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Potential of Probiotics for the Treatment of Parkinson's Disease: A Systematic Review of Clinical studies

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ABSTRACT: Millions of people in the world are suffering from neurological disorders such as Parkinson's, strokes, Alzheimer's, anxiety, Parkinson's and so on. Presently around 1 million people suffer from this disease in the united state. It influences around 1-2% adults with the age of 65 and 4% adults with the age of 80. Parkinson's disease is one of the most common neurodegenerative disorders that is marked by the damage of dopaminergic neurons and the accumulation of alpha-synuclein. It shows the motor and nonmotor symptoms like tremor, rigidity, and bradykinesia, hyposmia, pain, depression, tiredness, orthostatic hypotension and so on. probiotics are living microorganisms that prevent neurological disorders by altering the gut microbiota in the small intestine. Probiotics used in the treatments of Parkinson's disease which balances the gut microbiomes. Clinical and preclinical data shows the beneficial role of probiotics in the treatment of Parkinson's disease.

1. INTRODUCTION

Neurodegenerative disorders are the most emerging disorders nowadays. That leads to problems with imbalance, coordination and walking, talking, shaking, and stiffness. People around 1 million presently suffered from Parkinson's disease in the united state. It influences around in adults 1-2%with the age of 65 and 4% adults with the age of 80. In 2030 it was expected that because of life duration more than 50% of people more prone to this Parkinson's disease expected to be increased (Dorsey, E et al., 2007). PD is developing diseases that take place around 10 years or more. In the last stage resistance to medication is a major problem that can increase Parkinson's disease. It was reported that 50% of the PD patients showed symptoms like choking and 80% of the PD patients showed symptoms like freezing of gait with the falls, after 17 years of the disease (Hely, M.A et al., 2005). At the last stage of PD patients showing symptoms like dementia and falls. Parkinson's disease is a neurological disorder that is caused by various factors such as oxidative stress, deep brain stimulation, misfolding in protein, genetic mutation neuroinflammation, and the formation of toxic substances. Dopaminergic neurons lead to collapsing in the region ofthe midbrain (extrapyramidal tract).

Recent studies showed the contribution of gut microbiota in the development of neuroinflammation which leads to neurodegenerative disorders. The gut microbiota contains the trillions of bacteria that alter the bacterial composition and help in maintaining neurodegenerative disorders and it promotes the healthy immune system and digestive

system. Gut microbiota has also an impact on neurological results like memory, cognition, and learning. Gut microbiota helps in brain development and helpful in various disorders like sclerosis, Alzheimer's disease, Parkinson's disease, stress and anxiety (Parashar, A et al., 2017).

3. PARKINSON'S DISEASE

It is a complex growing neurodegenerative disease that is marked by the damage of dopaminergic neurons of the substantia nigra and by an accumulation of the alpha-synuclein. The symptoms are identified as rigidity and hyposmia, tremor, pain, depression, bradykinesiatiredness, orthostatic hypotension and most commonly, as the disease progress gastrointestinal (GI) dysfunction with postural instability appearing in some patients (Perez-Pardo et al., 2017).

Stages of Parkinson disease

STAGE 1: Lesions are produced at the vagal nerve plus olfactory bulb together at the anterior side of the olfactory nucleus.

STAGE 2: The dorsal motor nucleus worsens the pathology of Parkinson's disease by the destruction of spreading.

STAGE 3: The lesions can be seen in the substantia nigra by an accumulation of lewisbodies, granular aggregation and pale bodies within the neurons.

STAGE 4: The particular portion of the cerebral cortex which includes the transition zone namely allocortex and neocortex is involved in the disease process of the first time.

STAGE 5: The neurodegenerative disease attains the topographic extend.

STAGE 6: In the last stage, patients showed the full range of symptoms related to Parkinson's disease (Braak, H et al., 2004).

3.1 ETIOLOGY

3.1.1 ENVIRONMENTAL RISK FACTOR

Cigarette smoking

Most of the cohort studies and epidemiological studies showed a lessor risk of developing thid disease. Many of the metanalysis showing a reverse connection between smoking and PD which including 44 case-control studies and 8 cohort studies from 20 countries with a combined relative risk of 0.39 for current smokers(Hernán, M.A et al., 2002). It is also reported that the possibility of PD less in smokers as compared to the nonsmokers which are reported by the inverse correlation between a number of compact of years, the number of years with smoking and the probability of PD, with the probability of expanding PD. The other two meta-analyses also describe the relationship between smoking and PD, ranging from 0.23 to 0.70, which is specifying a protective mechanism against PD. According to the hypothesis, the reduced risk is not completely understood. In the experimental representation of PD, the cigarette components are neuroprotective in action by the energetic action of nicotinic acetylcholine by selective agonist and nicotine on dopaminergic neurons. The alternative hypothesis would be that the nicotine also activates the release of dopamine which is not shown the properly pathological hallmark of PD. Therefore it is not confirmed whether this disease prevents by smoking or whether it helps to stop the habitual use of smoking. Responsiveness to nicotine is decreased by suggesting this association that smoking was more easier than controls and this result were assisted by the actuality that patients with prodromal PD (Kouli, A et al., 2018).

Caffeine

Many studies reported the outcome of coffee in the arising of PD and lessor the possibility of growing it among caffeine users. In the meta-analysisit has been reported that a 25%

possibility for this disease for caffeine compounds addicted to the linear dose-response data. (Noyce, A. J et al., 2012). The putative action showed by the caffeine when it is acting as an adenosine receptor (A2A) antagonist. Regular tea drinkers also have been reported to have a lower risk of developing PD. Concerning gender, there were different studies. it has been reported, in different cohort data, the inverse relation between the rising of PD and caffeine by the men's are more prone to it rather than women's are weaker (Ascherio, A ET AL., 2004).

Herbicides, heavy metals, and pesticides

The (MPTP) 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine was the initial discovery that is related to nigrostriatal degeneration. It is assimilated as a neurotoxin. (1-methyl-4-phenylpyridinium) MPP+.Dopaminergic cells that are present in substantia nigra damaged by the special mitochondrial complex-I inhibitor (Xu, K et al., 2006). The recognization of MPTP as the source of degeneration substantia nigra that gives the idea that it could be developed by environmental factors. Many of the studies had shown a relationshipbetween PD and pesticides. Parquets is similar in structure with MPP+ and rotenone is a complex-I inhibitor and make dopaminergic exhaustion in PD of an animal model. Heavy metals and welding examples arelead, iron, aluminum, copper and zinc are also havebeen observed but the relationship between the heavy metals and it is remains indecisive (Betarbet, R et al., 2000).

3.1.2 METABOLIC RISK FACTOR

Body mass index (BMI)

In the different studies, there was not any relationship was found between BMI, overweight, obesity, and its possibility with PD patients who are having lesser BMI and weight rather than a control group.The studies are ongoing to determine whether the rise in BMI and weight gain

would carry a higher impact on cardiovascular diseases and it's had observed that after stimulation of the deep brain. (Zhang, P et al., 2014).

Diabetes, Hyperglycemia, Insulin resistance and Glucose

Many of the Meta-analysis reported that the anti-diabetic drugs named PPARg agonists, dipeptidyl-peptidase-4 inhibitors and glucagon-like peptide-1 analogs are causing the decreasing the possibility of PD in patients with diabetes. Cell death is induced by the high glucose level which is encouraged by mitochondrial superoxide generation and nitrosative stress through the breakdown of the caspase 3 to encourage the apoptotic pathway (Tsuruta, R et al., 2010). The hyperglycemia is also related to the PD, with the aging, the glucose causes damage to the central nervous system. The PD patient showed the same functional and cellular signs with higher oxidative stress and decreased in mitochondrial signs and higher peroxidation of the cellular membrane (Tomlinson, D. R et al., 2008).

Antihypertensive drugs

Many of the Meta-analysis has been reported that there was not any relation that was found with the antihypertensive drugs. Some of the studies reported that the dihydropyridine and nondihydropyridine protective action provided by thecalcium channel blockers for the PD. In vitro and in vivo models of PD disease were reported that neurotoxicity is protected by the dopaminergic neurons, by an isradipine which is a calcium channel blocker shifting the pace making of these kinds of neurons from the calcium-dependent to a sodium-dependent mode. According to this in phase 2 and phase 3, isradipine was tolerated and shown the success in 336 PD patients (Simon, K. C et al., 2007).

Urate

Several meta-analyses reported that PD patient has lower plasma uric acid level than a healthy person. The latest clinical trials describe that by the administration of inosine

precursors; cerebrospinal fluid and plasma uric acid level increases it was also reported that the inosine raised the plasma antioxidant property. When urate was correlating to MPTP and glutamate then it acts as a reactive oxygen species and reduces dysfunctioning of mitochondrial and necrosis of cell culture. (Tian, B. et al., 2014).

Anemia

The connection between the anemia and it was not found but may require in iron deficiency and involve in the extra neurological function in alpha-synuclein but anemia by itself as like as not straight increase the chance of it, as no new relationship association in chronic anemia, like thalassemia and PD, newly recognize anemia is linked with PD. (Hong, C. T et al., 2016).

Sexual hormones

It has been reported that oophorectomy was increased in the younger age of women with a higher probability of it. (Rocca, W.A et al., 2008). The other description suggested that estrogen has shown protective action with the risk of PD.

Non-steroidal anti-inflammatory drugs (NSAIDs)

Many several meta-analyses, it has been reported that ibuprofen was more prone to the reduced risk of PD. Ibuprofen is a ligand of PPARg and may thereby exert an anti-apoptotic and anti-oxidative effect (Beal, M. F et al., 2008). One more meta-analysis manifested that aspirin users revealed a negative effect and non-aspirin revealed a protective effect. (Power, M. C et al., 2010).

3.1.3 Genetic involved in Parkinson's disease

Many of the mutations in a certain gene and genetic factor are involved in PD. 11 genes are found to be involved in PD and 6 are recognized as: α synuclein (SNCA), LRRK 2, PINK 1, UCH-L1, (PARK) parkin and DJ-1 gene (Schulte, C et al.,2011). During the mutation of the genes, generated protein helpful in the identification of understanding the mechanism responsible for PD and NDDs. Usual causes of the familial or sporadic PD is the mutations in the LRRK 2 gene. A point mutation in the SNCA gene and duplication or triplication of this gene is responsible for the onset of PD and development of the symptoms in the later age respectively (AntoninaKouli et al., 2018)

4. FINDINGS OF GASTROINTESTINAL PATHOLOGY IN PATIENTS WITH PARKINSONS DISEASE

A gastrointestinal tract composed of four layers: innermost layer is mucosa, submucosa, muscular layer, and the outermost layer is serosa. It contains the intrinsic enteric nervous system and extrinsic autonomic nervous system, which is responsible for the PD. The ENS is composed of submucosal and myenteric plexuses. Asubmucosal plexuses further having four layers: (1) inner layer {Meissner plexuses} (2) intermediate layer (3) outermost layer {Henle plexuses}, which is involved in the blood flow and secretion. The plexuses of myenteric were responsible for the intestinal peristalsis (Derkinderen, P et al., 2011). Neurotransmitters consist of neurons in the CNS and in the enteric nervous system, which is composed of acetylcholine, catecholamine, nitric oxide and vasoactive intestinal peptide (Furness, J. B. 2012). The autonomic parasympathetic system initiates the regulation of ENS work from the vagus nerve to the dorsal nucleus at thesympathetic input from the load prevertebral and paraganglia.

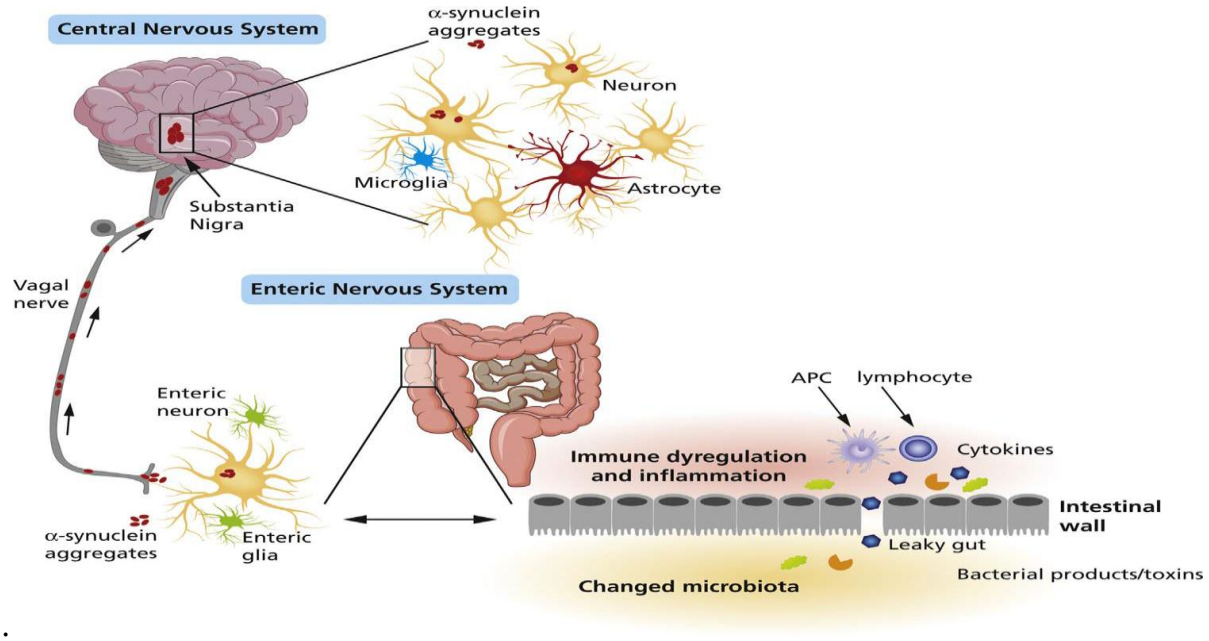

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Fig.1: Pathology of Parkinson's disease

Pathological mechanisms exist not only in the substantia nigra and other pigmented nuclei, like the locus coeruleus and the dorsal motor vagus nucleus but also in a variety of other areas, most often in the innominate tissue, the hypothalamus, the raphe nuclei of the midbrain and rostral pons, the sympathetic ganglia and less often in the spinal cord. (Jellinger, K. A.1991). It has been reported that pathology of it involved in the transmission of trans synaptic cells to a cell of α-synuclein from ENS tothe substantianigra and other brain areas between the olfactory bulb and vagus nerve (Anand *et al.*, 2017). This data, collected with the reality of ENS and olfactory bulbs are the doors of the atmosphere, indicates that environmental factors are involved in PD pathogenesis **(**Chiang, H.Let al., 2019).A lot of evidence indicates pathophysiological modifications in the digestive tract in Parkinson's disease pathophysiology, and many studies suggest that the enteric nervous system may be served as a receptor for the dissemination of α-synuclein, facilitating the typical spread of degeneration via the CNS. **(**Edwards, L. L et al.,1992)**.** PD pathogenesis may also be triggered or worsened by inflammatory responses caused by dysbiotic microbiota that may facilitate pathology of alpha-synuclein in the intestine and brain to alpha-synuclein cell-to-cell pathology due to increased oxidative stress (Perez-Pardo, P et al., 2017)

5. NEURO INFLAMMATION IN PD

In vitro and in vivo studies it has been reported that neuromelanin causes the activation of microglial cells, pro-inflammatory mediators are stimulated and the constitution of p38 mitogen-activated protein kinase (MAPK) signaling and NF-úB pathways (Lehmann, J. M et al.,1997). The existence of lymphocytes containing both CD8+ and CD4+ cells in the brain of Parkinson's disease patients. In the experimental studies in MPTP intoxicated mice has been shown that CD4+ T lymphocytes are involved in the degenerative process through a mechanism of the Fas/FasL pathway (Brochard, V et al.,2008). It was found that the accumulation of alpha-synuclein causes the neuroinflammation of the MPTP intoxication in mice, modified and the nitrated form of alpha-synuclein is more found in the CNS of PD patients.The release of inflammatory chemicals (proinflammatory cytokines, chemokines, prostaglandins, leukotrienes, reactive oxygen species, etc.) causes neuroinflammation (Hirsch, E. C et al., 2012).

At the beginning and pathological occurrence in the central nervous system is expected for the activation of glial cell types and secretion of factors involved in the balancing of inflammation.

Table 1: List of glial cells that regulate neuronal survival (Mosley, R. et al., 2006).

S NO.	NAME	FUNCTIONS
1.	Prostaglandin E2, Leukotrienes, Thromboxane.	Involved in pro-inflammatory activities.
2.	Macrophage-derived chemokine. Macrophage inflammatory protein 1α, 1β and 2	Involved in chemotaxis effect.
3.	Interleukin 3 and 15	Involved in proliferation and T cell regulation effect.
4.	Interleukin 18 Interleukin 6 Interleukin 1 beta Tumor necrosis	Increase oxidative stress and induction of nitrogen-oxygen species. Acting as pro-inflammatory. Neurotoxic effect.
5.	Superoxide, nitric oxide, hydrogen peroxide.	Involved in Neurotoxic and oxidative stress effects.
6.	Transforming growth factors beta. Nerve growth factors Glial derived and brain-derived neurotropic cells.	Acting as Anti-inflammatory. Involved in Neurotropic effect.

6. CURRENT TREATMENT FOR PARKINSON'S DISEASE

The current treatments for Parkinson's disease patients, with the development of symptomatic pharmacotherapy of non-motor and motor symptoms based on dopaminergic mode of action.

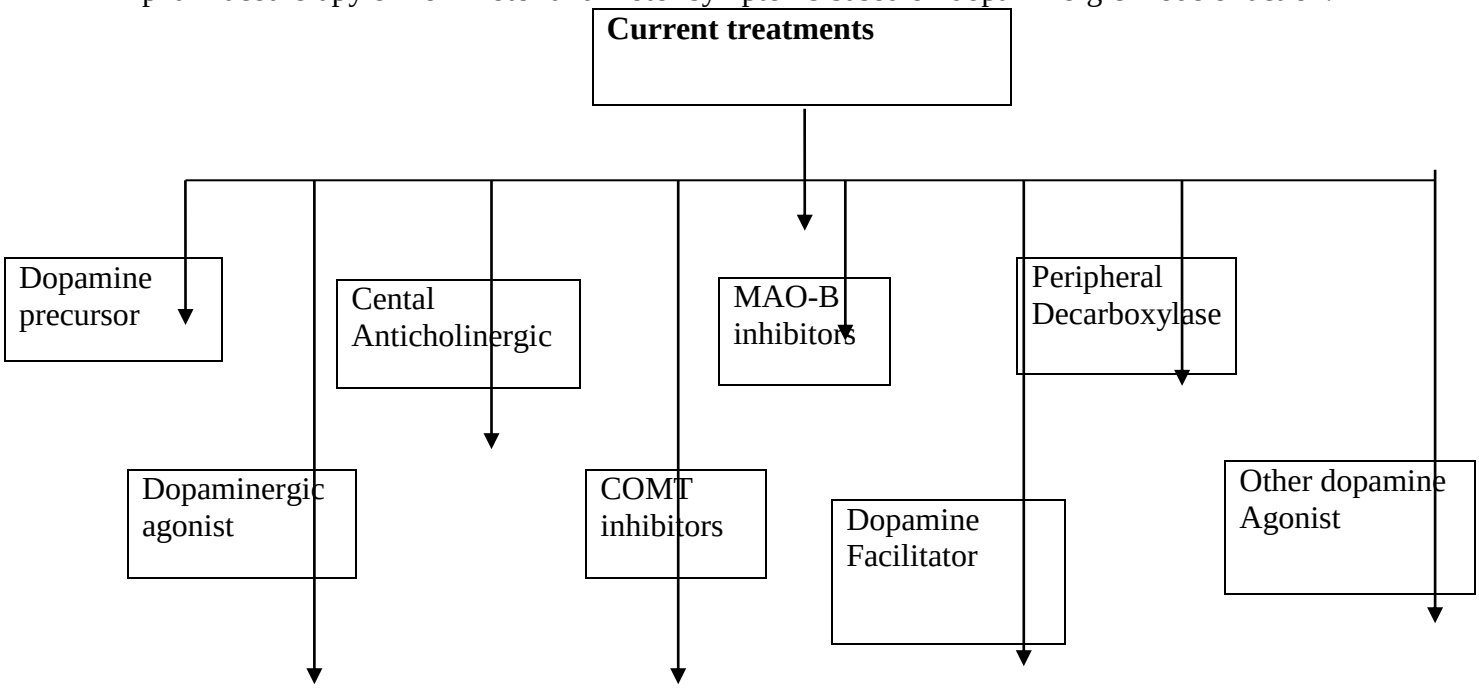

Fig.2: Current treatments

6.1 Levodopa therapy

According to the clinical studies and several comparative studies it has been reported that levodopa therapy was the most efficacious and symptomatic treatment of it. Based on the in vitro studies, L dopa treatment was approved for the PD with non-motor and motor symptoms. It has been suggested that take l dopa medication 1 hour before or after a meal. L dopa showing some side effects with all other PD medications like (Anticholinergics, MAO inhibitors, Amantadine hydrochloride).(Ellis, J. M et al., 2017)

The L dopa medication was more efficacious for Parkinson's disease patients. Oral l dopa medications have bioavailability 90% and slow-releasing medication bioavailability was 70%. Whereas slow L dopa preparations were taking at night time to overcome the riched protein meal, in command to lower the nocturnal akinesia (Olanow, C. W et al., 2004).

6.2 Levodopa-Infusion treatment

It has been approved that L dopa preparation was given by intrajejunal therapy with motor fluctuations, for the treatment of PD. This therapy provides a constant plasma concentration and this therapy was approved as a monotherapy (Honig, H et al., 2009).

Levo dopa infusion treatment is:

1. Dyskinesia and motor functions cannot be treated with oral pharmacotherapy.
2. Nursing attention is provided by enough support to percutaneous endoscopy jejunum.

6.3 Dopamine agonist

The ergot or non-ergot substances are obtainable to PD. The following are the derivatives which are used in the treatment (Poewe, W et al., 2003).

Table 2: Dopamine agonist derivatives

S no.	Ergot derivatives	Non-ergot derivatives
1.	Cabergoline	Pramipexol
2.	Bromocriptine	Ropinirole
3.	Lisuride	Piribedil
4.	Alpha dehydroergocriptine	Apomorphine
5.	Pergolide	Rotigotine

Dopamine agonists are approved for the advanced treatments in the PD, in CNS fluctuations, earlier PD patients with monotherapy and as an adjunct therapy. In some of the preparations, monotherapy (dopamine agonist) was efficacious for the recent preparations. L dopa plus dopamine agonist preparations showing the more efficacious activity for motor fluctuations. The recent advancements have been reported that in the first 4 years many of the patients are not relevant to dyskinesia. 6 to 10 long clinical trials comparing the pramipexole with non-ergot dopamine therapy versus this demonstrate that initially group undergo from the dopamine agonist to attain properly symptomatic therapy, secondly dyskinesia existence increases with time (Stowe, R et al., 2008).

Limitations of dopamine agonist

- Orthostatic dysregulation.
- Nausea.
- Ergot and non-ergot derivatives cause leg edema.

- It induces dopamimetic psychosis, impulse control disorder.
- Non-ergot dopamine agonist induces more sleepiness.
- Ergot dopamine agonist induces cardiac or pulmonary valvular fibrosis.

6.4 New symptomatic treatments

The current treatments for non-motor and motor symptoms of it. (Lindholm, D et al., 2016).

Table3: List of new symptomatic treatments:

S no.	Compound	Mode of action	Indication
1.	Opicapone	COMT_ inhibitors	Motor wearing off
2.	Soluble tablets of Levodopa, Carbidopa	A modified form of levodopa	Motor
3.	Safinamide	MAO-B-inhibitor, glutamate modulator	Motor wearing off

This review has been approved that, new compounds are used in it with the mode of action. The aim of this development based on the motor and non-motor fluctuations of symptomatic pharmacotherapy with a dopaminergic mode of action((Ellis, J. M et al., 2017).

Based on dopaminergic mode of action, new compounds are used in the PD like opicapone based on COMT inhibitors; Safinamide depends on the MAO_B inhibitors, based on the modified form of Levodopa the Melevodopa and Carbidopa are used in PD patients.

Table 4: Symptomatic therapy: New list of compounds based on the non-dopaminergic or antidopaminergic mode of action (Factor, S. A. (2008).

Compound	Mode of action	Indication
Donepezil	Anticholinesterase inhibitors	Non-motor dementia and gait in PD
Duloxetine	SSNRI(serotonin and norepinephrine reuptake inhibitors)	Based on non-motor pain
Zonisamide	Antiepileptic drug	Motor UPDRS III wearing off
Aripiprazole	D2 antagonist Anti dopaminergic	Used for impulse control disease(ICD) Dyskinesia
Naloxone	Opioids	Based on pain syndrome in PD

Table 5: Symptomatic therapy: List of compounds for motor symptoms or non-motor indication based on the action of nondopaminergic

Compound	Mode of action	Indications
Tozadenant	Adenosine 2A receptor antagonist	Motor dyskinesia wearing off
Pitolisant	Histamine autoreceptor antagonist	sleepiness time by non motor
Pimavanserin	5 HT2A inverse agonist	Cause non-motor psychosis
Istradefylline	Adenosine 2A antagonist receptor	Based on motor wearing off

Table 6: Plants showing Neuroprotection against Parkinson's disease
(Bagewadi, H. G et al., 2015)

S no.	Name of plants	Evaluation parameter
1.	*Hypericum perforatum*	Rotarod test, hang test, estimation of DOPAC, CAT, GSH, GPx, and SOD
2.	*Aloe vera*	Hang test, Tardive dyskinesia test, hole board test
3.	*Cynodon dactylon*	Catalepsy test, estimation of TBARS and SOD
4.	*Juniperus communis*	Estimation of TBARS, GSH, protein estimation, catalepsy test
5.	*Bacopa monnieri*	Estimation of glutamate dehydrogenase, glutamine synthetase and glutaminase
6.	*Gynostemmapenta phyllum*	Estimation of level of dopamine, DOPAC and HVA
7.	*Ficus religiosa*	Estimation of MDA, SOD, CAT, and GSH
8.	*Elaeocarpus ganitrus*	Rota rod test, estimation of MDA, GSH

7. Gastrointestinal dysfunction in PD

Gastrointestinal function is defined as the disorders occur within the gastrointestinal tract. The GI symptoms observed as nausea, constipation, and drooling, bloating, slow gastric emptying time and extend intestinal transit time. According to James Parkinson, non-motor symptoms were already observed in 1817. One of the international studies reported that PD patients are not aware of 62% of non-motor symptoms. Constipation is the most important motor symptom and related to a higher probability of it which shows 87% existence of constipation before resulting in the motor symptoms in PD patients (Pfeiffer, R. F. 2003).

Gastrointestinal features of Parkinson's disease

The gastrointestinal extension reported that Edwards and colleagues giving five features in 1991 that are given below:

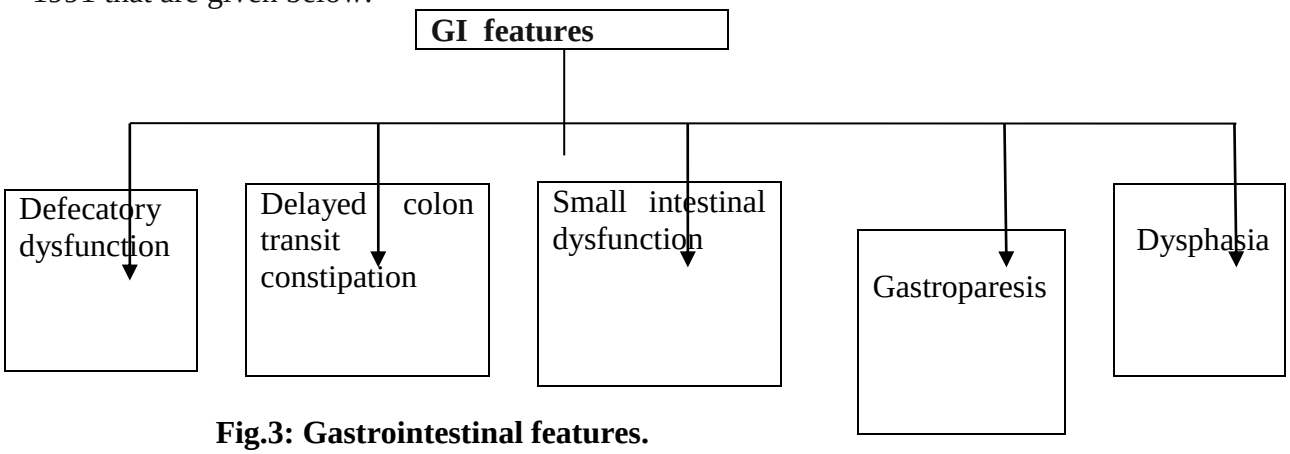

Fig.3: Gastrointestinal features.

1. **Defecatory dysfunction:** Difficulty in defecation is the second demonstration in PD patients. It is marked by painful defecation, increased straining, slow emptying in PD patients. For the normal defecation relaxation and contraction of muscles required to happen. The current treatments for defecatory dysfunction were pelvic floor exercise and modification in dopaminergic function is useful in PD patients.
2. **Delayed colon transit constipation:** Some of the studies have been reported the slow colon transit time in PD patients. The recent treatment approaches are growing in dietary fiber like stool softener, methylcellulose or psyllium seed is required for PD patients.
3. **Small intestinal dysfunction:** in the recent study it was reported in 54% of PD patients small intestinal bacterial overgrowth (SIBO) was observed. SIBO identified by accumulation of gas (flatulence), bacterial density increased in the small intestine, a sense of bloating and of the presence of bacterial species in the colon region. The treatment for this factor was mentioned that antibiotic treatment for SIBO was beneficial at some extends.
4. **Gastroparesis:** Gastroparesis defined as the slow emptying time which is observed by the symptoms like vomiting, nausea, weight loss, and reduction in appetite. Many of the studies reported the treatments for gastroparesis in PD patients but the studies are not successful. Thesmall pilot study has reported the histamine H2 receptor blocker, nizatidine successful in enhancing gastroparesis in PD, but to some extent.
5. **Dysphasia:** In the clinical studies it has been reported that swallowing symbiotic abnormalities may be present in several persons with PD. Some stages of swallowing are pharyngeal, esophageal and oral may be affected. It has been recommended that impaired pharyngeal sensation plays an imported role in PD. It was reported that upper and lower esophageal swallowing suggestive of PD.

8. PROBIOTICS

Probiotics are defined as the microorganisms that maintain health benefits and immune homeostasis by altering the gut microbiota. Probiotics examined to be novel and safe by producing antimicrobial agents in the intestinal microbiota by suppressing the growth of other microorganisms. It has been reported that different probiotic bacterial strains have shown the efficacious activity towards the lowering of gastrointestinal dysfunction and stimulating intestinal motility. Current used Probiotics are Enterococci, Lactobacilli, yeasts, Bifidobacteria, and different mixtures of advantageous bacteria(Barichella, M et al., 2018)
Probiotics are useful in the alteration in PD related microbiota composition and enhance the GI function and it lessens the alteration of bacterial, gut leakiness and related to neuroinflammation in the ENS. By alteration in the gut microbiota by Probiotics improving GI function and protection towards the intestine, but might also beneficial in levodopa absorption and lessor behavioral and cognitive deficits such as depression, anxiety and memory problems which are common in PD patients (Felice, V. D et al., 2016).

Properties involved in Probiotics

- Probiotics are resistant to the acidic medium of gastric fluid and suppress the growth of harmful bacteria.
- Probiotics can create resistance towards bile salt like in the small intestine bile juices digest the fatty food.
- Probiotics have shown antimicrobial action.

9. Clinical Data involved in Parkinson's disease

Table 7: Clinical Data

Model	Bacterial strain	Parameters evaluated	Result	References
	1. Lactobacillus salivarius			Magistrelli, L et al., 2019

40 Enrolled patients with PD (25 men and 15 women) and Healthy donors with matched 40 age	*2. Lactobacillus plantarum* *3. Lactobacillus acidophilus* *4. Lactobacillus rhamnosus* 5. *Bifidobacterium animalis subsp. Lactis* 6. *Bifidobacterium breve*	Cytokine release, Superoxide anion (O2 -) production, TEER evaluation, Inhibition of E. coli and K. Pneumoniae, Tyrosine decarboxylase (TDC) genes.	Lactobacillus acidophilus had shown the Anti-inflammatory action. Reduce ROS production and improvement in constipation, inhibiting E. coli and K. pneumonia.	
From 38 PD patients and 34 healthy controls, the 65 samples of fecal were collected.	*Blautia, Roseburia, and Coprococcus, Firmicutes, Proteobacteria, Verrucomicrobia, Oscillospira, Bacteroides,*	Comparison of fecal microbiota and mucosa, mucosa-associated bacteria, fecal microbiota.	Butyrate-producing bacteria acting as "anti-inflammatory". And this study confirms proinflammatory dysbiosis in patients of PD and activate inflammation-induced misfolding of a-synuclein in the de PD pathology development.	Keshavarzian, A et al., 2015
A randomized, double-blinded, placebo-controlled trial	*Bifidobacterium bifidum, Lactobacillus reuteri, Lactobacillus fermentum and Lactobacillus acidophilus*	Inflammation, parameters of metabolism in PD patients, Oxidative Stress, And measure the effects on lipid profile and insulin metabolism.	Probiotics do not show any side effect in PD patients and it decreases insulin level. Probiotics decreased MDS-UPDRS	Tamtaji, O. R et al., 2019
A randomized, double-blind, placebo-controlled trial Divided into 3 groups Probiotic capsule daily(n=13), Probiotic	**Probiotic yogurt** *Lactobacillus acidophilus* and *Bifidobacterium lactis* **The probiotic capsule contains seven probiotic bacteria spices** L*actobacillus casei*,	Evaluation of oxidative stress and inflammatory factors	It has been reported that beneficial effects of probiotic capsule and probiotic yogurt on the biomarkers of oxidative stress.	Mohammadi, A et al., 2015

yogurt(n=12), Conventional yogurt (n=10) for 6 weeks	*L. acidophilus*, *Lactobacillus rhamnosus*, *Lactobacillus bulgaricus*, *Bifidobacterium breve*, *Bifidobacterium longum*and *Streptococcus thermophilus* .			
A randomized, double-blind, placebo-controlled study	*Lactobacillus casei*	Constipation severity, Stool consistency	Improvement in constipation	Mazlyn, M. M et al., 2013
A randomized, double-blind, placebo-controlled clinical trial	*Lactobacillus casei*, *Lactobacillus fermentum*, *Bifidobacterium bifidum*, *Lactobacillus* acidophilus.	Gene expression of interleukin-8, tumor necrosis factor Alphagene expression related to insulin (PPAR-g) and lipids (oxidized low-density lipoprotein receptor LDLR)	An improvement was found in the gene expression of IL-8 and TNF-a but did not found any improvement in IL-1, PPAR-g, or LDLR.	Borzabadi, S et al., 2018

11. CONCLUSION

Based on the review literature it is seen that the microbes present in the gut have a direct impact on the central nervous system by releasing some neurotransmitters, hormones, and cytokines. Alterations in gut microbiota can be used as a potential treatment in Parkinson's disease. As per the studies, conducted probiotics has a beneficial role in the treatment of Parkinson's disease

As per preclinical and clinical data, it was found out the impact of probiotics in Parkinson's disease. Probiotics have shown its effectiveness by improving the pathological conditions both in animals and humans. Very few studies have been conducted on pre-clinical trials. More studies should be conducted on probiotics in clinical trials in the future as it has shown its potential effect in preclinical studies.

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