Revista Argentina de Clínica Psicológica
2024, Vol. XXXIII, N°1, 3642
DOI: 10.53555/03276716.2024.05

Deciphering The Gut-Brain Connection: Insights Into Neurodegenerative Disorders

Jyoti Phogat[1]*, Dipendra Kohar[2], Rajip Nepal[3], Deepak Ganghas[4], Gaurav Dhiman[5], Sahil Sethi[6], Shyam Sunder[7]

ABSTRACT:
The complex interaction between the gastrointestinal system and the central nervous system has become a captivating area of study, particularly about neurodegenerative diseases. This review critically examines the evolving understanding of the gut-brain axis and its significant implications for diseases such as Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis (ALS). The gut-brain axis represents a two-way communication system that involves neural, hormonal, and immunological pathways, which are mediated by the gut microbiota, microbial metabolites, and the enteric nervous system. Disruption of this axis has been implicated in the development and progression of neurodegenerative disorders. We delve into the role of gut dysbiosis in neuroinflammation, exploring how changes in the composition of the gut microbiota can trigger immune responses that affect neuronal function and survival. Additionally, we discuss the impact of microbial metabolites, such as short-chain fatty acids and neurotransmitters, on neuroprotective mechanisms, providing insight into the intricate communication between the gut and the brain. In the case of Alzheimer's disease, accumulating evidence suggests a connection between gut dysbiosis, amyloid-beta deposition, and neuroinflammation, opening up possibilities for microbiota-targeted interventions aimed at slowing down disease progression. Similarly, in Parkinson's disease, alterations in the composition of the gut microbiota have been linked to the aggregation of alpha-synuclein and motor dysfunction, indicating the potential therapeutic benefits of modulating the gut microbiota to alleviate symptoms and alter the course of the disease.

Keywords: Neurodegenerative, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis (ALS), gut microbiota

INTRODUCTION: -

Neurodegenerative disorders (ND) manifest as the progressive deterioration of axons and neurons in various regions of the central nervous system (CNS), leading to impairments in movement and/or cognitive functions. These intricate disorders are intricately linked to oxidative stress and inflammation, which are the primary systemic factors exacerbating the process of neurodegeneration (1,2). The number of individuals affected by neurodegenerative diseases (NDs) is on the rise, primarily due to the extension of human lifespan. It is projected that by the year 2030, the population of ND patients in the United States will exceed 8 million (3). Neurodegenerative disorders, including Parkinson's Disease (PD) and Alzheimer's Disease (AD), encompass a diverse range of conditions characterized by the progressive decline of the central and/or peripheral nervous systems. These ailments impact approximately 1% and 8% of the population, respectively (4) and In 1869, the renowned French neurologist Jean-Martin Charcot provided the initial description of amyotrophic lateral sclerosis (ALS). He established a correlation between the gradual paralysis experienced by patients and the presence of abnormalities in the white and gray matter of the central nervous system (CNS) (5). Amyotrophic lateral sclerosis (ALS) is a neurodegenerative condition that primarily affects adults and leads to the progressive degeneration and eventual demise of motor neurons. This debilitating disorder results in the targeted demise of motor neurons, ultimately resulting in paralysis and ultimately, death (6). The interaction between the gastrointestinal tract and the central nervous system is facilitated by the gut-brain axis, which plays a crucial role in promoting the growth and upkeep of neurons. However, when there is an imbalance in the gut microbiota, known as gut dysbiosis, it can lead to the manifestation of neurological disorders (7). The gut microbiota, a diverse group of bacteria in the gastrointestinal tract, plays a crucial role in human health due to its bidirectional communication with the brain via the gut-brain axis (8,9,10).

[1]*Research Scholar, MM College of Pharmacy, Maharishi Markandeshwar (Deemed to be University), Mullana, Ambala-133207, Haryana, India.
[2,3]College of Pharmacy, RIMT University, Mandigobindgarh, Punjab (147301).
[4]Assistant Pro., SOPS CT University, Ludhiana, Punjab (142024)
[5]Himalayan Institute of Pharmacy, Kala amb HP.
[6,7]Assistant Pro., at R J World College of Pharmacy Education &Technology, Jakhod

*Corresponding Author: Jyoti Phogat
*Research Scholar, MM College of Pharmacy, Maharishi Markandeshwar (Deemed to be University), Mullana, Ambala-133207, Haryana, India.

❖ **GUT MICROBIOTA AND NEURODEGENERATION**

The gut microbiota, a diverse collection of bacteria in the gastrointestinal tract, coexists with the human host, primarily comprising Firmicutes (51%), and Bacteroidetes (48%), forming a symbiotic relationship (11). The remaining 1% consists of various less populous phyla, such as Proteobacteria, Actinobacteria (which includes the genera Bifidobacteria), Fusobacteria, Spirochaetes, Verrucomicrobia, and Lentisphaerae [12]. Modern sequencing technology has successfully detected over 1000 distinct species and in excess of 7000 variations of bacteria, which collectively form the vast population of microorganisms within the microbiota, estimated to range between 10^13 and 10^14 [13]. There exists considerable inter-individual variability in the gut microbial communities; nevertheless, the fundamental functionality remains consistent, indicating the necessity of a core gut microbiota to uphold a fundamental array of physiological functions [14]. The gut microbiota can be regarded as an independent organ, playing a crucial role in numerous physiological functions such as host metabolism, neurological development, energy balance, immune modulation, vitamin production, and digestion [15]. The gut microbiota denotes a constantly changing assemblage of microorganisms that reside in the gastrointestinal tract of animals, encompassing humans. Predominantly comprised of bacteria, it also encompasses fungi, archaea, parasites, and to a lesser degree, viruses (16). According to recent research, gut bacteria may contribute to neurodegeneration by upsetting the equilibrium between the brain and the gut, therefore aggravating conditions including ALS, PD, MS, and AD (17). Neurodegenerative disorders are complex conditions in which the initiation of the pathological process appears to involve a combination of genetic and environmental factors (18). Chemicals, nutrition, and immunological factors influence microbial density and composition in the GI tract, with stomach and small intestine having high acidity and shorter transit duration, limiting microbiota growth [19]. On the other hand, the colon/large intestine is densely populated with microbiota due to its anaerobic environment, slower movement of food, absorption of water, and fermentation of undigested food [20]. Depression has been consistently linked to higher prevalence in neurodegenerative disorders like Alzheimer's disease, Parkinson's disease, and multiple sclerosis (21,22,23). Depression is traditionally believed to mimic cognitive symptoms in individuals with dementia 24]. Depression, Alzheimer's disease, Parkinson's disease, and multiple sclerosis are all characterized by heightened immune-inflammatory processes and oxidative and nitrosative stress (O&NS). Additionally, these conditions are associated with a decline in the levels of endogenous antioxidants [25,26], Neurodegenerative conditions often exhibit reduced levels of tryptophan, serotonin, N-acetylserotonin, and melatonin, alongside elevated TRYCATs [26,27,28]. The significance of TRYCAT pathways being influenced by O&NS and immune-inflammatory processes in relation to depression-associated conditions, such as Alzheimer's disease, is gaining more recognition [29], Parkinson's disease [26], and multiple sclerosis [28]. In general, the correlation between depression and neurodegenerative disorders is evident [30).

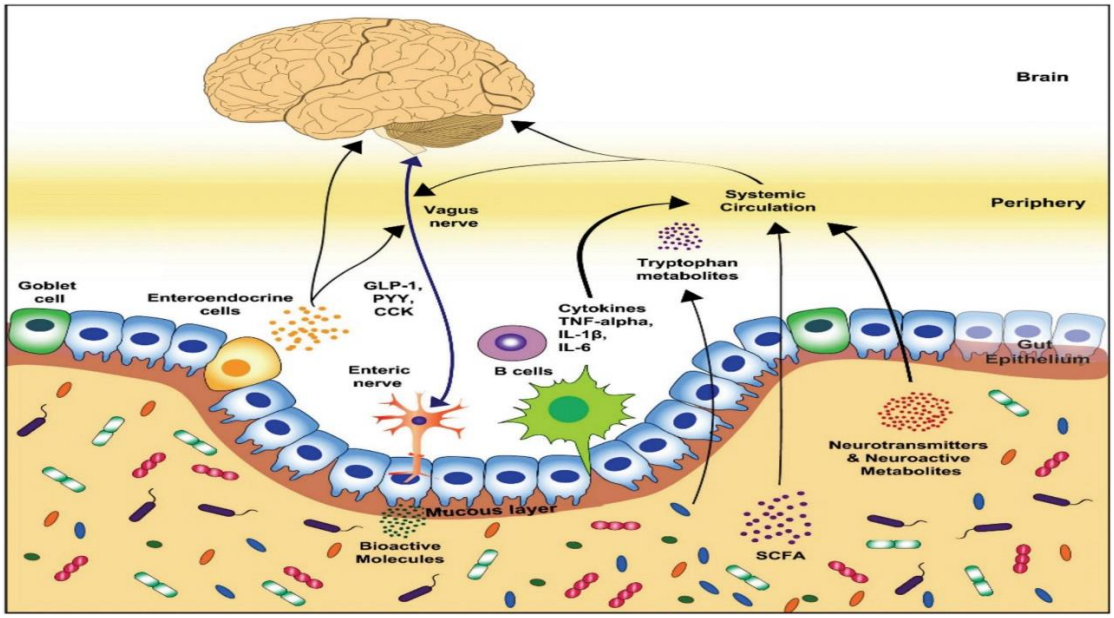

Fig.1 Gut Microbiota and Neurodegeneration

1. GUT-BRAIN AXIS IN ALZHEIMER'S DISEASE:

In the early months of 1989, the presence of Ab protein deposits was identified within the intestinal region [31]. The expression of Amyloid-b protein precursor (AbPP) and total tau in the enteric neurons suggests a potential involvement of the enteric nervous system (ENS) in the pathophysiology of Alzheimer's disease (AD) [32,33]. Nevertheless, additional validation is required for this notion as a result of conflicting reports that have demonstrated comparable levels of Ab and tau pathologies in both Alzheimer's disease patients and elderly individuals without the condition [34,35]. Animal research links gut microbiota to Alzheimer's disease (AD), with disruption causing intestinal inflammation, leading to AD onset and progression, increasing microglia activation and neuroinflammatory response. [36]. Gut-associated lymphoid tissue (GALT) cells in aged AD mice showed reduced IL-17 levels, suggesting potential immune barrier and gut microbiota surveillance impairment [37]. Reports have indicated that there is a modified composition of gut microbiota in the fecal samples obtained from patients with Alzheimer's disease (AD) as well as in AD mouse models [38–40]. The modified microbial composition has the potential to impact the concentrations of Ab42, the deposition of amyloid, and the presence of pro-inflammatory cytokines within the brain [38]. A recent study uncovered varying levels of fecal microbiota abundance in individuals with Alzheimer's disease (AD) compared to those with normal cognitive function. The report indicated an increase in the genera Dorea, Lactobacillus, Streptococcus, Bifidobacterium, Blautia, and Escherichia among AD patients. Conversely, a decrease in the genera Alistipes, Bacteroides, Parabacteroides, Sutterella, and Paraprevotella was observed in individuals with AD [41]. An inverse correlation was observed between the amyloid burden and the relative abundance of Lactobacillus in the feces of individuals with Alzheimer's disease (AD) [41]. A study found that cognitively impaired patients with brain amyloidosis had lower anti-inflammatory E. rectale abundance and higher pro-inflammatory Escherichia/Shigella abundance in their fecal samples, increased pro-inflammatory cytokines (IL-6, CXCL2, NLRP3 and IL-1b), and lower anti-inflammatory cytokine levels [42]. These findings provide evidence for a correlation between inflammation related to gut microbiota and the accumulation of amyloid plaques in the brain in individuals with Alzheimer's disease (AD) (43).

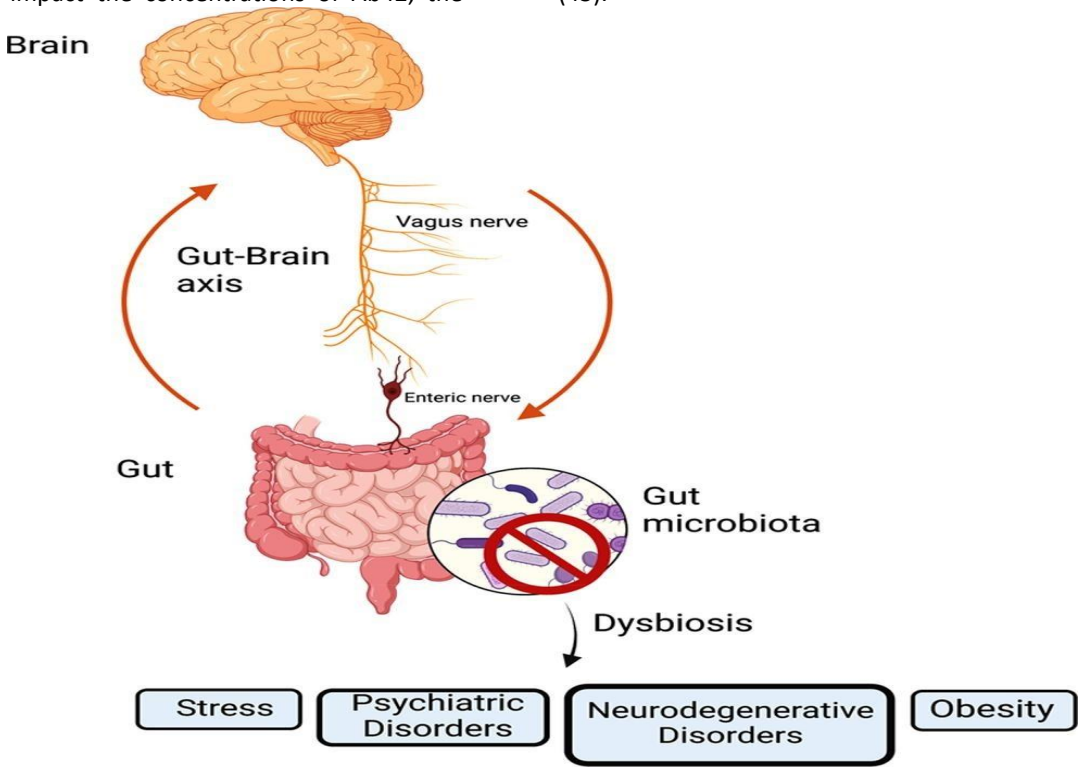

Fig.2 Gut-Brain Axis in Alzheimer's Disease

2. GUT-BRAIN AXIS IN PARKINSON'S DISEASE:

This review focuses on investigating the relationship between microbial composition and the observable changes in the metabolites of microbial species. It also explores the impact of this relationship on the immune response, which could potentially have significant implications for the development, persistence, and pathophysiology of Parkinson's disease through the gut-brain axis (44). The enteric nervous system interacts with a wide range of microorganisms, both beneficial and pathogenic, that reside in the gut, resulting in a rich diversity of microbial populations (45). The abundance and variety of commensal bacteria play a crucial role in supporting physiological functions and enhancing the

overall well-being of the host organism (46). The enzymatic activity and metabolic pathways of the gut microbiota are believed to play a crucial role in supporting human metabolism. This microbial community aids in various processes such as digestion, the production of essential vitamins and nutrients, and the removal of harmful substances from the body (46). Additionally, it may aid in preserving the structural soundness of the intestinal barrier, impeding the growth of harmful microorganisms, and facilitating the breakdown and elimination of pharmaceuticals and harmful substances (47). In addition, the host immune response can be regulated by the gut microbiome through the production of metabolites, such as short-chain fatty acids. These metabolites have the ability to modulate the activity of the immune system, including microglia, by either suppressing or stimulating its response (48). The commencement of constipation may also precede the motor symptoms and exacerbate with the progression of the disease [49,50]. Recent research has provided increasing empirical support regarding the microbiome, highlighting the potential influence of gut microbiota on disease development. This notion has been extensively examined and discussed in a recent publication authored by Sampson et al [51]. It is widely recognized that the primary pathological feature of PD SNpc neurons is the presence of Lewy bodies, which are characterized by the accumulation of toxic alpha-synuclein (αSyn) aggregates [52].

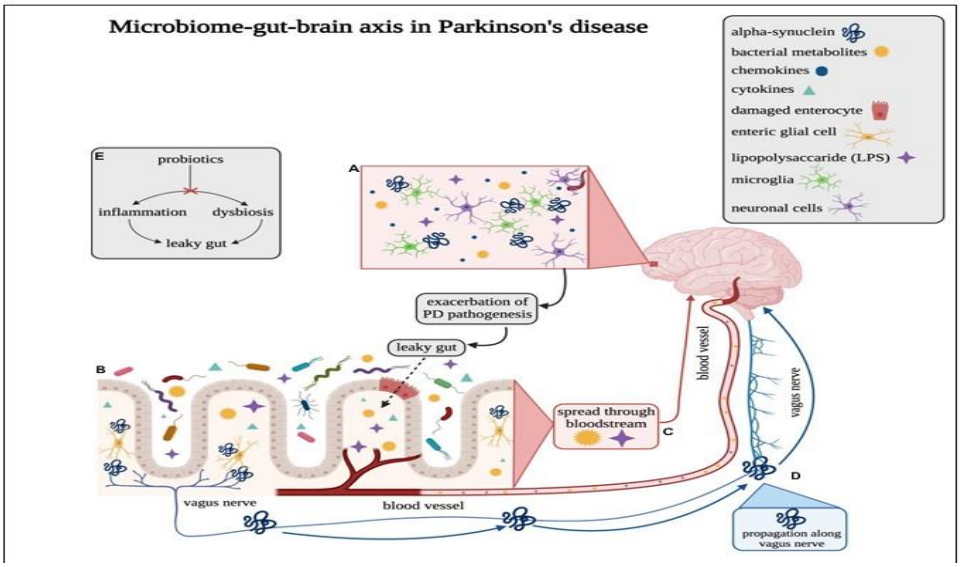

Fig.3 Gut-Brain Axis in Parkinson's Disease

3. GUT-BRAIN AXIS IN AMYOTROPHIC LATERAL SCLEROSIS (ALS):

ALS is a neurodegenerative disease-causing progressive paralysis and weakness in the spinal cord, brain stem, and motor cortex. Factors like microglia-activated inflammation, neurotoxicity, redox unbalance, and mitochondrial dysfunction are implicated, but the deep pathological mechanism remains unexplored (53). The 2019 study on the gut microbiome in ALS patients and the SOD1G93A mouse model is a significant advancement in understanding its functional characteristics. It identified alterations in the gut microbiome, which were linked to the biological activity of nicotinamide, potentially affecting mitochondrial gene expression in the spinal cord. These changes were found to be associated with disease severity (54).

ALS is a neurodegenerative disease that gradually worsens over time and impacts the neurons in both the brain and spinal cord. This disorder is characterized by its multi-system nature, as it also affects the gastrointestinal tract. One possible explanation for this is the heightened permeability of the intestine, leading to an increase in the presence of lipopolysaccharide in the bloodstream (LPS) (55,56).

a) Dysbiosis of gut microbiota in ALS

Research on aging is gaining prominence, with gut microbiota dysbiosis being one of the twelve characteristics of aging, revealing a close correlation between aging and gut microbiota [57]. The composition and diversity of gut microbiota, including the Firmicutes/Bacteroides ratio, will change with age [58, 59]. Dysbiosis of gut microbiota was also observed in two mouse models of progeria [60]. Dysbiosis in gut microbiota affects aging, as transplanting aged mice's fecal microbiota into young mice increases pro-inflammatory cytokines and activated microglia, leading to age-related neuroinflammation and other aging conditions [61]. The fecal microbiota of young mice was transplanted into old mice, resulting in a significant improvement in their aging condition [61]. ALS, an age-related neurodegenerative disease, is linked to gut microbiota. A study on SOD1G93A mice revealed that ALS progression can alter gut microbiota, affecting

mice's lifespan. Understanding ALS patients' gut microbiota could aid understanding (62).

FUTURE DIRECTIONS

Future research on neurodegenerative diseases and the gut-brain axis includes nutritional interventions, multi-omic approaches, personalized microbiome modulation, early detection biomarkers, microbiota-targeted therapies, advanced imaging techniques, clinical trials, and lifestyle modifications. These approaches aim to revolutionize treatment, provide early diagnosis, and explore the relationship between gut microbiota and disease progression.

CONCLUSION

The main point of the text is that the gut-brain axis, mediated by the gut microbiota, plays a significant role in the development and progression of neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis (ALS). Disruption of this axis, through gut dysbiosis, can trigger immune responses and neuroinflammation, leading to neuronal dysfunction and degeneration. Modulating the gut microbiota may have therapeutic benefits in slowing down disease progression and alleviating symptoms.

REFERENCE

1. Singh A, Kukreti R, Saso L, Kukreti S. Oxidative stress: a key modulator in neurodegenerative diseases. Molecules. 2019 Apr 22;24(8):1583.
2. Stephenson J, Nutma E, van der Valk P, Amor S. Inflammation in CNS neurodegenerative diseases. Immunology. 2018 Jun;154(2):204-19.
3. Dorsey EA, Constantinescu R, Thompson JP, Biglan KM, Holloway RG, Kieburtz K, Marshall FJ, Ravina BM, Schifitto G, Siderowf A, Tanner CM. Projected number of people with Parkinson disease in the most populous nations, 2005 through 2030. Neurology. 2007 Jan 30;68(5):384-6.
4. Endres K, Schäfer KH. Influence of commensal microbiota on the enteric nervous system and its role in neurodegenerative diseases. Journal of innate immunity. 2018 Jun 19;10(3):172-80.
5. Goetz CG. Amyotrophic lateral sclerosis: early contributions of Jean-Martin Charcot. Muscle & Nerve: Official Journal of the American Association of Electrodiagnostic Medicine. 2000 Mar;23(3):336-43.
6. https://www.sciencedirect.com/science/article/abs/pii/B9780123858832000023#preview-section-cited-by
7. Westfall S, Lomis N, Kahouli I, Dia SY, Singh SP, Prakash S. Microbiome, probiotics and neurodegenerative diseases: deciphering the gut brain axis. Cellular and molecular life sciences. 2017 Oct;74:3769-87.
8. Burokas A, Moloney RD, Dinan TG, Cryan JF. Microbiota regulation of the mammalian gut–brain axis. Advances in applied microbiology. 2015 Jan 1;91:1-62.
9. Forsythe P, Bienenstock J, Kunze WA. Vagal pathways for microbiome-brain-gut axis communication. Microbial endocrinology: the microbiota-gut-brain axis in health and disease. 2014 Jun 9:115-33.
10. Bauer KC, Huus KE, Finlay BB. Microbes and the mind: emerging hallmarks of the gut microbiota–brain axis. Cellular microbiology. 2016 May;18(5):632-44.
11. Qin J, Li R, Raes J, Arumugam M, Burgdorf KS, Manichanh C, Nielsen T, Pons N, Levenez F, Yamada T, Mende DR. A human gut microbial gene catalogue established by metagenomic sequencing. nature. 2010 Mar 4;464(7285):59-65.
12. Rajilić-Stojanović M, Smidt H, De Vos WM. Diversity of the human gastrointestinal tract microbiota revisited. Environmental microbiology. 2007 Sep;9(9):2125-36.
13. Huttenhower C, Gevers D, Knight R, Abubucker S, Badger JH, Chinwalla AT, Creasy HH, Earl AM, FitzGerald MG, Fulton RS, Giglio MG. Structure, function and diversity of the healthy human microbiome. Human Microbiome Project Consortium. Nature. 2012;486(7402):207-14.
14. Mandal RS, Saha S, Das S. Metagenomic surveys of gut microbiota. Genomics, Proteomics and Bioinformatics. 2015 Jun;13(3):148-58.
15. Everard A, Cani PD. Gut microbiota and GLP-1. Reviews in endocrine and metabolic disorders. 2014 Sep;15:189-96.
16. Illiano P, Brambilla R, Parolini C. The mutual interplay of gut microbiota, diet and human disease. The FEBS journal. 2020 Mar;287(5):833-55.
17. Dinan TG, Cryan JF. The microbiome-gut-brain axis in health and disease. Gastroenterology Clinics. 2017 Mar 1;46(1):77-89.
18. Greco V, Longone P, Spalloni A, Pieroni L, Urbani A. Crosstalk between oxidative stress and mitochondrial damage: focus on amyotrophic lateral sclerosis. Mitochondria in Health and in Sickness. 2019:71-82.
19. Piccioni A, Rosa F, Manca F, Pignataro G, Zanza C, Savioli G, Covino M, Ojetti V, Gasbarrini A, Franceschi F, Candelli M. Gut microbiota and Clostridium difficile: what we know and the new Frontiers. International Journal of Molecular Sciences. 2022 Nov 1;23(21):13323.
20. Thursby E, Juge N. Introduction to the human gut microbiota. Biochemical journal. 2017 Jun 1;474(11):1823-36.
21. Dhikav V, Sethi M, Anand KS. Medial temporal lobe atrophy in Alzheimer's disease/mild cognitive impairment with depression. The British journal of radiology. 2014 Oct 1;87(1042):20140150.

22. Lawrence BJ, Gasson N, Kane R, Bucks RS, Loftus AM. Activities of daily living, depression, and quality of life in Parkinson's disease. PloS one. 2014 Jul 15;9(7):e102294.
23. Feinstein A, Magalhaes S, Richard JF, Audet B, Moore C. The link between multiple sclerosis and depression. Nature Reviews Neurology. 2014 Sep;10(9):507-17.
24. Kiloh LG. Depressive illness masquerading as dementia in the elderly: Dementia in the elderly is not always what it seems to be—and may well be treatable. Medical Journal of Australia. 1981 Nov;2(10):550-3.
25. Anderson G, Maes M. Oxidative/nitrosative stress and immuno-inflammatory pathways in depression: treatment implications. Current pharmaceutical design. 2014 May 1;20(23):3812-47.
26. Anderson G, Maes M. TRYCAT pathways link peripheral inflammation, nicotine, somatization and depression in the etiology and course of Parkinson's disease. CNS & Neurological Disorders-Drug Targets (Formerly Current Drug Targets-CNS & Neurological Disorders). 2014 Feb 1;13(1):137-49.
27. Tan L, Yu JT, Tan L. The kynurenine pathway in neurodegenerative diseases: mechanistic and therapeutic considerations. Journal of the neurological sciences. 2012 Dec 15;323(1-2):1-8.
28. Anderson G, Rodriguez M. Multiple sclerosis, seizures, and antiepileptics: role of IL-18, IDO, and melatonin. European Journal of Neurology. 2011 May;18(5):680-5.
29. Anderson G, Ojala JO. Alzheimer's and seizures: interleukin-18, indoleamine 2, 3-dioxygenase and quinolinic Acid. International Journal of Tryptophan Research. 2010 Jan;3:IJTR-S4603.
30. Dotson VM, Beydoun MA, Zonderman AB. Recurrent depressive symptoms and the incidence of dementia and mild cognitive impairment. Neurology. 2010 Jul 6;75(1):27-34.
31. Joachim CL, Mori H, Selkoe DJ. Amyloid β-protein deposition in tissues other than brain in Alzheimer's disease. Nature. 1989 Sep 21;341(6239):226-30.
32. Dugger BN, Whiteside CM, Maarouf CL, Walker DG, Beach TG, Sue LI, Garcia A, Dunckley T, Meechoovet B, Reiman EM, Roher AE. The presence of select tau species in human peripheral tissues and their relation to Alzheimer's disease. Journal of Alzheimer's Disease. 2016 Jan 1;51(2):345-56.
33. Arai H, Lee VM, Messinger ML, Greenberg BD, Lowery DE, Trojanowski JQ. Expression patterns of β-amyloid precursor protein (β-APP) in neural and nonneural human tissues from alzheimer's disease and control subjects. Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society. 1991 Nov;30(5):686-93.
34. Shankle WR, Landing BH, Ang SM, Chui H, Villarreal-Engelhardt G, Zarow C. Studies of the enteric nervous system in Alzheimer disease and other dementias of the elderly: enteric neurons in Alzheimer disease. Modern pathology: an official journal of the United States and Canadian Academy of Pathology, Inc. 1993 Jan 1;6(1):10-4.
35. Puig KL, Lutz BM, Urquhart SA, Rebel AA, Zhou X, Manocha GD, Sens M, Tuteja AK, Foster NL, Combs CK. Overexpression of mutant amyloid-β protein precursor and presenilin 1 modulates enteric nervous system. Journal of Alzheimer's Disease. 2015 Jan 1;44(4):1263-78.
36. Montacute R, Foley K, Forman R, Else KJ, Cruickshank SM, Allan SM. Enhanced susceptibility of triple transgenic Alzheimer's disease (3xTg-AD) mice to acute infection. Journal of neuroinflammation. 2017 Dec;14:1-3.
37. Saksida T, Koprivica I, Vujičić M, Stošić-Grujičić S, Perović M, Kanazir S, Stojanović I. Impaired IL-17 production in gut-residing immune cells of 5xFAD mice with Alzheimer's disease pathology. Journal of Alzheimer's Disease. 2018 Jan 1;61(2):619-30.
38. Harach T, Marungruang N, Duthilleul N, Cheatham V, Mc Coy KD, Frisoni G, Neher JJ, Fåk F, Jucker M, Lasser T, Bolmont T. Reduction of Abeta amyloid pathology in APPPS1 transgenic mice in the absence of gut microbiota. Scientific reports. 2017 Feb 8;7(1):41802.
39. Bäuerl C, Collado MC, Diaz Cuevas A, Viña J, Pérez Martínez G. Shifts in gut microbiota composition in an APP/PSS1 transgenic mouse model of Alzheimer's disease during lifespan. Letters in applied microbiology. 2018 Jun 1;66(6):464-71.
40. Zhuang ZQ, Shen LL, Li WW, Fu X, Zeng F, Gui L, Lü Y, Cai M, Zhu C, Tan YL, Zheng P. Gut microbiota is altered in patients with Alzheimer's disease. Journal of Alzheimer's disease. 2018 Jan 1;63(4):1337-46.
41. Li B, He Y, Ma J, Huang P, Du J, Cao L, Wang Y, Xiao Q, Tang H, Chen S. Mild cognitive impairment has similar alterations as Alzheimer's disease in gut microbiota. Alzheimer's & Dementia. 2019 Oct 1;15(10):1357-66.
42. Cattaneo A, Cattane N, Galluzzi S, Provasi S, Lopizzo N, Festari C, Ferrari C, Guerra UP, Paghera B, Muscio C, Bianchetti A. Association of brain amyloidosis with pro-inflammatory gut bacterial taxa and peripheral inflammation markers in cognitively impaired elderly. Neurobiology of aging. 2017 Jan 1;49:60-8.
43. Minter MR, Zhang C, Leone V, Ringus DL, Zhang X, Oyler-Castrillo P, Musch MW, Liao F, Ward JF, Holtzman DM, Chang EB. Antibiotic-induced perturbations in gut microbial diversity influences neuro-inflammation and amyloidosis in a murine model of Alzheimer's disease. Scientific reports. 2016 Jul 21;6(1):30028.

44. Kaur G, Behl T, Bungau S, Kumar A, Uddin MS, Mehta V, Zengin G, Mathew B, Shah MA, Arora S. Dysregulation of the gut-brain axis, dysbiosis and influence of numerous factors on gut microbiota associated Parkinson's disease. Current Neuropharmacology. 2021 Feb 1;19(2):233-47.
45. Boyajian JL, Ghebretatios M, Schaly S, Islam P, Prakash S. Microbiome and human aging: probiotic and prebiotic potentials in longevity, skin health and cellular senescence. Nutrients. 2021 Dec 18;13(12):4550.
46. Belizário JE, Faintuch J, Garay-Malpartida M. Gut microbiome dysbiosis and immunometabolism: new frontiers for treatment of metabolic diseases. Mediators of inflammation. 2018 Oct;2018.
47. Fan Y, Pedersen O. Gut microbiota in human metabolic health and disease. Nature Reviews Microbiology. 2021 Jan;19(1):55-71.
48. Erny D, Hrabě de Angelis AL, Jaitin D, Wieghofer P, Staszewski O, David E, Keren-Shaul H, Mahlakoiv T, Jakobshagen K, Buch T, Schwierzeck V. Host microbiota constantly control maturation and function of microglia in the CNS. Nature neuroscience. 2015 Jul;18(7):965-77.
49. Chaudhuri KR, Odin P, Antonini A, Martinez-Martin P. Parkinson's disease: the non-motor issues. Parkinsonism & related disorders. 2011 Dec 1;17(10):717-23.
50. Savica R, Carlin JM, Grossardt BR, Bower JH, Ahlskog JE, Maraganore DM, Bharucha AE, Rocca WA. Medical records documentation of constipation preceding Parkinson disease: A case-control study. Neurology. 2009 Nov 24;73(21):1752-8.
51. Sampson T. The impact of indigenous microbes on Parkinson's disease. Neurobiology of disease. 2020 Feb 1;135:104426.
52. Lew M. Overview of Parkinson's disease. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy. 2007 Dec;27(12P2):155S-60S.
53. Greco V, Longone P, Spalloni A, Pieroni L, Urbani A. Crosstalk between oxidative stress and mitochondrial damage: focus on amyotrophic lateral sclerosis. Mitochondria in Health and in Sickness. 2019:71-82.
54. Blacher E, Bashiardes S, Shapiro H, Rothschild D, Mor U, Dori-Bachash M, Kleimeyer C, Moresi C, Harnik Y, Zur M, Zabari M. Potential roles of gut microbiome and metabolites in modulating ALS in mice. Nature. 2019 Aug 22;572(7770):474-80.
55. Oluwatobi PE, Ese IG, Oluwatumininu PA, Eghosa M. Microbiota Gut-Brain Axis and Neurodegenerative Disease: A systematic review on Alzheimer's disease, Amyotrophic lateral sclerosis and Parkinson Disease. Romanian Neurosurgery. 2020 Mar 15:116-22.
56. Lewis JJ, Antonescu CR, Leung DH, Blumberg D, Healey JH, Woodruff JM, Brennan MF. Synovial sarcoma: a multivariate analysis of prognostic factors in 112 patients with primary localized tumors of the extremity. Journal of Clinical Oncology. 2000 May 10;18(10):2087-94.
57. López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. Hallmarks of aging: An expanding universe. Cell. 2023 Jan 19;186(2):243-78.
58. Adav SS, Wang Y. Metabolomics signatures of aging: recent advances. Aging and disease. 2021 Apr;12(2):646.
59. Ling Z, Liu X, Cheng Y, Yan X, Wu S. Gut microbiota and aging. Critical reviews in food science and nutrition. 2022 May 3;62(13):3509-34.
60. Bárcena C, Valdés-Mas R, Mayoral P, Garabaya C, Durand S, Rodríguez F, Fernández-García MT, Salazar N, Nogacka AM, Garatachea N, Bossut N. Healthspan and lifespan extension by fecal microbiota transplantation into progeroid mice. Nature medicine. 2019 Aug;25(8):1234-42.
61. Parker A, Romano S, Ansorge R, Aboelnour A, Le Gall G, Savva GM, Pontifex MG, Telatin A, Baker D, Jones E, Vauzour D. Fecal microbiota transfer between young and aged mice reverses hallmarks of the aging gut, eye, and brain. Microbiome. 2022 Apr 29;10(1):68.
62. Figueroa-Romero C, Guo K, Murdock BJ, Paez-Colasante X, Bassis CM, Mikhail KA, Pawlowski KD, Evans MC, Taubman GF, McDermott AJ, O'Brien PD. Temporal evolution of the microbiome, immune system and epigenome with disease progression in ALS mice. Disease models & mechanisms. 2020 Feb 1;13(2):dmm041947.