain and improvement in the consistency of the stool	TLR1, TLR2, TLR6	[114, 139]
Dietary supplements			
Docosahexaenoic acid (DHA)	Improvement in the neuronal mitochondrial dysfunctioning by diminishing the oxidative stress	TLR2, TLR4	[111, 140, 141]
Panax Notoginseng	Repression of the microglial stimulation and limiting the release of TNF-α and IL-6 release	TLR4	[142]
Sylimarine	Neuroprotective effect and antioxidant (salvaging the free radicals)	TLR4	[143]

production. The production of the cytokines is crucial for the microglial polarization and termed as 'M1' state, a classically active state in the brain encouraging the neuroprotection. The response is shifted from M1 to M2 phenotype (alternatively active state) where the destruction can be repaired efficaciously, unless an unregulated or chronic inflammation due to prolonged production of inflammatory mediators leads to the tissue damage [117, 130-132]. Despite the fact that microbial components are potent and efficient TLR ligands, the intestine is extremely insensitive to TLR substrates because epithelium exhibits limited TLRs under its physiological environment [117]. By comparison, modified intestinal microbiota and impaired intestinal epithelial border stimulate TLRs that further cause descending signalling response, inducing inflammation and stress of oxidative factors in PD patients in the brain and gut. The studies that have centered focus upon the functioning of TLRs have displayed their role in transmitting signals to the brain. While the precise cause of the intermittent PD is yet to be identified, rising testimony suggests that α-syn stimulates microglias, causing inflammation, contributing to neuron deterioration. Extracellular fibrillar, α-syn produced by the oligodendrocytes is identified as "PAMP" *via* microglial TLR Type-2 (as TLR TYPE-1 heterodimer), that further stimulates descending pathways comprising NF-B and MyD88, inducing the formation of Tumour necrosis factor (TNF) and the Interleukin-1 [120, 121] and the localization and time-dependent specific activation of TLRs [122]. TLR4 also tends to interact with α-synuclein in in-vitro tests, activating microglial cells, including α-syn acquisition, pro-inflammatory release of cytokine, and stimulation of oxidative stress [123]. These results have been substantiated in a murine model induced by MPTP, wherein the genetic exclusion of TLR-4 transmitting, preserved the mice against deterioration of neurons, demonstrating the chief function of TLR4 in the inflammatory signaling during PD [124]. Current data from laboratories indicates a possible presence of the endogenous inflammatory sensor NLRP-3 that might be augmented by TLR signals. Limited caspase-1 stimulation and secretion of IL-1 along with depletion of dopaminergic neurons were observed in NLRP3-deficient mice after an assault to MPTP [125]. It has been documented that fibrillar α-syn requires TLR2 on a person's monocytes to prepare the inflammatory NLRP3 [126]. Interestingly, it has been shown that NLRP3 inflammatory repression is regulated by dopamine specifically, but is still uncertain if the presence of the inflammatory mediators precedes the degradation of the neurons, or is the consequence of neuronal arrest [127]. Thus, TLR2 and TLR4 have been found to be the most conclusive proof for a function of TLRs in PD. The role of TLR2 and TLR4 in Parkinson's can be paradoximal: their induction in microglia may cause neurotoxicity, yet on the other side, they may be necessary for the clearance of α-syn, which is therefore neuroprotective in nature [128]. Various evidence indicates that epigenetic reprogramming may induce microglial priming, as demonstrated in qualified immune cells. In patients suffering from PD, intestinal membrane function is disrupted, putting them at such a risk of microbial exposure [14], so translocating bacteria or products derived from bacteria, *e.g*., LPS (a TLR-4 ligand) that causes the systemic inflammation, contributes to more serious degeneration of neurons [129].

The role of TLRs in neuronal disintegration is progressively recognized on the basis of the following scientific evidence:

i. Specific nervous system cells transmit TLRs;

ii. TLRs triggered by the presence of α-synuclein;

iii. Prolonged recognition of pathogen stimulates inflammatory reaction preceding neural loss;

iv. Suppressing the role of TLRs slows the progression of Parkinson's disease [130].

According to the study, TLR(type-4) removal has been shown to inhibit the exposure of microglia (phagocytic) with a subsequent aggregation of microglia and intensified dopaminergic neurodegeneration [140], emphasizing the neuroprotective influence of TLR(Type-4) signalling induced by the dispersion of certain synuclein, similar to reported preserved function of TLR-2 against β-amyloid and certain synucleins. Further research based on the identification of the enteric microbiota-derived variables suggests that these variables are responsible for TLR activity and the corresponding signalling turn-out of TLR stimulation should offer new comprehension into its dynamic interaction between the host and microflora in PD and other related neurodeteriorating disorders [12, 133].

CONCLUSION

It can be concluded that a multitude of factors discussed above steadily induce the onset of dysbacteriosis that may exacerbate the etiologic mechanism of Parkinson's disease. GM performs a prominent appearance in its growth and equanimity of various body parts, and modifications in their content and configuration are assumed to commence prior to the actual onset of the motor characteristics in the PD. These adjustments may be linked to the fundamental pathogenesis of PD *via* different pathways, direct and indirect. Currently, various evidence support that the unidentified external pathogen that inevitably contributes to PD, travels within the gastrointestinal tract leading in GM dysfunctioning that slowly destroys the intestinal obstacle to enter the enteric region. The deposition of the α-syn in PD will begin in the enteric system, accelerating to a firm level and ultimately transmitting to the central regions through synapsis cell interaction. Greater knowledge of the impact of GM modifications in the CNS and ENS will help establish the association between gut microflora, inflammation, α-synucleinopathy, neuroprotection, neurodegeneration, neurotoxicity in patients suffering from PDs. Current studies and evidence from mice and clinical theories are mostly associated and the query is still unanswered about the outlook regarding the altered composition of the gut microbiota and PD pathology. One possible theory is that both factors relate to PD pathology:

I. Variations in the composition of gut microbial proceed the pathology and

II. Differences in the composition of gut microbial are not exclusively mutual

However, no treatment has yet been developed to fully cure PD, a better comprehension of microbiome and brain

function can elucidate light on PD's etiological progression and offer new possibilities for the treatment. A more detailed understanding of such factors may provide possible targeting attention for clinical testing to assess new disease-altering interventions for PD like probiotics, SCFA and GM-altering medications, recombinant ghrelin, and TNF-α antagonist.

LIST OF ABBREVIATIONS

CNS	=	Central nervous system
CRF	=	Corticotrophin releasing factor
DAMP	=	Damage associated molecular patter
EES	=	Enteroendocrine cell
EGC	=	Enteric glial cells
ENS	=	Enteric nervous system
GBA	=	Gut brain axis
GIT	=	Gastrointestinal tract
GM	=	Gut microbiota/microbiome
HPA	=	Hypothalamus pituitary adrenal axis
IEB	=	Intestinal epithelium barrier
LPS	=	Lipopolysaccharides
MPTP	=	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
NLR2	=	NOD like receptors-2
PAMP	=	Pathogen associated molecular pattern
PD	=	Parkinson's disease
PNS	=	Peripheral nervous system
PRR	=	Pattern recognition receptors
SCFA	=	Short chain fatty acids
TLR	=	Toll like receptors

FUTURE DIRECTIONS

Pharmaceutical and nutraceutical agents serve as possible modulators for the microflora-GBA and TLRs regulation in PD pathogenesis progression. For the future, numerous novel disease modulating medications provide possible targets for clinical testing to assess their role in PD. These include the Dietary supplements (Sylimarin, DHA), Prebiotics (SCFAs), probiotics (*L.rhamnosus*), TNF-α inhibitors, GM altering compounds, all of which target potential TLRs and may reduce the neural dysfunctioning, reduce oxidative stress, enhance BDNF expression and maintain gut integrity[134-144]. Apart from this, numerous recent studies emphasize the potential confounding effects of the other directly or indirectly acting medications in research on the GM. A plethora of drugs have been mentioned, such as Proton pump inhibitors (PPIs), metformin (anti-diabetic medication) and (escitaopram) selective serotonin reuptake inhibitors antidepressants have a well-described effect on GM *via* altering the microbial profiles or by activating the GBA signals [145-150].

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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