



Ageing, proteostasis, and the gut: Insights into neurological health and disease



Mahmood Akbar ^{a,b}, Pranoy Toppo ^{a,b}, Aamir Nazir ^{a,b,*}

^a Academy of Scientific and Innovative Research (AcSIR), Ghaziabad 201002, India

^b Division of Toxicology and Experimental Medicine, CSIR-Central Drug Research Institute, Lucknow 226031, India

ARTICLE INFO

Keywords:

Neurodegenerative disease
Gut dysbiosis
Microbial metabolite
Protein quality control

ABSTRACT

Recent research has illuminated the profound bidirectional communication between the gastrointestinal tract and the brain, furthering our understanding of neurological ailments facilitating possible therapeutic strategies. Technological advancements in high-throughput sequencing and multi-omics have unveiled significant alterations in gut microbiota and their metabolites in various neurological disorders. This review provides a thorough analysis of the role of microbiome-gut-brain axis in neurodegenerative disease pathology, linking it to reduced age-associated proteostasis. We discuss evidences that substantiate the existence of a gut-brain cross talk ranging from early clinical accounts of James Parkinson to Braak's hypothesis. In addition to understanding of microbes, the review particularly entails specific metabolites which are altered in neurodegenerative diseases. The regulatory effects of microbial metabolites on protein clearance mechanisms, proposing their potential therapeutic implications, are also discussed. By integrating this information, we advocate for a combinatory therapeutic strategy that targets early intervention, aiming to restore proteostasis and ameliorate disease progression. This approach not only provides a new perspective on the pathogenesis of neurodegenerative diseases but also highlights innovative strategies to combat the increasing burden of these age-related disorders.

1. Introduction

The human gut microbiome, encompassing a vast array of microbial species, exerts a profound influence on a multitude of physiological processes, ranging from metabolic functions and immune regulation to neurologic and endocrine pathways. The composition of the gut microbiota is highly dynamic, shaped extensively by factors such as diet, environmental exposures, lifestyle choices, and medication use amongst others. This interaction between external factors, intrinsic biological processes, and the gut microbiota plays a crucial role in shaping health outcomes and influencing disease pathways.

The impact of age associated diseases is increasing with extending human longevity. In absence of complete cure, Alzheimer's and Parkinson's disease are proving to be a burden, not only on the general well-being of the human kind but also to populous countries in terms of human and financial resources. The World Health Organization reported in 2022 that Parkinson's disease (PD) is the fastest growing neurological disorder (Schless et al., 2022). It is a degenerative condition of the brain characterized by progressive loss of dopaminergic neurons within the substantia nigra pars compacta region of mid brain. This loss of

dopaminergic neurons is mainly attributed to the formation of toxic aggregates of alpha-synuclein protein which is a presynaptic protein expressed widely in the nervous system (Rao and Gershon, 2016). Incidences of PD have doubled in the last 25 years, reaching 8.5 million in 2019. Disability adjusted life years associated with PD have also increased by 81 % since 2000, reaching 5.8 million in 2019 (World Health Organization, 2023). In India, a developing nation, where a large proportion of aged individuals is expected to reside in coming years, the prevalence of any neurological or psychiatric problem is 2.6 % among people aged 60 and above (International Institute for Population Sciences (IIPS), 2020). In 2016, India was reported to have 0.58 million people suffering from PD (Ray Dorsey et al., 2018).

Similar reports were released by WHO in 2020 for Alzheimer's disease (AD), addressing it as one of the leading cause of deaths in America and Europe (World Health Organisation, 2020). In AD also, there is a progressive aggregation of amyloid beta ($A\beta$) protein and hyperphosphorylated tau protein (neurofibrillary tangles) which majorly impairs cholinergic neuronal circuitry (Rao and Gershon, 2016). In 2021, there were more than 55 million people suffering from dementia which is bound to reach 139 million by 2050 (World Health

* Corresponding author at: Division of Toxicology and Experimental Medicine, CSIR-Central Drug Research Institute, Lucknow 226031, India.
E-mail address: anazir@cdri.res.in (A. Nazir).

[Organization, 2021](#)). In 2023, 8.8 million Indians aged 60 and above were reported to suffer from dementia with large variations among different states ([Lee et al., 2023](#)). Such massive prevalence of NDs has put immense pressure on the health and research sectors to come up with holistic and effective solutions in near future.

Medical advancements in the past few decades have resulted in the development of a number of invasive and non-invasive therapies, each targeting different aspects of the multifactorial etiology of these diseases. But be it drugs against enzymes, responsible for the degradation of neurotransmitters (MAO-B inhibitors, COMT inhibitors, cholinesterase inhibitors) ([Gray et al., 2022; Winblad et al., 2006](#)), neurotransmitter agonists ([Gray et al., 2022](#)), immunotherapies targeting protein aggregates ([Riederer, 2022](#)) or therapies stimulating deep regions of brain ([Camacho-Conde et al., 2022](#)), they all have not been able to provide a “one and done” therapy for these neurological disorders (NDs). This warrants a continuous expedition for discovering novel therapeutic approaches that target the root cause of these diseases. One such novel approach is the re-establishment of age-associated decline of protein homeostasis. Till date, therapeutic interventions have overlooked this proteostasis disruption as a viable target for curing NDs. However, this restoration of proteostasis network by inducing autophagy or improving lysosomal function has gained focus in last few years ([Jennings et al., 2022; Sanchez-Miras Sierra et al., 2022](#)).

As we age, the machineries regulating the clearance of misfolded and aggregated proteins go haywire due to which toxic aggregates are not efficiently cleared, particularly in brain, resulting in the manifestation of majority of neurological disorders ([Sarkar and Nazir, 2022](#)). Such disruption of protein quality control (PQC) machinery is mainly attributed to various exogenous and internal stresses that an individual experiences during ageing ([Hipp et al., 2019](#)). The nature of these stresses has not been defined clearly but the possible role of our gut and its associated enteric nervous system, in relaying these stress inducing factors, cannot be neglected, provided a large number of studies indicate that gastric symptoms arise early during the progression of NDs ([Rao and Gershon, 2016](#)). There are a large number of evidences, explained in later sections, that point towards early involvement of gut and ENS in the pathophysiological advancement of NDs. In this review, we aim to provide a comprehensive understanding of the role of gut-brain axis in the initiation and progression of neurological disorders and try to correlate it with the age-associated decline of protein homeostasis. We will describe the gut-associated changes that occur during diseased conditions and highlight the possibility for any gut-oriented pharmacological interventions that can restore the age-dependent decline in PQC machinery.

2. Early accounts implicating crosstalk between gut and brain

“All disease begins in the gut” a claim done by Greek physician Hippocrates more than 2000 years ago, still captures the imagination of many scientists. This holds great significance for neurological diseases as the evidences indicating the bi-directional crosstalk of gut and brain are mounting more than ever. Besides scientific suggestions, daily life experiences, such as, feeling butterflies in the stomach upon any stressful event also substantiate the existence of a gut-brain cross talk ([Lyon, 2018](#)). Physically this conduit is marked by a single nerve i.e. vagus nerve that transmits signals between the central nervous system (CNS) and enteric nervous system (ENS). Various other possible routes have also been suggested for this bi-directional communication viz., immune system, neurotransmitters, gastric hormones, microbial metabolites, etc ([Cryan et al., 2019](#)). There are a number of physiological evidences that put forth the notion of a bidirectional crosstalk between brain and gut.

2.1. Historical and clinical evidences

One of the earliest understandings of human digestion, obtained through the real-time observation of a patient named St. Martin hints

towards this notion of gut-brain axis. Surgeon William Beaumont made a fistula in his stomach during surgery, following a close range gun shot, and observed that the rate of digestion is directly influenced by the patient’s emotional state of mind ([Beaumont, 1835](#)). The effects these organs exert over each other during disease manifestation further corroborate this notion of a well-established gut-brain axis. The role of gastric dysfunction has been greatly suggested in the etiology of Parkinson’s disease, with first formal account coming from the description of disease by James Parkinson himself in his book “An Essay on the Shaking Palsy, 1817”. He claimed that although he is unable to trace the connection, yet it cannot be denied that “a disordered state of the stomach and bowels may induce a morbid action in a part of the medulla spinalis”. In one of the six cases described by Parkinson, administration of a laxative was found to relieve symptoms through gastric emptying ([Parkinson, 2002](#)). This points towards a common symptom of gastric dysfunction that has been found closely associated with neurological disorders i.e. constipation. Gastro-intestinal dysfunctions such as constipation can easily be considered consequence of severed neurochemical balance observed in NDs but their manifestation years prior to motor and cognitive impairments hints that there is more complexity in their development which must be understood. The prevalence of constipation is high among patients suffering from PD (80–90 %) and its occurrence may precede the motor symptoms by almost 15 years due to which it is considered a reliable prodromal symptom ([Fasano et al., 2015](#)). The severity of constipation is also able to predict the worsening of disease in case of both PD and AD, as low frequencies of bowel movements are associated with faster cognitive decline ([Camacho et al., 2021; Nakase et al., 2022](#)). Impairment of gastric motility resulting in gastroparesis or delayed gastric emptying is also observed in both early and late stages of PD ([Knudsen et al., 2018](#)). Reports of its prevalence vary greatly depending upon the means of examination, but one report claims it to be around 35 % among PD patients and its estimated onset is around 19 years prior to diagnosis ([Scott et al., 2021; Su et al., 2017](#)). Gastro-oesophageal reflux is another non-neuronal symptom that may precede diagnosis by significant amount of time (20.6 years). The earliest non-motor symptom that appears in case of PD is olfaction and taste impairment as it may occur 20.9 years prior to diagnosis ([Scott et al., 2021](#)). The prodromal nature of these gastro-intestinal dysfunctions signifies their value as a means of early diagnosis and hints towards a possible window for therapeutic interventions.

2.2. Histopathological and surgical evidences

Besides clinical symptoms, histopathological investigations also reveal that gut and its associated neuronal network (ENS) are adversely affected early in the progression of these diseases. In 1988, Wakabayashi et al. first detected the presence of Lewy body-like inclusions in the ENS. They examined the ENS of seven PD patients and all of them were found to have Lewy bodies in their Auerbach’s and Meissner’s plexuses. They employed light microscopy along with various staining procedures, mainly hematoxylin and eosin, for superficial examination. Upon close examination by electron microscopy, these inclusions were found to be ultrastructurally identical to those reported in substantia nigra ([Wakabayashi et al., 1988](#)). Upon the advent of immunocytochemistry, such histological studies of the ENS were further taken up by Heiko Braak and his wife Eva Braak. They validated the presence of immunoreactive alpha-synuclein aggregates in the Auerbach’s and Meissner’s plexuses of five autopsy samples derived from PD patients, whose brains were staged for synucleinopathy ([Braak et al., 2006](#)). In subsequent studies, they even detected the presence of PD-related lesions in the anterior olfactory nucleus, besides dorsal motor nucleus of the glossopharyngeal and vagal nerves, during initial periods of disease progression. They even traced the course of pathology in PD patients, both symptomatic and incidental, and proposed a staging scheme (now known as Braak’s staging) based on the topographical expansion of lesions ([Braak et al., 2003](#)). Their work ultimately led to the development

of Braak's hypothesis, which states that sporadic PD initiates and spreads from peripheral organs, particularly the nasal cavity and gut, and has a pathogenic component at play. These implications have been further backed by surgical investigations where truncal vagotomy has been found to decrease the risk of PD (Liu et al., 2017; Svensson et al., 2015). Such protective effect of truncal vagotomy has also been observed in animal models (Kim et al., 2019). However, in case of dementia, such association is not observed (S. Y. Lin et al., 2018). After such evident proofs one cannot deny the existence of a bidirectional communication between gut and brain, and its possible role in the etiology of neurological disorders, particularly PD. However, in recent years with the advent of "omics" techniques, another factor has come into play, i.e. the gut microbiota dysbiosis observed in neurological disorders. This has not only made the axis three-tier, making it microbiota-gut-brain axis, but it also supports the notion of a pathogenic trigger that is put forth by Braak's hypothesis. Details about this imbalance in gut microbiota are discussed in the following section.

3. Role of multi-omics approaches and high-throughput sequencing in decoding gut microbiota

3.1. Multi-omics technology

Analysis of complex microbial communities has been transformed by multi-omics approaches. These approaches combine metagenomics, metatranscriptomics, metaproteomics, metabolomics, and single-cell RNA sequencing (scRNA-seq) to obtain insight into gut microbiome (Fig. 1) (Meng et al., 2023). Metagenomics is mainly utilized to classify microbes based on the collective genetic information obtained from an environment. It provides information about the entire microbial community rather than individual microbes. Similarly, to obtain information regarding the functional aspect of a microbial community, metatranscriptomics is employed. It analyses the transcriptome of entire microbial community by taking into account the influence of external factors on gene expression (Urich et al., 2008). Metaproteomics is another multi-omics approach employed to gain insights into the proteome of a microbial assemblage at a specific time-point. It provides information regarding the functional changes that occur in living microbes without taking into account dead microorganisms (Wilmes and Bond, 2004). Within gut, microbes exist in a symbiotic relationship with their hosts, exchanging a diverse array of small molecules. To assess such metabolic

networks and to examine their alterations under various physiological, biochemical, and pathological conditions, metabolomics is routinely chosen (Vernocchi et al., 2016). These multi-omics approaches are exceptional in analysing large microbial communities but fall short in detecting the genetic potential and functional diversity of microorganisms at the cellular level (Lloréns-Rico et al., 2022). This shortcoming is addressed by single-cell RNA sequencing (scRNA-seq) integrated with microbial analysis. It allows classification of microorganisms into functional subgroups based on the genetic profiling, rather than treating them as a homogenous population (Jin et al., 2024).

3.2. High-throughput sequencing (HTS)

High through-put sequencing technique provides us unprecedented swiftness in understanding the relationship between gut microbiota and progression of neurodegenerative diseases. How different components of this modern technique help us in understanding these gut commensals are discussed as follows:

- **Comprehensive microbial profiling-** High-throughput sequencing (HTS) through its in-depth analysis can identify various gut commensals like bacteria, virus and fungi. This microbial profiling broadens our understanding about the variety and quantity of microorganism (Philip Mani et al., 2024).
- **Mechanistic insights-** High-throughput sequencing through its mechanistic approach helps in understanding the genetic composition of gut microbiome. This approach helps researchers to obtain deep insights into understanding the role of gut commensals in disease progression (Li et al., 2023).
- **Dysbiosis detection-** Imbalances in gut microbiota is known to be associated with many forms of neurodegenerative diseases like Parkinson's, Alzheimer's and Multiple Sclerosis. High-throughput sequencing helps in identifying the imbalances associated with these diseases (Seo and Holtzman, 2024).
- **Gut-brain axis exploration-** High-throughput sequencing helps (HTS) us in understanding this two-way communication pathway between gut and brain. It helps in identifying different metabolites produced by gut microbiota and their impact on normal brain

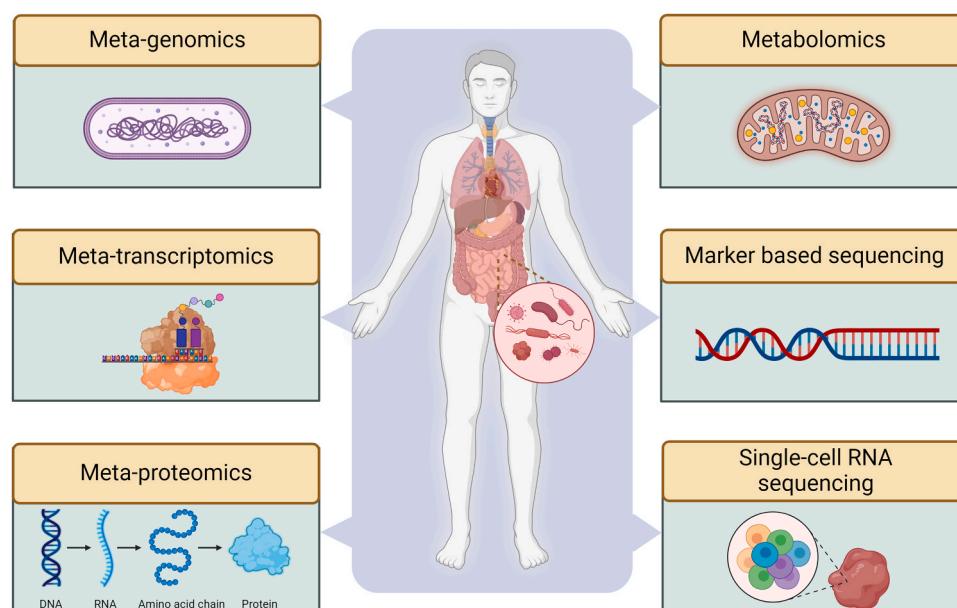


Fig. 1. Multi-omics technologies used to study the role of gut microbiota in neurological disorders.

functioning. This knowledge facilitates our understanding of disease progression (Fabi, 2024).

- **Therapeutic development-** High-throughput sequencing (HTS) technique helps in developing targeted therapies which include prebiotics, probiotics and faecal microbiota transplantation (FMT). By identifying potential beneficial strains, HTS provides information to re-establish the healthy gut microbiome profile which can lead to the development of new therapeutic interventions (Liang et al., 2023).

- **Clinical and Pre-clinical studies-** High-throughput sequencing or HTS is extremely useful in both pre-clinical and clinical studies in understanding the relationship between gut microbiota and various forms for neurodegenerative diseases. These studies help in generating valuable data which aids in the development of new therapeutic interventions targeting early disease progression (Li et al., 2023).

Overall high-throughput sequencing or HTS is a powerful tool that provides researchers opportunity to decipher the association between gut microbiota and neurodegenerative diseases.

4. Gut dysbiosis in neurological disorders: alterations in the gut microbiota

Gut dysbiosis is defined as alteration in gut microbiota composition, with an increase number of pathobionts and decrease number of symbionts. Presence of copious amount of bacterial taxa is an inclusive feature of human microbiota which plays an important role in nutrient absorption, immunity, development as well as pathology of certain diseases. Gut microbes share a symbiotic relationship with their host, as variations in the microbial population can influence host health and longevity (Thursby and Juge, 2017). Gut microbiota which is defined as an assemblage of all microorganisms including bacteria, archaea as well as viruses shows significant variation from one individual to other (Zhang et al., 2022). This microbiome population also greatly varies with age, sex and geographic location. On the recent trajectory of our understanding of neurodegenerative diseases the impact of gut dysbiosis cannot be overlooked. Gut dysbiosis has been known to play a very systemic role in the etiology of several neurological disorder. Gut microbes are known to interact with the intestinal mucosa, secrete a plethora of secondary metabolites and induce inflammatory immune responses which governs the host's physiology in a myriad of ways (Conway and A Dugal, 2021). In recent years, studies understanding

neurological disorders and their association with gut microbiota have revealed that alterations in the gut microbial diversity play a major role in disease progression (Gong et al., 2023).

Alterations in gut microbiota are found to be associated with the onset and progression of various kinds neurological pathologies, such as, inflammatory (MS- multiple sclerosis), developmental (ASD- autism spectrum disorder) and degenerative (Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis and Huntington's disease) disorders (Fig. 2)

4.1. Alzheimer's disease (AD)

Alzheimer's disease is one of the major neurodegenerative disease characterized by progressive decline in cognition and is responsible for around 90 % cases of dementia worldwide (Akhtar et al., 2024). There are still very few disease altering therapies available for AD, but insights regarding the molecular mechanisms underlying disease pathology have led to the advent of new biomarkers and therapeutic strategies (Maheshwari et al., 2024; Zeng et al., 2024). Amyloid beta plaques, neurofibrillary tangles, mitochondrial dysfunction and neuro-inflammation are some of the well characterized molecular aspects of AD pathology that ultimately causes cholinergic neuronal death manifesting in the form of various symptoms including dementia and cognitive decline (Akhtar et al., 2024). Dysbiosis of gut microbiome is increasingly being studied in patients suffering from age-associated diseases including Alzheimer's. Cognitive decline in such patients or even healthy aged individuals show strong correlation with the abundance or decline of specific bacterial taxa (Ghosh et al., 2022). In a recent study, association between gut microbiota and cognitive impairment was examined using SNPs linked to gut microbes and GWAS dataset. Among 211 gut microbial taxa, abundance of genus *Blautia*, *Catenibacterium*, *Roseburia* and *Oxalobacter* was found to be positively correlated with poor cognitive performance. On the other hand, *Dialister*, *Paraprevotella*, *Ruminococcaceae* and *Bacteroides* proved to be beneficial for cognitive performance (Wang et al., 2024). Interestingly, in few recent clinical studies cognitive function has been found to be closely associated with the abundance of *Bifidobacterium* (Kolobaric et al., 2024; Ni Lochlainn et al., 2024). Prebiotic interventions improving the levels of *Bifidobacterium* have shown promise in improving cognition under clinical settings (Ni Lochlainn et al., 2024). Surprisingly, infants having better median score in composite cognition also show abundance of certain bacterial genus such as *Bacteroides*, *Phocaeicola* and *Bifidobacterium* (Cerdó et al., 2023). Moreover, there are a number of clinical reports analysing the correlation of gut dysbiosis with Alzheimer's disease, some of which are reported in Table 1.

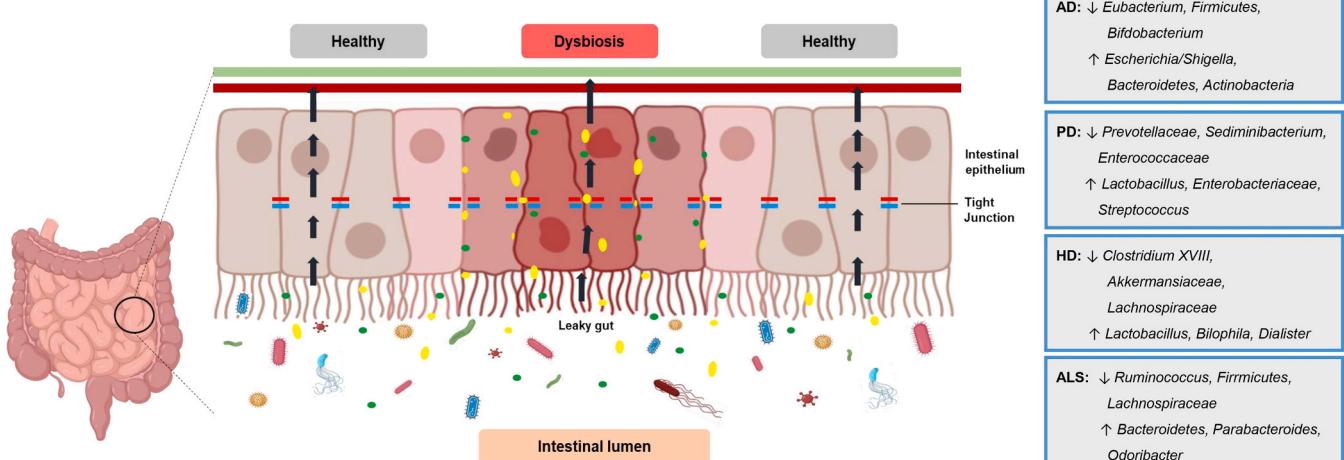


Fig. 2. Major alterations of gut microbiota observed in neurological disorders which can damage the integrity of epithelial barrier resulting in leaky gut.

Table 1

Microbiome alterations reported in clinical studies on Alzheimer's disease.

Sample size	Bacteria altered	Location	Age-matched (y/n)	Sex-matched (y/n)	Refs.
N = 83 total; 40 amyloid positive with cognitive impairment, 33 amyloid negative with cognitive impairment, 10 amyloid negative without cognitive impairment	Amyloid positive individuals had ↓ <i>Eubacterium rectale</i> and ↑ <i>Escherichia/Shigella</i> compared with both healthy controls and amyloid negative groups.	Eastern Lombardy, Italy	y	y	(Cattaneo et al., 2017)
N = 50 total; 25 AD, 25 healthy controls	AD patients had a ↓ in <i>Firmicutes</i> and <i>Bifidobacterium</i> and ↑ levels of <i>Bacteroidetes</i> compared with healthy controls	Wisconsin, USA	y	y	(Vogt et al., 2017)
N = 86; 43 AD, 43 healthy controls	AD patients had a ↓ in <i>Bacteroidetes</i> and an ↑ in <i>Actinobacteria</i> in AD patients compared with healthy controls	Chongqing, China	y	y	(Zhuang et al., 2018)
N = 97 total; 33 AD, 32 MCI, 32 healthy controls	AD patients had a ↓ in <i>Firmicutes</i> and an ↑ in <i>Proteobacteria</i> compared with healthy controls	Hangzhou, China	y	y	(Liu et al., 2019)

(↑ signifies increase, ↓ signifies decrease).

4.2. Parkinson's disease (PD)

Parkinson's disease is a progressive form of neurodegenerative disorder that is caused by the degeneration of dopamine producing nerve cells in the brain region called substantia nigra. Traditionally Parkinson's disease has been characterized by motor impairments, but modern research shed light on its multisystemic nature (Afsheen et al., 2024). Recent advancements for understanding disease etiology have deepened the notion of gut dysbiosis in the causation and progression of Parkinson's. The idea of PD being spread from gut has gathered significant momentum in recent years (Gorecki et al., 2019). People affected with PD exhibit imbalanced gut microbiome composition along with gastrointestinal immune response which results in impaired motor symptoms (Gorecki et al., 2019). Out of all gut commensals, elevated gram-negative bacteria are directly correlated with degree of postural unsteadiness and gait difficulty (Scheperjans et al., 2015). Elevated gram-negative bacteria are found to be associated with increased lipopolysaccharide (LPS) and endotoxin production which results in intestinal inflammation (Nighot et al., 2017). This section summarizes the clinical reports of gut microbial involvement in Parkinson's disease etiology. Table 2 sums up the specific bacterial taxa found altered in patients.

4.3. Huntington's disease (HD)

Huntington's disease or HD is a complex form of progressive neurodegenerative disorder resulting in uncontrolled body movements, facial grimaces with personality changes and apathy (Sharma et al., 2023). Its first non-specific symptoms can start as early as 10 years prior to full disease manifestation, which generally arise between 35 and 40 years of age. Studying the gut microbiota, both in terms of beta diversity (composition of microbial community) and alpha diversity (lower species richness) is an increasingly emerging trend in HD research (Chuang and Demontis, 2021). Table 3 covers the comprehensive overview of human gut microbes found altered in the clinical reports of HD.

4.4. Amyotrophic lateral sclerosis (ALS)

Much progress has been made in finding genetic abnormalities linked with amyotrophic lateral sclerosis or ALS, but the majority of cases are still left with unknown underlying reasons (Martin et al., 2022). Clinical studies of gut microbiome finding correlation with ALS have provided equivocal findings (Boddy et al., 2021). For the past few years, growing body of research has begun to shed light on the role of gut commensals in health and disease, with a number of studies connecting gut dysbiosis to ALS. In this section, microbial diversity which shows direct correlation with various prospects of ALS pathophysiology are mentioned (Table 4). It covers the data of different cohort studies which include different numbers of healthy and ALS affected individuals.

5. Mediators of gut-brain cross talk: microbially-derived neuroactive metabolites

As we have seen that gut dysbiosis is a common phenomenon occurring in the course of major neurodegenerative diseases. Therefore, last decade has witnessed the development of various therapies that target the gut microbiome, such as dietary interventions, prebiotics, postbiotics, faecal microbiota transplantation (FMT), antimicrobials, etc (Tan et al., 2022). However, a complete mechanistic understanding of any of these therapeutic interventions or gut dysbiosis per se still remains enigmatic, making it difficult to comprehend that how changes in the composition of gut bacteria or their food source can alter the host physiology in such a manner that it provides protection or results in disease manifestation. For this we need to understand that how do these microbes communicate with the host? Human body harbours more than trillions of micro-organisms, that influence various aspects of our physiology in a myriad of ways (Cani, 2018). These microbes are known to play a major role in the training and development of our immune system. Dysbiosis in the microbial community, as in case of NDS, has been reported to drive peripheral immune cells to induce neuro-inflammatory processes in the CNS (Main and Minter, 2017). Moreover, the release of local neurotransmitters (e.g., NO, GABA, serotonin) and enteric hormones (such as GLP-1, GLP-2 and PYY) can also be influenced by gut bacteria, providing them a means to regulate gastric functions, such as intestinal motility, acid secretions, etc., by acting on ENS neurons (Cani and Knauf, 2016).

Interestingly, the metabolites produced by these microbes, upon their action on ingested food, form the bedrock for all these physiological effects. These small-molecules are produced in great abundance and are released into the blood stream of host organism. A study found that almost 34 % of the blood metabolites have direct correlation with the metabolic activity of gut microbiome (Visconti et al., 2019). Be it immunomodulatory effects of gut-microbiota or direct regulation of neuronal activity, these metabolites seem to facilitate majority of aspects from the mechanistic viewpoint (Cani and Knauf, 2016). Recently, 4-ethylphenyl sulfate (4-EPS), a gut-microbial metabolite produced by *B. ovatus* and *L. plantarum*, has been shown to induce anxiety-like behaviour in mice owing to its effect on oligodendrocyte maturation and neuronal myelination (Needham et al., 2022). Similarly, another metabolite isoamylamine, produced by *Ruminococcaceae* family, regulates transcription in microglial cells and induces cognitive decline in young mice by promoting their apoptosis (Teng et al., 2022). Such neuromodulatory potential of metabolites can be exploited for therapeutic purpose. From the perspective of developing any therapeutic intervention, these metabolites also offer certain advantages, firstly, majority of them are naturally present in our body, therefore regulatory questions regarding their consumption can be easily answered. Secondly, these metabolites are readily absorbed into the blood stream and

Table 2

Microbiome alterations reported in clinical studies on Parkinson's disease.

Sample size	Altered microbiota	Refs.
N = 200; 100 PD, 100 healthy control	<i>Lactobacillus</i> ↑, <i>Clostridium coccoides</i> ↓, <i>Bacteroides fragilis</i> ↓, <i>Prevotella</i> (hydrogen sulfide producer) ↓	(Hasegawa et al., 2015)
N = 72; 38 PD (untreated naive/ 26 treated), 34 healthy control	<i>Ralstonia</i> ↑, <i>Blautia</i> ↓, <i>Coprococcus</i> ↓, <i>Faecalibacterium</i> ↓, <i>Roseburia</i> ↓	(Keshavarzian et al., 2015)
N = 142; 72 PD, 72 healthy control	<i>Enterobacteriaceae</i> ↑, <i>Prevotellaceae</i> ↓	(Schepersjans et al., 2015)
N = 34; 34 PD (24 male, 10 female)	<i>Enterobacteriaceae</i> ↑, <i>Bifidobacterium</i> ↑, <i>Enterococcaceae</i> ↓, <i>Lactobacillaceae</i> ↓, <i>Faecalibacterium prausnitzii</i> ↓, <i>Prevotellaceae</i> ↓	(Unger et al., 2016)
N = 59; 31 PD, 28 healthy control	<i>Verrucomicrobiaceae</i> ↑, <i>Firmicutes</i> ↑, <i>Erysipelotrichaceae</i> ↓, <i>Prevotellaceae</i> ↓	(Bedarf et al., 2017)
N = 348; 212 PD, 136 healthy control	<i>Akkermansia</i> ↑, <i>Ruminococcaceae</i> ↑, <i>Lactobacillus</i> ↑, <i>Bifidobacterium</i> ↑, <i>Lachnospiraceae</i> (SCFAs producer) ↓	(Hill-Burns et al., 2017)
N = 38; 24 PD, 14 healthy control	<i>Escherichia-Shigella</i> ↑, <i>Streptococcus</i> ↑, <i>Proteus</i> ↑, <i>Enterococcus</i> ↑, <i>Blautia</i> (butyrate produce) ↓, <i>Faecalibacterium</i> (butyrate produce) ↓, <i>Ruminococcus</i> ↓, <i>Clostridium IV</i> ↑, <i>Aquabacterium</i> ↑, <i>Holdemania</i> ↑, <i>Sphingomonas</i> ↑, <i>Clostridium XVII</i> ↑, <i>Butyrivibrio</i> ↑, <i>Anaerotruncus</i> ↑, <i>Lactobacillus</i> ↓, <i>Sediminibacterium</i> ↓, <i>Verrucomicrobiaceae</i> ↑, <i>Lachnospiraceae</i> ↓, <i>Prevotellaceae</i> ↓, <i>Lactobacillaceae</i> ↑, <i>Verrucomicrobiaceae</i> ↑, <i>Lactobacillaceae</i> ↑, <i>Enterococcaceae</i> ↑	(Qian et al., 2018)
N = 144; 72 PD, 72 healthy control	<i>Verrucomicrobiaceae</i> ↑	(Keshavarzian et al., 2015)
N = 59; 29 PD (23 male, 6 female), 30 healthy control (13 male, 16 female)	<i>Lachnospiraceae</i> ↓, <i>Bifidobactellaceae</i> ↑, <i>Pasteurellaceae</i> ↓	(Scheperjans et al., 2015)
N = 154; 76 PD, 78 healthy control	<i>Prevotellaceae</i> ↓	(Hopfner et al., 2017)
N = 120; 75 PD, 45 age-matched control	<i>Lachnospiraceae</i> ↓, <i>Bifidobactellaceae</i> ↑, <i>Pasteurellaceae</i> ↓	(Heintz-Buschart et al., 2018)
N = 128; 64 PD, 64 healthy control	<i>Prevotellaceae</i> ↓	(Lin et al., 2018)
N = 350; 237 PD, 113 healthy control	<i>Lactobacillaceae</i> ↑, <i>Verrucomicrobiaceae</i> ↑, <i>Lachnospiraceae</i> ↓, <i>Bifidobactellaceae</i> ↑, <i>Enterobacteriaceae</i> ↑, <i>Christensenellaceae</i> ↑	(Aho et al., 2019)
N = 21; 14 PD, 7 healthy control	<i>Verrucomicrobiaceae</i> ↑	(Barichella et al., 2019)
N = 152; 80 PD, 72 healthy control	<i>Lactobacillaceae</i> ↑, <i>Lachnospiraceae</i> ↓, <i>Enterobacteriaceae</i> ↑, <i>Enterococcaceae</i> ↑	(Gorecki et al., 2019)
N = 99, 51 PD, 48 healthy control	<i>Lactobacillaceae</i> ↑, <i>Verrucomicrobiaceae</i> ↑, <i>Prevotellaceae</i> ↓, <i>Verrucomicrobiaceae</i> ↑, <i>Lachnospiraceae</i> ↑, <i>Pasteurellaceae</i> ↑	(Pietrucci et al., 2019)
N = 20, 10 PD, 10 healthy control	↑	(C. Li et al., 2019)
	↑	(F. Li et al., 2019)

(↑ signifies increase, ↓ signifies decrease).

can also cross the blood brain barrier in majority of the cases (Fischbach, 2020; Parker et al., 2020). Interestingly, it is not only the provision of such molecules that is beneficial but their sequestration is also coming up as an effective strategy (Campbell et al., 2022). Therefore, homing on such microbially derived molecules for therapeutic interventions can

prove to be effective in the treatment of neurological disorders. So, in this section we will try to summarize major groups of the human gut microbial metabolites that are found to be altered in majority of the NDs and will also shed light over their possible neurological influences (Fig. 3).

5.1. Short chain fatty acids (SCFAs)

Short chain fatty acids (SCFAs) are the most extensively studied group of metabolites produced by the gut microbes. Acetate (C2), propionate (C3) and butyrate (C4) are the major SCFAs found in the small intestine. They are produced by the fermentation of undigested or partially digested complex polysaccharides (dietary fibres) that are found in plant cell walls (van der Hee and Wells, 2021). These metabolites are known inhibitors of histone deacetylases (HDACs) and can thereby cause hyper-acetylation of host proteins such as histones (Sealy and Chalkley, 1978). They can also serve as energy substrates for host cells and regulate the level of ATP production, mTOR activity, fatty acid synthesis and intestinal gluconeogenesis (De Vadder et al., 2014; Kim et al., 2014). They are sensed by three well-defined G-protein coupled receptors (GPCRs) that are expressed over a variety of immune and endocrine cells: GPCR41, GPCR43 and GPCR109A (Brown et al., 2003; Thangaraju et al., 2009). The production of these SCFAs is carried out by many bacterial groups as shown in Table 5. These metabolites play a crucial role in translating the effects of gut dysbiosis observed in NDs, and thereby manifestation of the disease. One animal study found that the SCFAs produced by gut microbiota are essential for the development of PD related pathophysiology as they are able to modulate microglial activation and alpha-synuclein aggregation (Sampson et al., 2016). Similar observations were reported by another group, where they found that administration of sodium butyrate exacerbated neuroinflammation, motor dysfunction and dopaminergic neuronal decline in a mouse model of PD (Qiao et al., 2020). In AD models also, SCFAs were found to increase Aβ plaque formation via microglia mediated neuroinflammation (Colombo et al., 2021). Acetate alone has been reported to drive microglia maturation and regulate its ability to remove Aβ plaques (Erny et al., 2021). Conversely, some studies have also reported beneficial effects of SCFA administration (Paiva et al., 2017; Sun et al., 2023). To completely understand the effects of SCFAs in disease manifestation and progression, further investigations are required, in both rodent models and human subjects, that effectively recapitulate disease pathology.

5.2. Amino acid derivatives

Another major group of microbially derived metabolites are the amino acid derivatives, particularly those from aromatic amino acids (AAA) i.e., tyrosine, phenylalanine and tryptophan. Gut microbes produce a variety of secondary metabolites, upon catabolizing aromatic amino acids, that serve as signalling molecules for host-microbiome interactions (Liu et al., 2020). This metabolism of AAA by gut microbiota is multifaceted including many interconvertible metabolic pathways such as decarboxylation, oxidation, transamination, deamination, etc (Bortolato et al., 2008; Saito et al., 2018; Xiang and Moore, 2005). Tyramine, octopamine, epinephrine, nor-epinephrine, p-cresol sulfate, p-cresol glucuronide, etc., are some of the tyrosine and phenylalanine derived secondary metabolites found altered in the body fluids of patients suffering from neurological disorders. Likewise, tryptophan also gives rise to various disease implicated metabolites, such as indole derivatives, kynurenine derivatives, serotonin, etc. (Table 5). It is difficult to attribute any single microbe to the production of any metabolite as the metabolic pathways are often conserved in many evolutionarily distinct species. A complete understanding of how these metabolites interact with the host is still lacking, however, names of few receptors have come up lately, such as, trace amine-associated receptor (TAARs for trace amines), pregnane X receptor (PXR for indole derivatives) and aryl hydrocarbon receptor (AhR for indole derivatives)

Table 3

Microbiome alterations reported in clinical studies on Huntington's disease.

Host	Sample size	Phylum	Class/Order	Family/Genus	Refs.
Human Males	N = 78; 42 HD, 36 healthy controls	<i>Firmicutes</i> ↓, <i>Euryarchaeota</i> , <i>Verrucomicrobia</i>		<i>F Lachnospiraceae</i> ↓, <i>F Akkermansiaceae</i> ↓, <i>F Acidaminococcaceae</i> , <i>F Akkermansiaceae</i> , <i>F Bacteroidaceae</i> , <i>F Bifidobacteriaceae</i> , <i>F Christensenellaceae</i> , <i>F Clostridiaceae</i> , <i>F Coriobacteriaceae</i> , <i>F Eggerthellaceae</i> , <i>F Enterobacteriaceae</i> , <i>F Erysipelotrichaceae</i> , <i>F Flavobacteriaceae</i> , <i>F Lachnospiraceae</i> , <i>F Methanobacteriaceae</i> , <i>F Peptococcaceae</i> , <i>F Peptostreptococcaceae</i> , <i>F Rikenellaceae</i>	(Wasser et al., 2020)
Human	N = 66; 33 HD, 33 healthy controls	<i>Actinobacteria</i> ↑	<i>C Deltaproteobacteria</i> ↑, <i>C Actinobacteria</i> ↑, <i>O Desulfovibrionales</i> ↑	<i>F Oxalobacteraceae</i> ↑, <i>F Lactobacillaceae</i> ↑, <i>F Desulfovibrionaceae</i> ↑, <i>G Clostridium</i> XVIII ↓, <i>G Intestinimonas</i> ↑, <i>G Bilophila</i> ↑, <i>G Lactobacillus</i> ↑, <i>G Oscillibacter</i> ↑, <i>G Gemmiger</i> ↑, <i>G Dialister</i> ↑	(Du et al., 2021)

(↑ signifies increase, ↓ signifies decrease; C – Class, O – Order, F – Family, G – Genus).

Table 4

Microbiome alterations reported in clinical studies on amyotrophic lateral sclerosis.

Study	Sample size	Key bacterial changes	Refs.
Microbial diversity in ALS	N = 11; 6 ALS, 5 healthy control	<i>Bacteroides</i> ↑, <i>Bacteroidia</i> ↑, <i>Bacteroidales</i> ↑, <i>Oscillibacter</i> ↓, <i>Anaerostipes</i> ↓, <i>Lachnospiraceae</i> ↓	(Fang et al., 2016)
The alteration of gut microbiome and metabolism in ALS patients	N = 40; 20 ALS, 20 healthy controls	<i>Bacteroidetes</i> ↑, <i>Kineothrix</i> ↑, <i>Parabacteroides</i> ↑, <i>Odoribacter</i> ↑, <i>Sporobacter</i> ↑, <i>Eisenbergiella</i> ↑, <i>Mannheimia</i> ↑, <i>Anaerotruncus</i> ↑, <i>Firmicutes</i> ↓, <i>Megamonas</i> ↓	(Zeng et al., 2020)
Gut inflammation and dysbiosis	N = 101; 5 ALS, 96 healthy controls	<i>Bacteroides-Prevotella</i> ↑, <i>Odoribacter</i> spp. ↑, <i>Barnesiella</i> spp. ↑, <i>Bacteroides vulgatus</i> ↑, <i>Firmicutes</i> / <i>Bacteroidetes</i> ratio ↓, <i>Ruminococcus</i> spp. ↓	(Rowin et al., 2017)
The human gut microbiota in people with ALS	N = 139; 66 ALS, 61 healthy controls, 12 neurodegenerative controls	<i>Roseburia intestinalis</i> ↓, <i>Eubacterium rectal</i> ↓, <i>Lachnospiraceae</i> ↓ A higher abundance of butyrate-producing bacteria were associated with a significantly lower risk of ALS	(Nicholson et al., 2021)

(↑ signifies increase, ↓ signifies decrease).

(Cervantes-Barragan et al., 2017; Gainetdinov et al., 2018; Venkatesh et al., 2014). Contributions of these microbial metabolites in disease manifestation or protection are also getting substantiated. Tryptophan derived metabolites have been shown to regulate microglial activation and neuroinflammation (Rothhammer et al., 2019). Indole-3-propionic acid (IPA), a tryptophan derivative, has been reported to exert neuroprotective effects by the virtue of its antioxidant property against Aβ induced oxidative damage and death (Chyan et al., 1999). Moreover, IPA has also been reported to promote axonal regeneration through neutrophil chemotaxis and protect intestine against inflammation by regulating gastrointestinal barrier function (Serger et al., 2022; Venkatesh et al., 2014). Nevertheless, dysregulation of serotonergic system has been widely described in case of both Alzheimer's and Parkinson's disease (Aaldijk and Vermeiren, 2022; Politis and Niccolini, 2015). Intermediates of kynurenine pathway have also displayed neuroprotective (kynurenic acid) as well as neurotoxic abilities (quinolinic acid and 3-hydroxy kynurene). Quinolic acid is an excitotoxin that activates the N-methyl-D-aspartate (NMDA) receptor by inducing the release of glutamate. Its neurotoxicity is also mediated by lipid peroxidation (Guillemin, 2012). Modulation of such intermediates is also considered as one of the therapeutic approaches for PD (Szabó et al., 2011). Similarly, tyrosine and phenylalanine derivatives are also reported to exert influence on neuronal functions. A tyrosine derivative, p-cresol sulfate has been suggested to induce neurodegeneration (Sun et al., 2020). Trace amines, such as octopamine have shown to confer neuroprotective effects against alpha-synuclein by modulating astrocyte function (Shum et al., 2023). However, tyramine, has been reported to exacerbate Aβ42 toxicity by inducing oxidative damage (Dhakal and Macreadie, 2020). Other neurotransmitters, such as catecholamines, stimulate the release of serotonin from enterochromaffin cells and regulate gut motility (Bellono et al., 2017; Mittal et al., 2017).

5.3. Vitamins

Vitamins constitute another group of microbially-derived bioactive metabolites. Besides dietary intake, gut microbiota also supplements

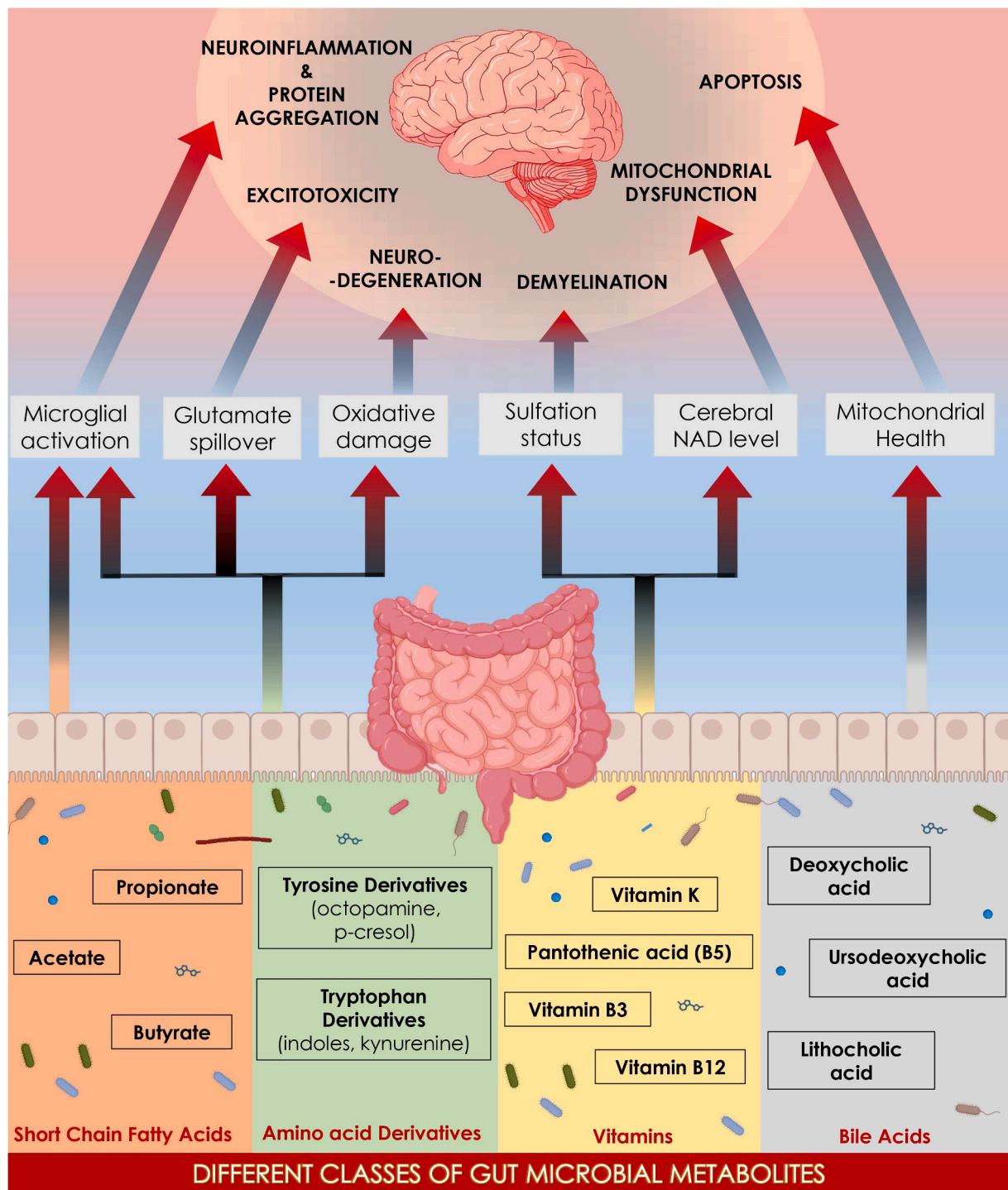


Fig. 3. Mechanistic overview of the gut derived microbial metabolites altered in neurological disorders.

certain vitamins such as cobalamin, folate, pantothenic acid, nicotinamide, thiamine, vitamin K, etc. Deficiency of these vitamins has often been found related to neurodegeneration and cognitive impairment (Allison, 2001; Anamnart and Kitjarak, 2021; Finsterer et al., 2021; Moore et al., 2012). It has been reported that deficiency of vitamin K dampens the sulfation status of the brain, which may in turn disrupt the myelination of neurons and results in the development of AD pathology (Allison, 2001; Han et al., 2002; Papuc and Rejdak, 2020). Consequently, administration of vitamin K has also been found protective as it inhibits fibrillization of alpha-synuclein protein and protects against A β toxicity (Da Silva et al., 2013; Huy et al., 2013). Similarly, a number of

reports have shown that administration of vitamin B12 and folate, in combination, alleviates the neurotoxicity of plasma homocysteine found elevated in levodopa treated PD patients (Anamnart and Kitjarak, 2021; Obeid et al., 2007). Recently, nicotinamide adenine dinucleotide (NAD) replenishment therapy has shown prospects in both AD and PD. Oral administration of nicotinamide riboside, a member of vitamin B3 family, has been shown to effectively replenish the level of cerebral NAD and improve the pathological symptoms associated with AD and PD (Brakedal et al., 2022; Hou et al., 2018).

Table 5

Human gut microbial metabolites found altered in clinical cases of Alzheimer's and Parkinson's disease.

Class of metabolite	Common name	Source microbes	Status in clinical samples		Ref.
			Parkinson's disease	Alzheimer's disease	
Short chain fatty acids (SCFAs)	Acetate	<i>Bacteroidetes</i> species	Decreased faecal level and increased plasma level	Low serum level is associated with higher risk of dementia. Increased levels are reported in saliva	(Aho et al., 2021; Chen et al., 2022; Cui et al., 2020; van der Hee and Wells, 2021; Yilmaz et al., 2017)
	Butyrate	Clostridial clusters	Decreased faecal level and Increased plasma level	Brain amyloidosis was found to be negatively correlated with blood butyrate level	(Aho et al., 2021; Chen et al., 2022; Marizzoni et al., 2020; van der Hee and Wells, 2021)
	Propionate	<i>Akkermansia muciniphila</i> , <i>Bacteroides vulgatus</i> , <i>Bacteroides thetaiotaomicron</i> and <i>Coprococcus catus</i>	Decreased faecal level and Increased plasma level	Increased level in saliva samples	(Aho et al., 2021; Chen et al., 2022; van der Hee and Wells, 2021; Yilmaz et al., 2017)
Amino acids and their derivatives	Tryptophan		Decrease level in plasma and serum but increased in CSF	Decrease levels in serum, plasma and blood but increased in CSF	(Chang et al., 2018; Gil et al., 2017; González-Sánchez et al., 2020; Iwaoka et al., 2020; Kaur et al., 2019; Oxenkrug et al., 2017)
	Kynurenic acid (Tryptophan)	Bacteria belonging to phyla Actinobacteria, Firmicutes, Bacteroidetes, Proteobacteria, and Fusobacteria	Decreased level in CSF and plasma but increased in serum	Decreased level in serum and plasma but increased level in CSF	(Chang et al., 2018; Gil et al., 2017; González-Sánchez et al., 2020; Heilman et al., 2020; Iwaoka et al., 2020; Kaur et al., 2019; Oxenkrug et al., 2017)
	Kynurenine (Tryptophan)	Bacteria belonging to phyla Actinobacteria, Firmicutes, Bacteroidetes, Proteobacteria, and Fusobacteria	Decreased level in plasma but increased in serum and CSF	Increased level in Serum and CSF but decreased level in plasma	(Chang et al., 2018; Gil et al., 2017; Iwaoka et al., 2020; Kaur et al., 2019; Oxenkrug et al., 2017; Sorgdrager et al., 2019)
	3-hydroxykynurenone (Tryptophan)	Bacteria belonging to phyla Actinobacteria, Firmicutes, Bacteroidetes, Proteobacteria, and Fusobacteria	Increased level in the plasma and CSF but decreased in serum	Increased level in serum and decreased level in plasma	(Chang et al., 2018; Gil et al., 2017; Heilman et al., 2020; Iwaoka et al., 2020; Kaur et al., 2019; Oxenkrug et al., 2017; Sorgdrager et al., 2019)
	3-hydroxyanthranilic acid (Tryptophan)	Bacteria belonging to phyla Actinobacteria, Firmicutes, Bacteroidetes, Proteobacteria, and Fusobacteria	Decreased level in the plasma	Decreased level in plasma	(Gil et al., 2017; Heilman et al., 2020; Kaur et al., 2019)
	Anthranilic acid (Tryptophan)	Bacteria belonging to phyla Actinobacteria, Firmicutes, Bacteroidetes, Proteobacteria, and Fusobacteria	Decreased level in the plasma but increased in serum and CSF	Decreased level in Serum and plasma	(Chang et al., 2018; Gil et al., 2017; Havelund et al., 2017; Kaur et al., 2019; Oxenkrug et al., 2017)
	Quinolinate (Tryptophan)	Bacteria belonging to phyla Actinobacteria, Firmicutes, Bacteroidetes, Proteobacteria, and Fusobacteria	Increased level in CSF and plasma	Decreased level in plasma	(Chang et al., 2018; Gil et al., 2017; Heilman et al., 2020; Kaur et al., 2019)
	Indole acetic acid (Tryptophan)	<i>Clostridium</i> , <i>Bacteroides</i> , and <i>Bifidobacterium</i>	Decreased level in plasma	Increased level in plasma	(Gao et al., 2020; Kalecký et al., 2022; Shao et al., 2021)
	Indole propionic acid (Tryptophan)	<i>Clostridium sporogenes</i>		Decreased level in plasma	(Dodd et al., 2017; Kalecký et al., 2022)
	Tyrosine		Increased level in plasma and CSF	Decreased level in serum	(González-Domínguez et al., 2015; Jiménez-Jiménez et al., 2020)
Neurotransmitters	p-Cresol glucuronide (tyrosine)	<i>Coriobacteriaceae</i> and <i>Clostridium</i> clusters produce p-Cresol only.	Increased level in plasma	-	(Shao et al., 2021)
	p-Cresol sulfate (tyrosine)	<i>Coriobacteriaceae</i> and <i>Clostridium</i> clusters produce p-Cresol only.	Increased level in plasma	Increased level in plasma	(Kalecký et al., 2022; Saito et al., 2018; Shao et al., 2021)
	Proline	Plasma proline levels are positively correlated with <i>Parabacteroides</i> and <i>Prevotella</i> spp.	Increased level in plasma	Increased level in plasma	(Mayneris-Perxachs et al., 2022; Shao et al., 2021; Wang et al., 2014)
	Ornithine Glutamate	<i>Lactobacillus</i> spp., <i>Corynebacterium glutamicum</i> , <i>L. plantarum</i> , <i>L. paracasei</i> , and <i>L. lactis</i>	Increased in serum Decreased level in CSF	Increased in serum Decreased level in plasma	(Çelik et al., 2018; Qi et al., 2019) (Corso et al., 2017; Jiménez-Jiménez et al., 2020; Miri et al., 2023)
	Taurine	Proteobacteria phylum (only metabolizes)	Decreased in CSF and plasma	Decreased level in plasma	(Aquilani et al., 2020; Jiménez-Jiménez et al., 2020; Zhang et al., 2016)
	Phenylalanine		Decreased level in serum	Decreased level in CSF, plasma and serum	(Aquilani et al., 2022; Corso et al., 2017; Figura et al., 2018; González-Domínguez et al., 2015)
	Gamma aminobutyric acid	Genus <i>Bacteroides</i> , <i>Parabacteroides</i> , <i>Escherichia</i> and <i>Bifidobacterium adolescentis</i>	Decreased level in CSF and plasma	Decreased level in plasma	(Jiménez-Jiménez et al., 1998; Otaru et al., 2021; Strandwitz et al., 2019; Tohgi et al., 1991; Tong et al., 2015)
	Tyramine	Genus <i>Enterococcus</i> and <i>Lactobacillus</i>	Increased level in plasma	-	(Albillas et al., 2021; Aydin et al., 2018; D'Andrea et al., 2019)

(continued on next page)

Table 5 (continued)

Class of metabolite	Common name	Source microbes	Status in clinical samples		Ref.
			Parkinson's disease	Alzheimer's disease	
	Octopamine	Genus <i>Enterococcus</i> and <i>Lactobacillus</i>	Decreased in plasma	-	(D'Andrea et al., 2019; van Kessel et al., 2019)
	Epinephrine		Decreased level in plasma	Increased level in CSF	(Henjum et al., 2022; Wichit et al., 2021)
	Norepinephrine	<i>Bacillus mycoides</i> , <i>Bacillus subtilis</i> , <i>Proteus vulgaris</i> , and <i>Serratia marcescens</i>	Increased level in plasma	Increased level in CSF. High plasma level is associated with cognitive dysfunction	(Henjum et al., 2022; Miri et al., 2023; Pillet et al., 2020; Wichit et al., 2021)
	Serotonin	<i>Streptococcus spp.</i> , <i>Enterococcus spp.</i> , <i>Escherichia spp.</i> , <i>Lactobacillus plantarum</i> , <i>Klebsiella pneumonia</i> , and <i>Morganella morgani</i>	Decreased level in plasma	Decreased level in platelets	(Barandouzi et al., 2022; Kumar et al., 1995; Wichit et al., 2021)
Vitamins	Cobalamin (B12)	<i>Pseudomonas</i> and <i>Klebsiella spp.</i>	Decreased level in plasma	Decreased level in serum	(Albert et al., 1980; Refsum and Smith, 2003; Shen, 2015)
	Folate (B9)	<i>Bifidobacterium spp.</i>	Decreased level in plasma	Decreased in plasma/serum	(Dong and Wu, 2020; Rossi et al., 2011; Zhang et al., 2021)
	Pantothenic acid (B5)	<i>Escherichia coli</i>	Decreased level in faeces	-	(Vascellari et al., 2020)
	Nicotinamide (B3)	<i>Akkermansia muciniphila</i>	Decreased level in blood	-	(Blacher et al., 2019; Wakade et al., 2014)
	Thiamine (B1)	<i>Bacteroides fragilis</i> , <i>Prevotella</i> , <i>Fusobacterium varium</i> , <i>Actinobacteria</i> , and <i>Clostridium</i>	Decreased level in plasma	Decreased level of thiamine diphosphate, active form of thiamine, in blood	(Gold et al., 1998; Håglin et al., 2020; Pan et al., 2016; Wan et al., 2022)
	Vitamin K2	<i>Enterobacter agglomerans</i> , <i>Serratia marcescens</i> and <i>Enterococcus faecium</i> .	Decreased level in serum	-	(Cooke et al., 2006; Yu et al., 2020)
Secondary Bile acids	Deoxycholic acid	<i>Clostridium scindens</i>	Increased level in plasma	Increased level in serum	(Funabashi et al., 2020; MahmoudianDehkordi et al., 2019; Yakhine-Diop et al., 2020)
	Lithocholic acid	<i>Clostridium scindens</i>	Increased level in plasma	Increased level in plasma	(Funabashi et al., 2020; Marksteiner et al., 2018; Yakhine-Diop et al., 2020)
	Ursodeoxycholic acid	<i>Clostridium</i> , <i>Ruminococcus</i> , and <i>Collinsella</i>	Decreased level in plasma	-	(He et al., 2022; Nie et al., 2022)
Other metabolites	Succinic acid	<i>Bacteroides spp.</i> , <i>Prevotella ruminoccola</i> , <i>Prevotella copri</i> and <i>Ruminococcus flavefaciens</i>	Decreased level in plasma and faeces	Increased level in plasma	(Fernández-Veledo and Vendrell, 2019; Gatarek et al., 2022; Kalecký et al., 2022; Voigt et al., 2022)
	Hippuric acid	<i>Clostridium sporogenes</i>	Increased level in plasma	-	(Gatarek et al., 2022; Pruss et al., 2023)
	Trimethylamine oxide (TMAO)	Bacteria belonging to phyla Firmicutes and Proteobacteria	Increased level in plasma	Increased level in CSF	(Liu and Dai, 2020; Vogt et al., 2018; Voigt et al., 2022)

5.4. Bile acids

The gut microbiota produces another set of neuroactive metabolites, bile acids, whose levels are found to be altered in major NDs (Table 5). These bile acids are referred to as secondary bile acids, as they are produced by the dehydroxylation of primary bile acids, mainly cholic acid and chenodeoxycholic acid. Deoxycholic acid (DCA), lithocholic acid (LCA) and ursodeoxycholic acid (UDCA) are the major secondary bile acids produced within the gut. These bile acids may further undergo conjugation with amino acids (mainly taurine and glycine) to produce various derivatives. A number of preclinical and clinical studies implicate their involvement in the pathology of AD and PD (Abdelkader et al., 2016; Graham et al., 2018; Nho et al., 2019). Among secondary bile acids, ursodeoxycholic acid (UDCA) and its taurine conjugate tauroursodeoxycholic acid (TUDCA), have increasingly been reported to exert ameliorative effects in neurological disorders. UDCA administration has been shown to suppress apoptosis by improving mitochondrial health, in both in-vivo and in-vitro models of PD (Abdelkader et al., 2016; Chun and Low, 2012). Likewise, TUDCA has proven to be neuroprotective as it reduces inflammation and improves motor symptoms (Rosa et al., 2018).

There are numerous other gut-derived metabolites whose neurological functions are yet to be deciphered. Such alterations in the levels of neuroactive molecules not only provide a window for early diagnosis of neurological diseases but also hold the keys to understand the intricate

crosstalk existing between microbiota-gut-brain during pathophysiological progression. A comprehensive understanding of this three-way axis will facilitate the advancement of gut-microbiota mediated therapeutic interventions. Fig. 4 provides an elaborate overview of the neurological influences exerted by gut microbial metabolites.

6. Implication of gut dysbiosis in proteostasis disruption

As we age, the efficiency of our overall protein quality control (PQC) machinery declines. This decline is not only reflected in the improper folding of proteins but also in the accumulation of toxic protein aggregates. In healthy young cells, such dysregulation of protein homeostasis is kept in check by the balanced functioning of molecular chaperones, proteolytic pathways and their regulators. The major proteolytic pathways responsible for the clearance of misfolded and aggregated proteins are ubiquitin-proteasome system (UPS) and autophagy (Labbadia and Morimoto, 2015). It is autophagy that mainly removes large aggregates by engulfing them in double membrane bound structures, autophagosomes, and then degrading them through lysosome-mediated enzymatic hydrolysis (Sarkar and Nazir, 2022). Besides UPS and autophagy, molecular chaperones and unfolded protein responses of endoplasmic reticulum (UPR^{ER}) and mitochondria (UPR^{mt}) are the key stress responsive pathways that are responsible for sensing and maintaining organismal proteostasis (Kulkarni et al., 2023; Zhou et al., 2022). However, as we age various internal and external stressors (such as mutations, heavy

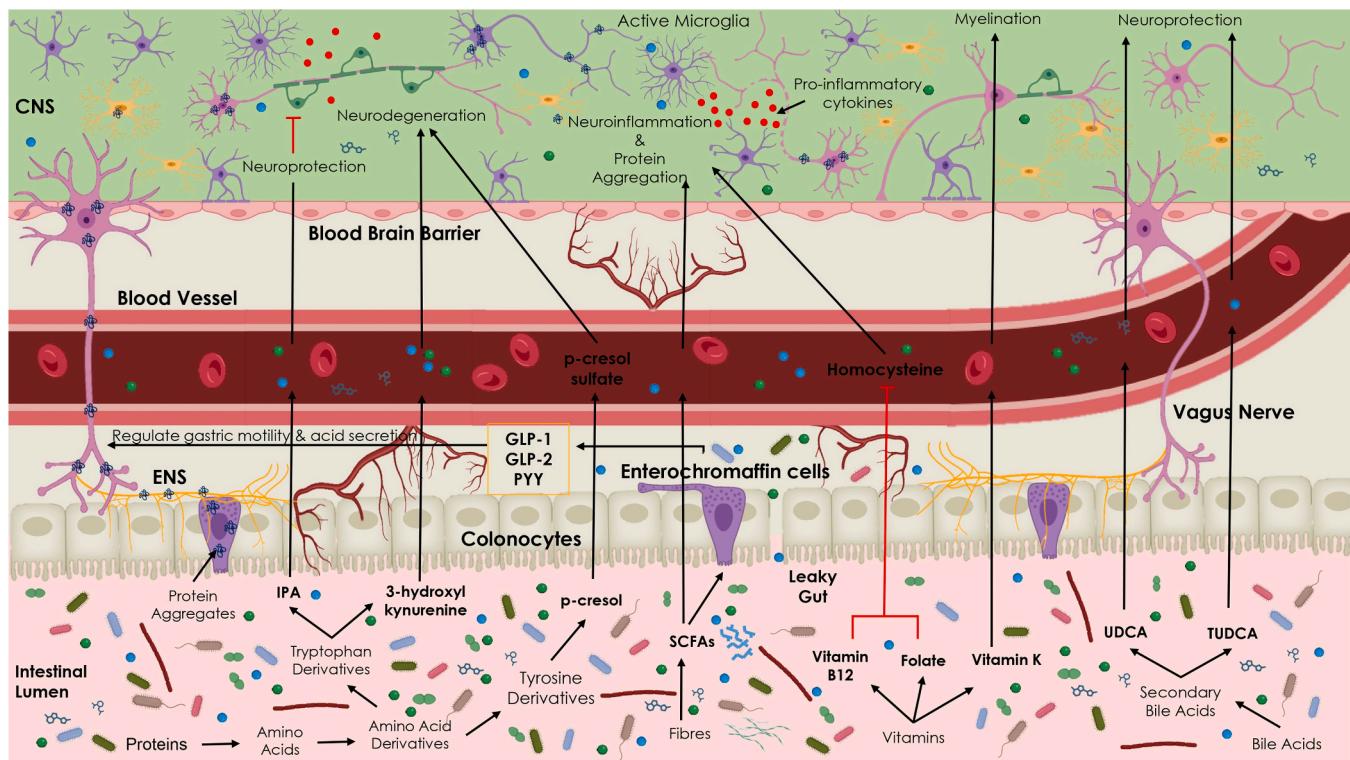


Fig. 4. Human gut microbiota derived neuroactive metabolites and their effects on the CNS.

metals, reactive oxygen species, etc.) cause these proteostasis machineries to become less efficient, resulting in protein misfolding and aggregation. Such age dependent decline in PQC machinery has been regularly implicated in the manifestation of neurodegenerative diseases (Hipp et al., 2019). Pharmacological interventions that regulate the autophagic process or UPS have become a realistic approach towards treating these proteinopathies (Harris and Rubinsztein, 2012; Rusmini et al., 2019). Small natural molecules are increasingly being screened for

their regulatory properties and many of them have shown potential in regulating the PQC machinery (Chai et al., 2019; Zhang et al., 2007). Thus, the role of gut microbiota and their derived metabolites in regulating these processes becomes increasingly important as major NDs have largely been suggested to progress from the gut (Fig. 5). Homing in on this aspect also becomes critical because majority of the gut associated pathologies are prodromal in nature, therefore providing us opportunities for early diagnosis and intervention.

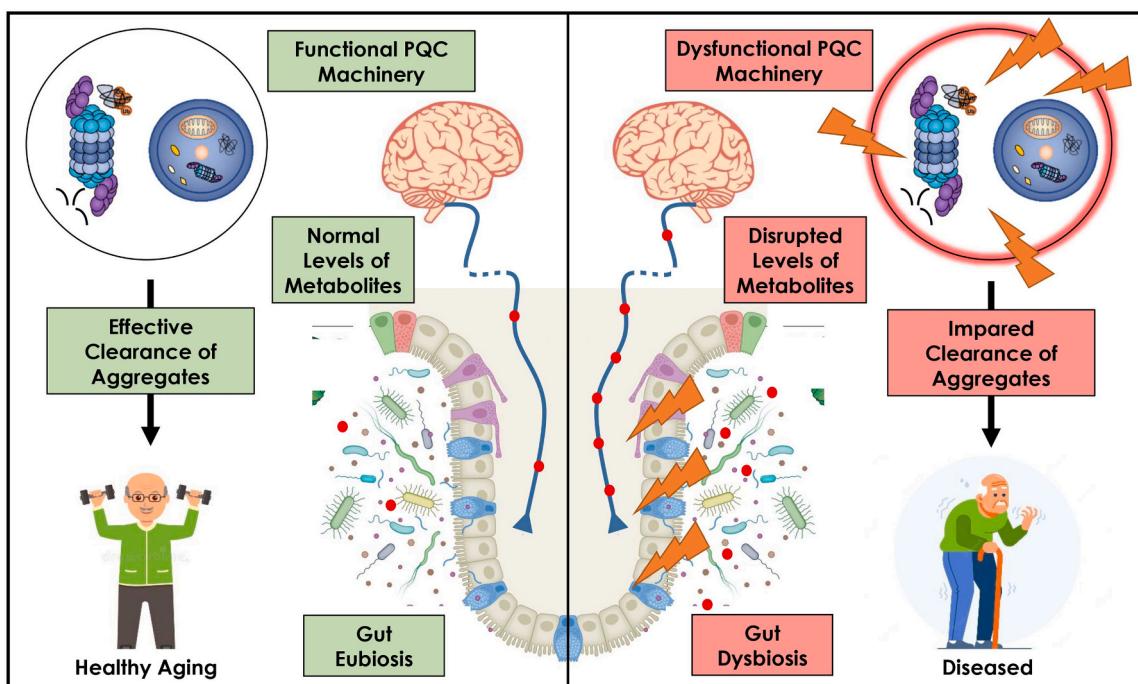


Fig. 5. Age-associated decline in proteostasis machinery due to gut dysbiosis.

6.1. Role of gut microbes in proteostasis regulation

Regulation of PQC machinery by gut microbes is not new as it has been reported previously. Four types of *Bifidobacteria*; *B. infantis*, *B. longum*, *B. bifidum* and *B. adolescentis*; were found to induce autophagy in intestinal epithelial cells. They were found to increase the expression of autophagy genes; ATG5, ATG12 and ATG16, thus indicating towards the activation of Atg12-Atg5-Atg16 conjugation system. This Atg12-Atg5-Atg16 multimeric complex is one of the novel conjugation systems that are involved in the initiation and elongation of autophagosome membrane (Lin et al., 2014). Similarly, a pathogenic strain of *E. coli* also exhibited the ability to regulate UPS in intestinal epithelial cells. This strain induced the NF- κ B mediated inflammatory response by promoting the proteasome-dependent degradation of I κ B- α . It was found to modulate UPS by decreasing the accumulation of poly-ubiquitin conjugates and increasing 26S proteasome activity in intestinal epithelial cells (Cleynen et al., 2014). Conversely a probiotic cocktail VSL#3, containing *Streptococcus thermophilus* and species of *Lactobacillus* and *Bifidobacteria*, was reported to inhibit proteasomal degradation of I κ B in colonic epithelial cells, resulting in the suppression of NF- κ B mediated inflammatory response (Petrof et al., 2004). Such perturbation of inflammatory response was also reported in case of nonvirulent *Salmonella* strains, that hampered the I κ B/NF- κ B pathway (Neish et al., 2000). Likewise, in patients suffering from metabolic syndrome *Desulfovibrio* is speculated to regulate unfolded protein response in intestinal cells. This symbiont is reported to suppress the synthesis of a gut hormone, glucagon-like peptide (GLP-1) via H₂S production that inhibits mitochondrial respiration and induces unfolded protein response (Qi et al., 2024). UPR^{ER} induction in the intestinal epithelial cells has been found to promote the differentiation of IL-17-producing T helper (Th17) cells. Such development of Th17 cells requires the adhesion of *Citrobacter rodentium*, *Escherichia coli* OH157 or segmented filamentous bacteria (SFB) to intestinal epithelium (Duan et al., 2023). Regulatory effects of probiotic bacterial species have also been observed in various murine models, such as modulation of autophagy by *Lactobacilli*, *Bifidobacteria* and *Bacillus* species (Cui et al., 2017; Wu et al., 2019; Zaylaa et al., 2019). Autophagy plays an important role in the protection and maintenance of intestinal integrity. *Lactobacilli* can suppress autophagy via mTOR-dependent pathways and thus help in maintaining the intestinal integrity (Cui et al., 2017). Similarly, *Bacillus* species can alleviate oxidative stress induced intestinal injury by promoting p38 MAPK dependent autophagy (Wu et al., 2019). Suppression of autophagy has also been attributed to *Bifidobacterium bifidum* which functions by preventing the fusion of autophagolysosome (Han et al., 2016).

6.2. Role of gut microbiota derived metabolites in regulating proteostasis machinery

The role of microbially derived metabolites has also been speculated in mediating these regulatory influences. There are many studies that substantiate these speculations, showing innate abilities of metabolites to regulate PQC machinery (Table 6). SCFAs, which are known inhibitors of HDACs, have been investigated for this purpose as inhibition of HDACs is widely reported to induce autophagy (Shao et al., 2004; Zhou et al., 2020). One such SCFA, butyrate has been reported to induce autophagy via hypoxia-inducible factor-1 α (HIF-1 α) in a mouse model for colitis. The exact mechanism by which HIF-1 α regulates autophagy is not known but it has been previously shown to involve BNIP3, Bcl-2/Bcl-XL or PI3K/Akt pathways (Zhou et al., 2020). Conversely, gut-microbiota derived butyric acid has also been reported to inhibit UPS resulting in reduced degradation of peroxisome proliferator-activated receptor δ (PPAR δ) (Shou and Shaw, 2023). Another SCFA, acetate has been suggested to repress autophagy via AcCoA-synthetase, Acs2p, driven histone acetylation that results in the transcriptional repression of autophagy genes (Eisenberg et al., 2014). Similar autophagic regulations are witnessed in case of amino acid

Table 6

Effect of human gut microbes and their metabolites on protein homeostasis.

Microbe/Metabolite	Component of PQC affected	Pathway	Ref.
Gut Microbes			
<i>Bifidobacteria</i> (<i>B. infantis</i> , <i>B. longum</i> , <i>B. bifidum</i> and <i>B. adolescentis</i>)	Autophagy induction	Activation of Atg12-Atg5-Atg16 conjugation system	(Lin et al., 2014)
Pathogenic strain of <i>E. coli</i>	Ubiquitin-proteasome system (UPS) induction	Decreasing the accumulation of poly-ubiquitin conjugates and increasing 26S proteasome activity in	(Cleynen et al., 2014)
A probiotic cocktail VSL#3, containing <i>Streptococcus thermophilus</i> and species of <i>Lactobacillus</i> and <i>Bifidobacteria</i>	Ubiquitin-proteasome system (UPS) inhibition	-	(Petrof et al., 2004)
Nonvirulent <i>Salmonella</i> strains	Ubiquitin-proteasome system (UPS) inhibition	-	(Neish et al., 2000)
<i>Desulfovibrio</i>	Unfolded protein response (UPR) induction	suppress the synthesis of a gut hormone, glucagon-like peptide (GLP-1) via H ₂ S production	(Qi et al., 2024)
<i>Citrobacter rodentium</i> , <i>Escherichia coli</i> OH157 or segmented filamentous bacteria (SFB)	UPR ^{ER} induction	Adhesion of these bacteria to intestinal epithelial cells	(Duan et al., 2023)
<i>Lactobacilli</i>	Autophagy inhibition	mTOR-dependent pathways	(Cui et al., 2017)
<i>Bacillus</i> species	Autophagy induction	p38 MAPK pathway	(Wu et al., 2019)
<i>Bifidobacterium bifidum</i>	Autophagy inhibition	Preventing the fusion of autophagolysosome	
Metabolites			
Butyrate	Autophagy induction	hypoxia-inducible factor-1 α pathway that involves BNIP3, Bcl-2/Bcl-XL or PI3K/Akt pathways	(Zhou et al., 2020)
	Ubiquitin-proteasome system (UPS) inhibition	-	(Shou and Shaw, 2023)
Acetate	Autophagy inhibition	AcCoA-synthetase, Acs2p, driven histone acetylation resulting in transcriptional repression of autophagy genes	(Eisenberg et al., 2014)
Kynureneine and its downstream derivatives, quinolinic acid and kynurenic acid	Autophagy inhibition	AhR pathway	(Kondrikov et al., 2021)
Vitamin K2	Autophagy induction	-	(Yokoyama et al., 2008)
Queuine (Depletion)	UPR ^{ER} and UPR ^{mt} induction upon queuine depletion	Translational dysregulation resulting in protein misfolding	(Richard et al., 2021)
Methylglyoxal (Depletion)	UPR ^{mt} induction upon methylglyoxal depletion	Simultaneous activation of ATFS-1 and RICT-1/SGK-1 pathways	(Shin et al., 2020)
Colonic acid	UPR ^{mt} induction	Activation of ATFS-1 pathway	(Han et al., 2017)

derivatives. Kynurenine and its downstream derivatives, quinolinic acid and kynurenic acid, have been reported to inhibit autophagy via AhR pathway in bone marrow stem cells (Kondrikov et al., 2021). Neurotransmitters such as epinephrine and norepinephrine are known for autophagic regulation in response to stress (Sinha et al., 2017). Induction of autophagy is also observed upon treatment of vitamin K2 in leukemia cells (Yokoyama et al., 2008).

A gut microbial metabolite, queuine has been found crucial in maintaining protein homeostasis. It is a hypermodified nucleobase produced exclusively by gut microbes. Its depletion in human and mice cells has been shown to induce translational dysregulation and mitochondrial dysfunction that result in protein misfolding and activation of stress responsive pathways i.e., UPR^{ER} and UPR^{mt}. Its administration has also been found therapeutic in various in-vitro models of neurodegeneration as it reduces the aggregation of hyperphosphorylated alpha-synuclein and tau hyperphosphorylation in both acute and chronic models of AD (Richard et al., 2021). Depletion of another microbial metabolite, methylglyoxal, has been reported to extend the lifespan of *C. elegans*. *E. coli* mutants producing low levels of methylglyoxal have been shown to induce lifespan extension by activating UPR^{mt}. Such modulation of UPR^{mt} and longevity occurs via two pathways: ATFS-1 and RICT-1/SKG-1, simultaneously. ATFS-1 (Activating Transcription Factor associated with stress) is a major transcription factor that regulates UPR^{mt} and RICT-1 is the *C. elegans* orthologue of mammalian target of rapamycin complex 2 (mTORC2) that interacts with SGK-1 (serum-glucocorticoid-inducible kinase 1) to regulate mitochondrial dynamics and stress responsive pathways (Shin et al., 2020). Besides depletion, some *E. coli* mutants induce lifespan extension in *C. elegans* by overproducing a polysaccharide colonic acid. This microbial metabolite promotes mitochondrial fragmentation and induces UPR^{mt} via ATFS-1 pathway (Han et al., 2017). Apart from microbially derived metabolites, plant-derived polyphenols have also been attributed to UPS regulation, as summarized in this review article (Nargeh et al., 2021). These examples show us that how hosts have evolved to sense their environment through microbial disruptions in their gut. Under normal conditions such disruptions are resolved by appropriate response pathways but under extreme conditions such disruptions may lead to disease manifestation.

6.3. Cell non-autonomous regulation of proteostasis

Although from these events, it appears that autophagy can only be regulated locally, but its regulation can also occur cell non-autonomously across tissues. Interestingly in *Drosophila*, a nutrient sensing pathway involving AMPK or Atg1 can relay these signals between gut and brain. Intestinal upregulation of AMPK has been shown to induce autophagy cell non-autonomously in the brain (Ulgherait et al., 2014). Similar regulation of autophagy has also been observed in *Cae-norhabditis elegans*, where overexpression of a transcription factor in glial cells, XBP-1s, activates another transcription factor in the intestine, HLH-30/TFEB, which in turn induces intestinal autophagy (Metcalf et al., 2022). This gives another nod for the existence of a gut-brain axis, notably, in terms of autophagic regulation. The existence of such an axis has also been realized repeatedly in various studies exploring the inter-tissue regulation of ER and mitochondrial stress. In *C. elegans*, upregulation of neuronal UPR^{ER} by ectopic expression of XBP-1s has been found to induce UPR^{ER} in intestinal cells through the secretion on small clear vesicles, conferring stress resistance and prolonging the lifespan of organism. Such cell non-autonomous regulation of UPR^{ER} by neuronal XBP-1s has also been found conserved in mammals where it protects against metabolic disorders by improving leptin and insulin sensitivity; and decreasing the production of glucose by hepatocytes (Frakes and Dillin, 2017). Induction of mitochondrial stress in neurons has also been reported to reflect in peripheral tissues. Expression of a toxic aggregation prone mutant Q40 protein in neurons has been shown to induce intestinal UPR^{mt} cell non-autonomously. This inter-tissue

communication is mediated by the release of a neurotransmitter, serotonin and a Wnt ligand, EGL-20 from the neurons, and is dependent upon the health of germline mitochondria (Shen et al., 2024). Similar to UPR^{ER}, cell non-autonomous regulation of mitochondrial stress has been found conserved in mice. Dysregulation of OXPHOS in the hypothalamic POMC neurons by AIF (a caspase independent inducer of cell death) deletion was found to exert protective effects in obese mice. Induction of mitochondrial stress in neurons improved glucose metabolism and increased the sensitivity towards insulin and leptin, cell non-autonomously (Timper et al., 2018). These examples describe a unidirectional regulation of protein homeostasis from neurons to intestine as the evidences for bidirectional crosstalk are still limited. Instead communication of other kinds of stresses (oxidative and dietary) from intestine to neurons has been described previously (Kim and Sieburth, 2018; Minnerly et al., 2017), suggesting a potential for the existence of bidirectional pathways of proteostasis regulation. Exploiting such pathways for therapeutic interventions can delay or prevent age dependent decline in proteostasis machinery observed in neurological disorders right from the early days of disease progression. Leads for such interventions can be acquired from the neuroactive metabolites produced by the altered gut microbes upon dysbiosis in diseased conditions. Understanding the physiological effects of such large number of microbes and their metabolites is a cumbersome task which requires rapid screening models that are able to recapitulate disease conditions and are amenable to genetic manipulations. One such model system is *Caenorhabditis elegans*. Besides its usual relevance in various fields, such as gerontology, genetics, developmental biology, etc., *C. elegans* is coming up as effective model organism to understand the gut-brain axis (Ortiz de Ora and Bess, 2021; Rani et al., 2023). Its bacterivorous diet makes it an ideal model organism to study host-microbiome interactions (Backes et al., 2021). Interestingly, its gut shares some morphological and functional similarities with that of humans as it has an autonomously acting enteric nervous system, comprising of 20 neurons, and it can communicate with the nervous system through neuropeptide production (Backes et al., 2021; Ortiz de Ora and Bess, 2021; Vidal et al., 2022). Moreover, the connectome of all 302 neurons along with their transcriptional profiling is well known in case of *C. elegans* (Cook et al., 2019; Liska et al., 2023).

7. Recent breakthroughs

A plethora of studies are available that highlight the role of gut microbial dysbiosis in neurological disorders (Sun and Shen, 2018). However, with the technical advances and computational assistance these studies have become more mechanistic rather than correlative. Researchers are now capable of studying specific features of any microbe, dwelling in the gut, which they find pathologically relevant to any disease, including NDs. A recent study investigated a specific kind of protein that is structurally essential for biofilm production by microbes. It dissected the amyloidogenic propensity of these proteins found associated with biofilms (Biofilm Associated Proteins or BAPs) produced by microbes within the human gastrointestinal tract. Structurally, these BAPs were found to be constituted of β -sheet rich domains that assemble as amyloids and promote the aggregation of α -synuclein by impeding its degradation through chaperon mediated autophagy (CMA) by lysosomes. The BAP encoding genes were even found to be enriched in the microbiome of PD patients (Fernández-Calvet et al., 2024). Interestingly, these physiological effects between the host and microbiome are proving to be more bi-directional with further investigations. Recently, a group of scientist hailing from university of Michigan, showed how microbes can effectively evolve during any stressful condition experienced by the host and in-turn affect the host physiology in longer run. They showed that, owing to their short generation time, microbes evolve rapidly during oxidative stress condition and develop mutations in their iron-sulfur cluster pathway. Such microbes when fed to *C. elegans* were found to confer stress tolerance and increased life-span by modulating

the p38-MAPK (PMK-1) signalling in worm and iron metabolism in bacteria (Bhat et al., 2024). Such pro-longevity alterations within the microbiome can prove to be remedial in age-associated diseases.

To improve the window of early diagnosis in neurological disorders, longitudinal studies are being carried out on large cohorts addressing various end-points associated with the gut microbiota. Recently, a longitudinal study followed a birth cohort for 20 years in order to establish an association between early life factors and diagnosis of neurodevelopment disorder. They investigated various end-points ranging from stool, cord serum, health records and signatures associated with microbes and their metabolites, that increase the risk for neurodevelopment disorders. The microbial and metabolic signals were found to effectively differentiate between healthy controls and future NDs. The risk of neurodevelopment disorder was reported to increase with infection, pre-term birth, stress, parental smoking and a specific human leucocyte antigen (HLA), DR4-DQ8. They even found that the lower levels of linolenic acid and higher perfluorodecanoic acid (PFDA) in cord serum effectively correlates with the risk of future autism spectrum disorder (Ahrens et al., 2024). Pin-pointing of specific microbial metabolites for the diagnosis or as therapeutic intervention has become possible with extensive metabolome profiling and rapid screening methods involving alternate animal models such as *C. elegans*. One such study published this year, highlights the therapeutic capabilities of one of the short-chain fatty acid (SCFA), propionate. Supplementation or enhancement of propionate production in the intestine of *C. elegans* was found to rescue human A53T α -syn mutant driven dopaminergic neurodegeneration and also improved defects in locomotion. This rescue by propionate was attributed to the inter-organ communication between neurons and intestine, by energy substrates such as lactate or signalling molecules like insulin-like peptide, and was mainly driven by the restoration of energy metabolism in intestine (Wang et al., 2024). Dietary fibres are one of the major sources of these short-chain fatty acids, and their deprivation has also been recently observed to exacerbate PD associated pathological symptoms such as motor dysfunction, α Syn aggregation in the ENS and CNS, and nigrostriatal degeneration. These symptoms were the result of microbiome dysbiosis mainly reflecting as an increment in the levels of *Akkermansia* spp. and *Bacteroides* spp., sparking mucus erosion (Schmit et al., 2023). This signifies the importance of a balanced diet to keep the gut microbiota healthy and further consolidates the notion of prebiotics as a promising therapeutic intervention for neurological disorders. One of recent studies showed that along with resistance exercise and supplementation of branched chain amino acids, treatment with prebiotics, containing fructose and fructo oligosaccharides, for 12 weeks can improve cognition in aged individuals by bringing changes in the level of *Bifidobacterium* (Ni Lochlainn et al., 2024). Diet plays a pivotal role in shaping the composition and function of the gut microbiome. It serves as essential “fuel” for both hosts and microbes. Additionally, diet represents a critical modifiable risk factor for NDs (Glans et al., 2023). The intricate interplay between diet and the microbiome may partially elucidate why dietary choices can impact the development of NDs.

Faecal Microbiota Transplantation (FMT) is an emerging method for restoring the gut ecosystem (T. Zhang et al., 2022). It involves transferring diverse microbiomes, their products, and metabolites from healthy donors to recipients. FMT can enhance microbial diversity, influence metabolite production, and modulate the recipient's immune response. Recent research has shown that Faecal Microbiota Transplantation (FMT)—when performed using microbiomes from young and healthy wild-type mice—can improve cognitive impairments associated with A β plaques in a mouse model of Alzheimer's disease (5 \times FAD mice) (Elangovan et al., 2023). Additionally, clinical trials exploring the effects of FMT in patients with Alzheimer's disease (AD) and Parkinson's disease (PD) have yielded promising results. Recent clinical studies investigating the effects of FMT in AD and PD patients have shown promising results. For example, after stopping antibiotics (vancomycin and metronidazole) for 48 h, dementia patients with cognitive decline

and *Clostridioides difficile* infection underwent FMT via colonoscopy. They demonstrated improved cognitive function one month after undergoing faecal microbiota transplantation (FMT) from healthy donors, as compared to the baseline (Park et al., 2022).

Recent observational studies highlighted abnormal changes in trimethylamine N-oxide (TMAO) levels within the peripheral circulatory system of Parkinson's disease patients. TMAO, a metabolite produced by gut microbiota, can cross the blood-brain barrier and is closely associated with neuroinflammation—a key driver of PD pathogenesis (Quan et al., 2023). Recently, researchers have found that inhibiting TMAO formation using 3, 3 dimethyl-1-butanol can ameliorate cognitive dysfunction in APP/PS1 transgenic mice (Quan et al., 2023; Wang et al., 2022). This discovery suggests that therapeutics aimed at reducing harmful gut microbiome-derived metabolites, such as TMAO, hold promise for treating neurodegenerative disease.

In summary, exploring the gut-brain axis and its impact on neurodegenerative diseases unveils exciting possibilities for novel therapeutic approaches. This understanding has opened up exciting possibilities for novel therapeutic approaches. A number of clinical studies are exploring this possibility of developing effective therapies by targeting gut microbiota (Table 7). Interventions that specifically target the gut microbiome hold promise for positively influencing disease outcomes.

8. Conclusion and future perspectives

The emerging role of gastrointestinal dysfunctions in neurological disorders highlights an important dimension of their complex pathogenesis, particularly via gut-brain axis. The early onset of gastrointestinal symptoms serves as a prodromal marker, positioning such symptoms as potential early indicators of neurodegenerative diseases. Research in patients with these conditions has revealed that the composition of the gut microbiota as well as their specific metabolites exhibit unique, disease-specific signatures. These microbial and metabolic profiles offer valuable insights into the pathophysiology of neurological disorders and present opportunities for developing specific therapeutic strategies. In contrast, impairments in protein clearance pathways, such as autophagy and the ubiquitin-proteasome system, are typically observed during more advanced stages of ailments, reflecting distinct mechanisms of progression of neurodegeneration. The growing burden of neurodegenerative diseases on healthcare resources necessitates an early and combinatorial therapeutic approach. One promising strategy involves leveraging neuroactive metabolites produced by the gut microbiota to prevent or delay the age-associated decline in protein quality control (PQC) mechanisms. These metabolites, identified during the prodromal phase by screening alterations in gut microbial outputs, hold significant potential in modulating disease pathophysiology, as evidenced by their altered concentrations in patient body fluids. Many of these metabolites inherently possess the capability to influence autophagy, a critical component of the PQC system. Early intervention using supplementation or modulation of these metabolites via pharmacologic or metabolic interventions, could potentially slow the progression of proteostatic decline in the central nervous system. Integrating such interventions derived from enteric sources alongside existing therapeutic modalities could enhance the management and treatment of neurodegenerative diseases, offering a multipronged approach to mitigating these complex disorders. As research efforts to uncover the complex interplay between the gut microbiome and neurological health continue, future research in this field could benefit from mechanistic studies, intervention trials and technological advances particularly in terms of developing novel theranostic tools towards diagnosing and treating complex neurological diseases.

CRediT authorship contribution statement

M. Akbar: Conceptualization, Writing – original draft. **P. Toppo:** Conceptualization, Writing – original draft. **A. Nazir:**

Table 7

Summary of clinical studies targeting gut microbiota for the treatment of neurological disorders.

S.No.	Clinical trial ID	Study Title	Study Overview	Status	Study Timeline (Study start date & completion date)	Sponsor
1.	NC T06487975	Effects of <i>Bacillus Subtilis</i> on Blood and Gut Biomarkers in Parkinson's Disease	The aim of this study is to evaluate whether the administration of <i>Bacillus subtilis</i> influences gut and blood biomarkers relevant Parkinson's disease.	Looking for participants (Recruiting)	2023-05-02 to 2025-12-31 (Estimated)	University of Edinburgh
2.	NC T06199193	Design of Personalised supplements Based on the Gut microbiota through Artificial Intelligence for Alzheimer's Patients (TREAT)	This study aims to examine if changes in the intestinal microbiota through diet may serve as a new treatment or an adjuvant treatment for Alzheimer's disease	Looking for participants (Recruiting)	2024-02-01 to 2025-12-31 (Estimated)	Universidad Complutense de Madrid
3.	NC T06039267	Brain Health & the Microbiome: A Proof-of-Concept Study in Patients With Mild Cognitive Impairment	This research will provide the pilot data to begin to understand if changes in the gut microbiome are beneficial to health and/or may slow or halt the progression of MCI or early Alzheimer's	Looking for participants (Recruiting)	2023-08-25 to 2024-08-24 (Estimated)	George Washington University
4.	NC T05943925	Dementias and Microbiota Composition: Is Possible to Revert the Dementia Symptoms Reverting the Microbiota Composition?	DEM-BIOTA will explore the microbiota differences between dementias: AD, LBDs, that includes: Parkinson disease dementia (PDD) and Lewy Body Dementia (LBD) and FTD-behavioral variant, also in Mild Cognitive Impairment (MCI) to study the progression and characterize them in relation to neurocognitive and neuropsychiatric symptoms as well as patient functionality (dependency level). The capacity of a probiotic compound in reverting or improving neurocognitive and neuropsychiatric symptoms and patient functionality in a sample of AD patients will be also studied.	Looking for participants (Recruiting)	2021-04-16 to 2025-02-01 (Estimated)	University Rovira i Virgili
5.	NC T05934188	Role of the Gut-microbiota on Ageing and Neurodegeneration: a Clinical and Brain Imaging Study	The goal of this observational study is to characterize the gut-microbiota composition associated with alterations in brain structure and function during the ageing process and across neurodegenerative disorders	Looking for participants (Recruiting)	2023-05-01 to 2026-04-30 (Estimated)	IRCCS San Camillo, Venezia, Italy
6.	NC T06463769	"Impact of Diet on the Microbiome-Immune-Brain Axis in Parkinson's Disease" as Part of the Collaborative Research Center 1697 "Targeting the Microbiome-Immune-Brain Interaction in Neurodegeneration"	The investigators hypothesize that compared to an average German diet, the predominantly plant-based New Nordic LPF-diet, as a culturally adapted diet, which is rich in fermentable fiber and phytochemicals, will have beneficial effects on the gut microbiome of patients with PD by increasing the abundance of short-chain fatty acid (SCFA)-producing bacteria (primary outcome) and will improve gut motility, metabolic resilience, and inflammation (secondary outcomes)	Looking for participants (Not Yet Recruiting)	2025-05 to 2028-07 (Estimated)	University of Kiel
7.	NC T06448546	Investigating the Role of the Gut Microbiome in Huntington's Disease	The investigators are trying to determine if patients who are diagnosed with adult-onset HD and who exhibit a rapid rate of disease progression have unique populations of bacteria in their gut as compared to patients with slower progression.	Looking for participants (Not Yet Recruiting)	2024-06 to 2029-06 (Estimated)	University of Central Florida
8.	NC T06207136	Canadian Parkinson's Microbiome Initiative: A Pilot Phase 2 Feasibility Randomized Controlled Trial of the MIND Diet in Parkinson's Disease	The goal of this pilot study is to examine the feasibility and effects of an 18-month intervention diet compared to an active control diet (standard diet) in those living with Parkinson's Disease (PD), without dementia.	Looking for participants (Not Yet Recruiting)	2024-10-03 to 2027-12-31 (Estimated)	University of British Columbia
9.	NC T05532644	Correlation of P-glycoprotein Polymorphisms With Microbial Metabolites in Patients With Alzheimer's Disease (AD) on Medication	The importance of the proposed study concerns the understanding of the way in which each drug acts in each organism separately, both at the genome level and at the microbiome level	Looking for participants (Not Yet Recruiting)	2022-09 to 2024-09	Aristotle University Of Thessaloniki
10.	NC T04956939	Levodopa (LD) Response and Gut Microbiome in Patients with Parkinson's Disease	This study is an observational cohort study that tracks PD patients using both low- and high-frequency doses of LD	Completed	2018-07-17 to 2021-03-31	Ali Keshavarzian, Rush University Medical Center

(continued on next page)

Table 7 (continued)

S.No.	Clinical trial ID	Study Title	Study Overview	Status	Study Timeline (Study start date & completion date)	Sponsor
11.	NC T05558787	Aromatic L-amino Acid Decarboxylase Activity, Tyrosine Decarboxylase Activity and Gut Microbiome in Patients with Advanced Parkinson's Disease	Relevant enzyme's activity and composition of gut microbiome determination	Completed	2023-06-28 to 2024-08-14	Radboud University Medical Center
12.	NC T03671785	Study of the Faecal Microbiome in Patients with Parkinson's Disease	Study the intestinal microbiome of Parkinson's disease (PD) patients, as well as the safety and patterns of improvement in the diversity of the colonic microbiome after administering lyophilized PRIM-DJ2727.	Completed	2019-05-15 to 2022-10-12	Herbert DuPont, MD, The University of Texas Health Science Center, Houston
13.	NC T01536769	Intestinal and Nasal Microbiota of Patients With Idiopathic Parkinson's Disease	Identification of bacterial biomarkers to determine early progression of PD pathogenesis	Completed	2011-11 to 2015-12	Filip Schepersjans, Helsinki University Central Hospital
14.	NC T03808389	A Double-blind, Placebo-controlled, Randomized Clinical Trial Investigating Faecal Microbiota Transplantation for Parkinson's Disease and Its Effect on Symptoms and Disease Progression	This study is designed to explore the role of faecal microbiota transplantation (FMT) and gut dysbiosis in restoring gut homeostasis and their impact on the development and progression of Parkinson's disease (PD).	Completed	2020-12-01 to 2022-12-09	University Ghent
15.	NC T05889572	Safety, Tolerability and Gut microbiota Analysis of an Oral Micro biotherapy in Amyotrophic Lateral Sclerosis; an Open-label Phase 1b Pilot Trial	Purpose of this pilot study is to assess the safety and tolerability of multiple doses of MaaT033 in ALS patients and to analyse the gut microbiota composition and evolution before considering a larger randomized controlled efficacy study.	Active, Not-recruiting	2023-06-08 to 2024-12	MaaT Pharma
16.	NC T05145881	Evaluation of Clinical Effect of Probiotics in Alzheimer's Disease: a Randomized, Double-blind Clinical Trial	In this clinical trial, five probiotic strains with anti-oxidant and anti-inflammatory properties are used to control the immune system and gut flora of patients with mild to moderate Alzheimer's disease symptoms. The main objective is to slow down the progression of the disease and assess the effectiveness of probiotic therapy in preventing Alzheimer's disease.	Active, Not-recruiting	2020-04-02 to 2023-12-31	Hsieh-Hsun Ho, Glac Biotech Co., Ltd
17.	NC T03766321	Interplay Between Gut Microbiota and Adaptive Immunity in Amyotrophic Lateral Sclerosis: a Clinical Trial	Assessing the safety, tolerability, and biological activity of FMT in ALS patients, including evaluation of various biomatrices.	Active, Not-recruiting	2020-07-01 to 2025-02	JESSICA MANDRIOLI, Azienda Ospedaliero-Universitaria di Modena

(Source: ClinicalTrials.gov).

Conceptualization, Writing – original draft, Supervision.

Funding

M. Akbar is funded by Council of Scientific and Industrial Research for Senior Research Fellowship (31/004(1400)/2020-EMR-I). P. Toppo is funded by University Grants Commission for Senior Research Fellowship [740/(CSIR-UGC NET JUNE 2019)]. A. Nazir is funded by CSIR-CDRI Grant MLP0013.

Declaration of Competing Interest

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

Data availability

No data was used for the research described in the article.

Acknowledgments

Authors express their sincere gratitude to Academy of Scientific and Innovative Research (AcSIR) and CSIR-Central Drug Research Institute for providing infrastructure. The CSIR-CDRI communication number is

10855.

References

- Aaldijk, E., Vermeiren, Y., 2022. The role of serotonin within the microbiota-gut-brain axis in the development of Alzheimer's disease: a narrative review. Ageing Res. Rev. 75, 101556 <https://doi.org/10.1016/j.arr.2021.101556>.
- Abdelkader, N.F., Safar, M.M., Salem, H.A., 2016. Ursodeoxycholic acid ameliorates apoptotic cascade in the rotenone model of Parkinson's disease: modulation of mitochondrial perturbations. Mol. Neurobiol. 53, 810–817. <https://doi.org/10.1007/s12035-014-9043-8>.
- Afsheen, S., Rehman, A.S., Jamal, A., Khan, N., Parvez, S., 2024. Understanding role of pesticides in development of Parkinson's disease: insights from Drosophila and rodent models. Ageing Res. Rev. 98, 102340 <https://doi.org/10.1016/j.arr.2024.102340>.
- Aho, V.T.E., Houser, M.C., Pereira, P.A.B., Chang, J., Rudi, K., Paulin, L., Hertzberg, V., Auvinen, P., Tansey, M.G., Schepersjans, F., 2021. Relationships of gut microbiota, short-chain fatty acids, inflammation, and the gut barrier in Parkinson's disease. Mol. Neurodegener. 16, 1–14. <https://doi.org/10.1186/s13024-021-00427-6>.
- Aho, V.T.E., Pereira, P.A.B., Voutilainen, S., Paulin, L., Pekkonen, E., Auvinen, P., Schepersjans, F., 2019. Gut microbiota in Parkinson's disease: temporal stability and relations to disease progression. EBioMedicine 44, 691–707. <https://doi.org/10.1016/j.ebiom.2019.05.064>.
- Ahrens, A.P., Hyötyläinen, T., Petrone, J.R., Igelström, K., George, C.D., Garrett, T.J., Orešić, M., Triplett, E.W., Ludvigsson, J., 2024. Infant microbes and metabolites point to childhood neurodevelopmental disorders. Cell 187, 1853–1873.e15. <https://doi.org/10.1016/j.cell.2024.02.035>.
- Akhtar, A., Singh, S., Kaushik, R., Awasthi, R., Behl, T., 2024. Types of memory, dementia, Alzheimer's disease, and their various pathological cascades as targets for potential pharmacological drugs. Ageing Res. Rev. 96 <https://doi.org/10.1016/j.arr.2024.102289>.

- Albert, M.J., Mathan, V.I., Baker, S.J., 1980. Vitamin B12 synthesis by human small intestinal bacteria. *Nature*. <https://doi.org/10.1038/283781a0>.
- Albillos, S.M., Montero, O., Calvo, S., Solano-Vila, B., Trejo, J.M., Cubo, E., 2021. Plasma acyl-carnitines, bilirubin, tyramine and tetrahydro-21-deoxycortisol in Parkinson's disease and essential tremor. A case control biomarker study. *Park. Relat. Disord.* 91, 167–172. <https://doi.org/10.1016/j.parkreldis.2021.09.014>.
- Allison, A.C., 2001. The possible role of vitamin K deficiency in the pathogenesis of Alzheimer's disease and in augmenting brain damage associated with cardiovascular disease. *Med. Hypotheses* 57, 151–155. <https://doi.org/10.1054/mehy.2001.1307>.
- Anamnart, C., Kitjarak, R., 2021. Effects of vitamin B12, folate, and entacapone on homocysteine levels in levodopa-treated Parkinson's disease patients: a randomized controlled study. *J. Clin. Neurosci.* 88, 226–231. <https://doi.org/10.1016/j.jocn.2021.03.047>.
- Aquilani, R., Costa, A., Maestri, R., Ramusino, M.C., Perini, G., Boselli, M., Iadarola, P., Buonocore, D., Verri, M., Dossena, M., Boschi, F., 2022. Is the brain undernourished in Alzheimer's disease? *Nutrients* 14. <https://doi.org/10.3390/nu14091872>.
- Aquilani, R., Costa, A., Maestri, R., Ramusino, M.C., Pierobon, A., Dossena, M., Solerte, S.B., Condino, A.M., Torlaschi, V., Bini, P., Boselli, M., Ceroni, M., Buonocore, D., Boschi, F., Bruni, M., Verri, M., 2020. Mini nutritional assessment may identify a dual pattern of perturbed plasma amino acids in patients with Alzheimer's disease: a window to metabolic and physical rehabilitation? *Nutrients* 12, 1–18. <https://doi.org/10.3390/nu12061845>.
- Aydin, Suna, Ugur, K., Aydin, Suleyman, 2018. Could excessive production of tyramine by the microbiota be a reason for essential hypertension? *Biosci. Microbiota Food Heal.* 37, 77–78. <https://doi.org/10.12938/bmfh.18-010>.
- Backes, C., Martinez-Martinez, D., Cabreiro, F., 2021. *C. elegans*: a biosensor for host-microbe interactions. *Lab. Anim.* 50, 127–135. <https://doi.org/10.1038/s41684-021-00724-z>.
- Barandouzi, Z.A., Lee, J., del Carmen Rosas, M., Chen, J., Henderson, W.A., Starkweather, A.R., Cong, X.S., 2022. Associations of neurotransmitters and the gut microbiome with emotional distress in mixed type of irritable bowel syndrome. *Sci. Rep.* 12, 1–11. <https://doi.org/10.1038/s41598-022-05756-0>.
- Barichella, M., Severgnini, M., Cilia, R., Cassani, E., Bolliri, C., Caronni, S., Ferri, V., Cancello, R., Ceccarani, C., Faierman, S., Pinelli, G., De Bellis, G., Zecca, L., Cereda, E., Consolandi, C., Pezzoli, G., 2019. Unraveling gut microbiota in Parkinson's disease and atypical parkinsonism. *Mov. Disord.* 34, 396–405. <https://doi.org/10.1002/mds.27581>.
- Beaumont, W., 1835. Experiments and observations of the gastric juice and the physiology of digestion. *Med.-Chir. Rev.* 22, 49–69.
- Bedarf, J.R., Hildebrand, F., Coelho, L.P., Sunagawa, S., Bahram, M., Goeser, F., Bork, P., Wüllner, U., 2017. Functional implications of microbial and viral gut metagenome changes in early stage L-DOPA-naïve Parkinson's disease patients. *Genome Med.* 9, 1–13. <https://doi.org/10.1186/s13073-017-0428-y>.
- Bellono, N.W., Bayrer, J.R., Leitch, D.B., Castro, J., Zhang, C., O'Donnell, T.A., Brierley, S.M., Ingraham, H.A., Julius, D., 2017. Enterochromaffin cells are gut chemosensors that couple to sensory neural pathways. *Cell* 170, 185–198.e16. <https://doi.org/10.1016/j.cell.2017.05.034>.
- Bhat, A., Cox, R.L., Hendrickson, B.G., Das, N.K., Schaller, M.L., Tuckowski, A.M., Wang, E., Shah, Y.M., Leiser, S.F., 2024. A diet of oxidative stress-adapted bacteria improves stress resistance and lifespan in *C. elegans* via p38-MAPK. *Sci. Adv.* 10. <https://doi.org/10.1126/sciadv.adk8823>.
- Blacher, E., Bashirades, S., Shapiro, H., Rothschild, D., Mor, U., Dori-Bachash, M., Kleimeyer, C., Moresi, C., Harnik, Y., Zur, M., Zabari, M., Brik, R.B.Z., Kviatcovsky, D., Zmora, N., Cohen, Y., Bar, N., Levi, I., Amar, N., Mehlman, T., Brandis, A., Biton, I., Kuperman, Y., Tsoryot, M., Alfahel, L., Harmelin, A., Schwartz, M., Israelson, A., Arike, L., Johansson, M.E.V., Hansson, G.C., Gotkine, M., Segal, E., Elinav, E., 2019. Potential roles of gut microbiome and metabolites in modulating ALS in mice. *Nature* 572, 474–480. <https://doi.org/10.1038/s41586-019-1443-5>.
- Boddy, S.L., Giovannelli, I., Sassani, M., Cooper-Knock, J., Snyder, M.P., Segal, E., Elinav, E., Barker, L.A., Shaw, P.J., McDermott, C.J., 2021. The gut microbiome: a key player in the complexity of amyotrophic lateral sclerosis (ALS). *BMC Med.* 19, 1–14. <https://doi.org/10.1186/s12916-020-01885-3>.
- Bortolato, M., Chen, K., Shih, J.C., 2008. Monoamine oxidase inactivation: From pathophysiology to therapeutics. *Adv. Drug Deliv. Rev.* 60, 1527–1533. <https://doi.org/10.1016/j.addr.2008.06.002>.
- Braak, H., De Vos, R.A.I., Bohl, J., Del Tredici, K., 2006. Gastric α -synuclein immunoreactive inclusions in Meissner's and Auerbach's plexuses in cases staged for Parkinson's disease-related brain pathology. *Neurosci. Lett.* 396, 67–72. <https://doi.org/10.1016/j.neulet.2005.11.012>.
- Braak, H., Tredici, Del, Rüb, K., De Vos, U., Jansen Steur, R.A.I., Braak, E.N.H., 2003. Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiol. Aging* 24, 197–211. [https://doi.org/10.1016/S0197-4580\(02\)00065-9](https://doi.org/10.1016/S0197-4580(02)00065-9).
- Brakedal, B., Dölle, C., Riemer, F., Mai, Y., Nido, G.S., Skeie, G.O., Craven, A.R., Schwarzmüller, T., Brekke, N., Diab, J., Sverkeli, L., Skjeie, V., Varhaug, K., Tysnes, O.B., Peng, S., Haugavoll, K., Ziegler, M., Grüner, R., Eidelberg, D., Tzoulis, C., 2022. The NADPARK study: a randomized phase I trial of nicotinamide riboside supplementation in Parkinson's disease. *Cell Metab.* 34, 396–407.e6. <https://doi.org/10.1016/j.cmet.2022.02.001>.
- Brown, A.J., Goldsworthy, S.M., Barnes, A.A., Eilert, M.M., Tcheang, L., Daniels, D., Muir, A.I., Wigglesworth, M.J., Kinghorn, I., Fraser, N.J., Pike, N.B., Strum, J.C., Steplewski, K.M., Murdock, P.R., Holder, J.C., Marshall, F.H., Szekeres, P.G., Wilson, S., Ignar, D.M., Foord, S.M., Wise, A., Dowell, S.J., 2003. The orphan G protein-coupled receptors GPR41 and GPR43 are activated by propionate and other short chain carboxylic acids. *J. Biol. Chem.* 278, 11312–11319. <https://doi.org/10.1074/jbc.M211609200>.
- Camacho-Conde, J.A., Gonzalez-Bermudez, M. del R., Carretero-Rey, M., Khan, Z.U., 2022. Brain stimulation: a therapeutic approach for the treatment of neurological disorders. *CNS Neurosci. Ther.* 28, 5–18. <https://doi.org/10.1111/cns.13769>.
- Camacho, M., Macleod, A.D., Maple-Grödém, J., Evans, J.R., Breen, D.P., Cummins, G., Wijeyekoon, R.S., Greenland, J.C., Alves, G., Tysnes, O.B., Lawson, R.A., Barker, R.A., Williams-Gray, C.H., 2021. Early constipation predicts faster dementia onset in Parkinson's disease. *npj Park. Dis.* 7. <https://doi.org/10.1038/s41531-021-00191-w>.
- Campbell, A.S., Needham, B.D., Meyer, C.R., Tan, J., Conrad, M., Preston, G.M., Bolognani, F., Rao, S.G., Heussler, H., Griffith, R., Guastella, A.J., Janes, A.C., Frederick, B., Donabedian, D.H., Mazmanian, S.K., 2022. Safety and target engagement of an oral small-molecule sequestrant in adolescents with autism spectrum disorder: an open-label phase 1b/2a trial. *Nat. Med.* 28. <https://doi.org/10.1038/s41591-022-01683-9>.
- Cani, P.D., 2018. Human gut microbiome: hopes, threats and promises. *Gut*. <https://doi.org/10.1136/gutjnl-2018-316723>.
- Cani, P.D., Knauf, C., 2016. How gut microbes talk to organs: the role of endocrine and nervous routes. *Mol. Metab.* 5, 743–752. <https://doi.org/10.1016/j.molmet.2016.05.011>.
- Cattaneo, A., Cattane, N., Galluzzi, S., Provasi, S., Lopizzo, N., Festari, C., Ferrari, C., Guerra, U.P., Paghera, B., Muscio, C., Bianchetti, A., Volta, G.D., Turla, M., Cotelli, M.S., Gennuso, M., Prelli, A., Zanetti, O., Lussignoli, G., Mirabile, D., Bellandi, D., Gentile, S., Belotti, G., Villani, D., Harach, T., Belmont, T., Padovani, A., Boccardi, M., Frisoni, G.B., 2017. Association of brain amyloidosis with pro-inflammatory gut bacterial taxa and peripheral inflammation markers in cognitively impaired elderly. *Neurobiol. Aging* 49, 60–68. <https://doi.org/10.1016/j.neurobiolaging.2016.08.019>.
- Çelik, V.K., Çığdem, B., Kapancık, S., Kılıçgün, H., Bolayır, E., 2018. The importance of increased serum ornithine levels in the pathogenesis of Alzheimer and Parkinson's diseases. *Asian J. Res. Rep. Neurol.* 1, 1–8. <https://doi.org/10.9734/AJORRN/2018/42254>.
- Cerdó, T., Ruiz-Rodríguez, A., Acuña, I., Torres-Espínola, F.J., Menchén-Márquez, S., Gámiz, F., Gallo, M., Jehmlrich, N., Haange, S.B., von Bergen, M., Campoy, C., Suárez, A., 2023. Infant gut microbiota contributes to cognitive performance in mice. *Cell Host Microbe* 31, 1974–1988.e4. <https://doi.org/10.1016/j.chom.2023.11.004>.
- Cervantes-Barragan, L., Chai, J.N., Tianero, M.D., Di Luccia, B., Ahern, P.P., Merriman, J., Cortez, V.S., Caparon, M.G., Donia, M.S., Gilfillan, S., Celli, M., Gordon, J.I., Hsieh, C.S., Colonna, M., 2017. Lactobacillus reuteri induces gut intraepithelial CD4+CD8α+ T cells. *Science* 357 (80), 806–810. <https://doi.org/10.1126/science.aah5825>.
- Chai, M., Jiang, M., Vergnes, L., Fu, X., de Barros, S.C., Doan, N.B., Huang, W., Chu, J., Jiao, J., Herschman, H., Crooks, G.M., Reue, K., Huang, J., 2019. Stimulation of hair growth by small molecules that activate autophagy. *Cell Rep.* 27, 3413–3421. <https://doi.org/10.1016/j.celrep.2019.05.070> e3.
- Chang, K.H., Cheng, M.L., Tang, H.Y., Huang, C.Y., Wu, Y.R., Chen, C.M., 2018. Alterations of metabolic profile and kynurene metabolism in the plasma of Parkinson's disease. *Mol. Neurobiol.* 55, 6319–6328. <https://doi.org/10.1007/s12035-017-0845-3>.
- Chen, S.J., Chen, C.C., Liao, H.Y., Lin, Y.T., Wu, Y.W., Liou, J.M., Wu, M.S., Kuo, C.H., Lin, C.H., 2022. Association of fecal and plasma levels of short-chain fatty acids with gut microbiota and clinical severity in patients with Parkinson disease. *Neurology* 98, E848–E858. <https://doi.org/10.1212/WNL.00000000000013225>.
- Chuang, C.L., Demontis, F., 2021. Systemic manifestation and contribution of peripheral tissues to Huntington's disease pathogenesis. *Ageing Res. Rev.* 69, 101358. <https://doi.org/10.1016/j.arr.2021.101358>.
- Chun, H.S., Low, W.C., 2012. Ursodeoxycholic acid suppresses mitochondria-dependent programmed cell death induced by sodium nitroprusside in SH-SY5Y cells. *Toxicology* 292, 105–112. <https://doi.org/10.1016/j.tox.2011.11.020>.
- Chyan, Y.J., Poeggeler, B., Omar, R.A., Chain, D.G., Frangione, B., Ghiso, J., Pappolla, M.A., 1999. Potent neuroprotective properties against the Alzheimer β -amyloid by an endogenous melatonin-related indole structure, indole-3-propionic acid. *J. Biol. Chem.* 274, 21937–21942. <https://doi.org/10.1074/jbc.274.31.21937>.
- Cleynen, I., Vazeille, E., Artieda, M., Verspaget, H.W., Szczypiorska, M., Bringer, M.A., Lakatos, P.L., Seibold, P., Parnell, K., Weersma, R.K., Mahachie John, J.M., Morgan-Walsh, R., Staelens, D., Arijs, I., De Hertogh, G., Müller, S., Tordai, A., Hommes, D.W., Ahmad, T., Wijmenga, C., Pender, S., Rutgeerts, P., Van Steen, K., Lottaz, D., Vermeire, S., Darfeuille-Michaud, A., 2014. Genetic and microbial factors modulating the ubiquitin proteasome system in inflammatory bowel disease. *Gut* 63, 1265–1274. <https://doi.org/10.1136/gutjnl-2012-303205>.
- Colombo, A.V., Sadler, R.K., Llovera, G., Singh, V., Roth, S., Heindl, S., Monasor, L.S., Verhoeven, A., Peters, F., Parhizkar, S., Kamp, F., de Aguero, M.G., Macpherson, A.J., Winkler, E., Herms, J., Benakis, C., Dichgans, M., Steiner, H., Giera, M., Haass, C., Tahirovic, S., Liesz, A., 2021. Microbiota-derived short chain fatty acids modulate microglia and promote α β plaque deposition. *Elife* 10, 1–23. <https://doi.org/10.7554/ELIFE.59826>.
- Conway, J., A Duggal, N., 2021. Ageing of the gut microbiome: potential influences on immune senescence and inflammageing. *Ageing Res. Rev.* 68, 101323. <https://doi.org/10.1016/j.arr.2021.101323>.
- Cook, S.J., Jarrell, T.A., Brittin, C.A., Wang, Y., Bloniarz, A.E., Yakovlev, M.A., Nguyen, K.C.Q., Tang, L.T.H., Bayer, E.A., Duerr, J.S., Bülow, H.E., Hobert, O., Hall, D.H., Emmons, S.W., 2019. Whole-animal connectomes of both *Caenorhabditis elegans* sexes. *Nature* 571, 63–71. <https://doi.org/10.1038/s41586-019-1352-7>.
- Cooke, G., Behan, J., Costello, M., 2006. Newly identified vitamin K-producing bacteria isolated from the neonatal faecal flora. *Microb. Ecol. Health Dis.* 18, 133–138. <https://doi.org/10.1080/08910600601048894>.
- Corso, G., Cristofano, A., Sapere, N., La Marca, G., Angiolillo, A., Vitale, M., Fratangelo, R., Lombardi, T., Porcile, C., Intrieri, M., Di Costanzo, A., 2017. Serum

- amino acid profiles in normal subjects and in patients with or at risk of Alzheimer dementia. *Dement. Geriatr. Cogn. Dis. Extra* 7, 143–159. <https://doi.org/10.1159/000466688>.
- Cryan, J.F., O'riordan, K.J., Cowan, C.S.M., Sandhu, K.V., Bastiaanssen, T.F.S., Boehme, M., Codagnone, M.G., Cussotto, S., Fulling, C., Golubeva, A.V., Guzzetta, K.E., Jaggar, M., Long-Smith, C.M., Lyte, J.M., Martin, J.A., Molinero-Perez, A., Moloney, G., Morelli, E., Morillas, E., O'connor, R., Cruz-Pereira, J.S., Peterson, V.L., Rea, K., Ritz, N.L., Sherwin, E., Spichak, S., Teichman, E.M., van de Wouw, M., Ventura-Silva, A.P., Wallace-Fitzsimons, S.E., Hyland, N., Clarke, G., Dinan, T.G., 2019. The microbiota-gut-brain axis. *Physiol. Rev.* 99, 1877–2013. <https://doi.org/10.1152/physrev.00018.2018>.
- Cui, M., Jiang, Y., Zhao, Q., Zhu, Z., Liang, X., Zhang, K., Wu, W., Dong, Q., An, Y., Tang, H., Ding, D., Chen, X., 2020. Metabolomics and incident dementia in older Chinese adults: the Shanghai Aging Study. *Alzheimer's Dement.* 16, 779–788. <https://doi.org/10.1002/alz.12074>.
- Cui, Y., Liu, L., Dou, X., Wang, C., Zhang, W., Gao, K., Liu, J., Wang, H., 2017. Lactobacillus reuteri ZJ161 maintains intestinal integrity via regulating tight junction, autophagy and apoptosis in mice challenged with lipopolysaccharide. *Oncotarget* 8, 77489–77499. <https://doi.org/10.18632/oncotarget.20536>.
- D'Andrea, G., Pizzolato, G., Gucciaridi, A., Stocchero, M., Giordano, G., Baraldi, E., Leon, A., 2019. Different circulating trace amine profiles in de novo and treated Parkinson's disease patients. *Sci. Rep.* 9, 1–11. <https://doi.org/10.1038/s41598-019-42535-w>.
- Da Silva, F.L., Coelho Cerqueira, E., De Freitas, M.S., Gonçalves, D.L., Costa, L.T., Foilmer, C., 2013. Vitamins K interact with N-terminus α -synuclein and modulate the protein fibrillization in vitro. Exploring the interaction between quinones and α -synuclein. *Neurochem. Int.* 62, 103–112. <https://doi.org/10.1016/j.neuint.2012.10.001>.
- De Vadder, F., Kovatcheva-Datchary, P., Goncalves, D., Vinera, J., Zitoun, C., Duchamp, A., Bäckhed, F., Mithieux, G., 2014. Microbiota-generated metabolites promote metabolic benefits via gut-brain neural circuits. *Cell* 156, 84–96. <https://doi.org/10.1016/j.cell.2013.12.016>.
- Dhakal, S., Macreadie, I., 2020. Tyramine and amyloid beta 42: a toxic synergy. *Biomedicines* 8, 1–10. <https://doi.org/10.3390/BIOMEDICINES8060145>.
- Dodd, D., Spitzer, M.H., Van Treuren, W., Merrill, B.D., Hryckowian, A.J., Higginbottom, S.K., Le, A., Cowan, T.M., Nolan, G.P., Fischbach, M.A., Sonnenburg, J.L., 2017. A gut bacterial pathway metabolizes aromatic amino acids into nine circulating metabolites. *Nature* 551, 648–652. <https://doi.org/10.1038/nature24661>.
- Dong, B., Wu, R., 2020. Plasma homocysteine, folate and vitamin B12 levels in Parkinson's disease in China: a meta-analysis. *Clin. Neurol. Neurosurg.* 188, 105587. <https://doi.org/10.1016/j.clineuro.2019.105587>.
- Du, G., Dong, W., Yang, Q., Yu, X., Ma, J., Gu, W., Huang, Y., 2021. Altered gut microbiota related to inflammatory responses in patients with Huntington's disease. *Front. Immunol.* 11, 1–12. <https://doi.org/10.3389/fimmu.2020.60394>.
- Duan, J., Matute, J.D., Unger, L.W., Hanley, T., Schnell, A., Lin, X., Krupka, N., Griebel, P., Lambden, C., Sit, B., Grootjans, J., Pyzik, M., Sommer, F., Kaiser, S., Falk-Paulsen, M., Grasberger, H., Kao, J.Y., Fuhrer, T., Li, H., Paik, D., Lee, Y., Refetoff, S., Glickman, J.N., Paton, A.W., Bry, L., Paton, J.C., Sauer, U., Macpherson, A.J., Rosenstiel, P., Kuchroo, V.K., Walder, M.K., Huh, J.R., Kaser, A., Blumberg, R.S., 2023. Endoplasmic reticulum stress in the intestinal epithelium initiates purine metabolite synthesis and promotes Th17 cell differentiation in the gut. *Immunity* 56, 1115–1131.e9. <https://doi.org/10.1016/j.immu.2023.02.018>.
- Eisenberg, T., Schroeder, S., Andryushkova, A., Pendl, T., Küttner, V., Bhukel, A., Maríño, G., Pietrocasa, F., Harger, A., Zimmermann, A., Mustafa, T., Sprenger, A., Jany, E., Büttner, S., Carmona-Gutierrez, D., Ruckenstuhl, C., Ring, J., Reichelt, W., Schimmel, K., Leeb, T., Moser, C., Schatz, S., Kamolz, L.P., Magnes, C., Sinner, F., Sedej, S., Fröhlich, K.U., Juhasz, G., Pieber, T.R., Dengel, J., Sigrist, S.J., Kroemer, G., Madeo, F., 2014. Nucleocytosolic depletion of the energy metabolite acetyl-coenzyme A stimulates autophagy and prolongs lifespan. *Cell Metab.* 19, 431–444. <https://doi.org/10.1016/j.cmet.2014.02.010>.
- Engelovan, S., Borody, T.J., Hollinger, R.M.D., 2023. Fecal microbiota transplantation reduces pathology and improves cognition in a mouse model of Alzheimer's disease. *Cells* 12. <https://doi.org/10.3390/cells12010119>.
- Erny, D., Dokalis, N., Mező, C., Castoldi, A., Mossad, O., Staszewski, O., Frosch, M., Villa, M., Fuchs, V., Mayer, A., Neuber, J., Sosat, J., Tholen, S., Schilling, O., Vlachos, A., Blank, T., Gomez de Agüero, M., Macpherson, A.J., Pearce, E.J., Prinz, M., 2021. Microbiota-derived acetate enables the metabolic fitness of the brain innate immune system during health and disease. *Cell Metab.* 33, 2260–2276.e7. <https://doi.org/10.1016/j.cmet.2021.10.010>.
- Fabi, J.P., 2024. The connection between gut microbiota and its metabolites with neurodegenerative diseases in humans. *Metab. Brain Dis.* 39, 967–984. <https://doi.org/10.1007/s11011-024-01369-w>.
- Fang, X., Wang, Xin, Yang, S., Meng, F., Wang, Xiaolei, Wei, H., Chen, T., 2016. Evaluation of the microbial diversity in amyotrophic lateral sclerosis using high-throughput sequencing. *Front. Microbiol.* 7, 1–7. <https://doi.org/10.3389/fmicb.2016.01479>.
- Fasano, A., Visanji, N.P., Liu, L.W.C., Lang, A.E., Pfeiffer, R.F., 2015. Gastrointestinal dysfunction in Parkinson's disease. *Lancet Neurol.* [https://doi.org/10.1016/S1474-4422\(15\)00007-1](https://doi.org/10.1016/S1474-4422(15)00007-1).
- Fernández-Calvet, A., Matilla-Cuenca, L., Izco, M., Navarro, S., Serrano, M., Ventura, S., Blesa, J., Herráiz, M., Alkorta-Aranburu, G., Galera, S., Ruiz de los Mozos, I., Mansego, M.L., Toledo-Arana, A., Alvarez-Erviti, L., Valle, J., 2024. Gut microbiota produces biofilm-associated amyloids with potential for neurodegeneration. *Nat. Commun.* 15 <https://doi.org/10.1038/s41467-024-48309-x>.
- Fernández-Veledo, S., Vendrell, J., 2019. Gut microbiota-derived succinate: friend or foe in human metabolic diseases? *Rev. Endocr. Metab. Disord.* 20, 439–447. <https://doi.org/10.1007/s11154-019-09513-z>.
- Figura, M., Kuśmierska, K., Bucior, E., Szlufik, S., Koziorowski, D., Jamrozik, Z., Janik, P., 2018. Serum amino acid profile in patients with Parkinson's disease. *PLoS One* 13. <https://doi.org/10.1371/journal.pone.0191670>.
- Finsterer, J., Scorzà, C.A., de Almeida, A.C.G., Rodrigues, A.M., Scorzà, F.A., 2021. Parkinson's disease: research puts spotlight on thiamine deficiency and cardiovascular health. *J. Clin. Neurosci.* 93, 270–271. <https://doi.org/10.1016/j.jocn.2021.06.024>.
- Fischbach, M., 2020. Michael Fischbach investigates the effects of molecules produced by gut microbes. *Nature* 577. <https://doi.org/10.1038/d41586-020-00195-1>.
- Frakes, A.E., Dillin, A., 2017. The UPRE: sensor and coordinator of organismal homeostasis. *Mol. Cell* 66, 761–771. <https://doi.org/10.1016/j.molcel.2017.05.031>.
- Funabashi, M., Grove, T.L., Wang, M., Varma, Y., McFadden, M.E., Brown, L.C., Guo, C., Higginbottom, S., Almo, S.C., Fischbach, M.A., 2020. A metabolic pathway for bile acid dehydroxylation by the gut microbiome. *Nature* 582, 566–570. <https://doi.org/10.1038/s41586-020-2396-4>.
- Gainetdinov, R.R., Hoener, M.C., Berry, M.D., 2018. Trace amines and their receptors. *Pharm. Rev.* 70, 549–620. <https://doi.org/10.1124/pr.117.015305>.
- Gao, K., Mu, C.L., Farzi, A., Zhu, W.Y., 2020. Tryptophan metabolism: a link between the gut microbiota and brain. *Adv. Nutr.* 11, 709–723. <https://doi.org/10.1093/advances/nmz127>.
- Gątarek, P., Sekulska-Nalewajko, J., Bobrowska-Korczaka, B., Pawełczyk, M., Jastrzębski, K., Gąbiński, A., Kalińska-Czaplińska, J., 2022. Plasma metabolic disturbances in Parkinson's disease patients. *Biomedicines* 10, 1–17. <https://doi.org/10.3390/biomedicines1012305>.
- Ghosh, T.S., Shanahan, F., O'Toole, P.W., 2022. The gut microbiome as a modulator of healthy ageing. *Nat. Rev. Gastroenterol. Hepatol.* 19, 565–584. <https://doi.org/10.1038/s41575-022-00605-x>.
- Giil, L.M., Midtun, O., Refsum, H., Ulvik, A., Advani, R., Smith, A.D., Ueland, P.M., 2017. Kynurenone pathway metabolites in Alzheimer's disease. *J. Alzheimer's Dis.* 60, 495–504. <https://doi.org/10.3233/JAD-170485>.
- Glans, I., Sonestedt, E., Nägga, K., Gustavsson, A.M., González-Padilla, E., Borne, Y., Stomrud, E., Melander, O., Nilsson, P.M., Palmqvist, S., Hansson, O., 2023. Association between dietary habits in midlife with dementia incidence over a 20-year period. *Neurology* 100, E28–E37. <https://doi.org/10.1212/WNL.0000000000201336>.
- Gold, M., Hauser, R.A., Chen, M.F., 1998. Plasma thiamine deficiency associated with Alzheimer's disease but not Parkinson's disease. *Metab. Brain Dis.* 13, 43–53. <https://doi.org/10.1023/A:102067891230>.
- Gong, Y., Chen, A., Zhang, G., Shen, Q., Zou, L., Li, J., Miao, Y.-B., Liu, W., 2023. Cracking brain diseases from gut microbes-mediated metabolites for precise treatment. *Int. J. Biol. Sci.* 19, 2974–2998. <https://doi.org/10.7150/ijbs.85259>.
- González-Domínguez, R., García-Barrera, T., Gómez-Ariza, J.L., 2015. Metabolite profiling for the identification of altered metabolic pathways in Alzheimer's disease. *J. Pharm. Biomed. Anal.* 107, 75–81. <https://doi.org/10.1016/j.jpba.2014.10.010>.
- González-Sánchez, M., Jiménez, J., Narváez, A., Antequera, D., Llamas-Velasco, S., Martín, A.H.S., Arjona, J.A.M., Munain, A.L., de Bisa, A.L., Marco, M.P., Rodríguez-Núñez, M., Pérez-Martínez, D.A., Villarejo-Galende, A., Bartolome, F., Domínguez, E., Carro, E., 2020. Kynurenic acid levels are increased in the CSF of Alzheimer's disease patients. *Biomolecules* 10, 1–15. <https://doi.org/10.3390/biom10040571>.
- Gorecki, A.M., Preskey, L., Bakeberg, M.C., Kenna, J.E., Gildenhuys, C., MacDougall, G., Dunlop, S.A., Mastaglia, F.L., Akkari, Anthony, Koengten, P., Anderton, R.S., F., 2019. Altered gut microbiome in Parkinson's disease and the influence of lipopolysaccharide in a human α -synuclein over-expressing mouse model. *Front. Neurosci.* 13 <https://doi.org/10.3389/fnins.2019.00839>.
- Graham, S.F., Rey, N.L., Ugur, Z., Yilmaz, A., Sherman, E., Maddens, M., Bahado-Singh, R.O., Becker, K., Schulz, E., Meyerdirk, L.K., Steiner, J.A., Ma, J., Brundin, P., 2018. Metabolomic profiling of bile acids in an experimental model of prodromal parkinson's disease. *Metabolites* 8. <https://doi.org/10.3390/metabo8040071>.
- Gray, R., Patel, S., Ives, N., Rick, C., Woolley, R., Muzerengi, S., Gray, A., Jenkinson, C., McIntosh, E., Wheatley, K., Williams, A., Clarke, C.E., 2022. Long-term effectiveness of adjuvant treatment with catechol-O-methyltransferase or monoamine oxidase b inhibitors compared with dopamine agonists among patients with Parkinson disease uncontrolled by Levodopa therapy: the PD MED randomized clinical trial. *JAMA Neurol.* 79, 131–140. <https://doi.org/10.1001/jamaneurol.2021.4736>.
- Guillemin, G.J., 2012. Quinolinic acid, the inescapable neurotoxin. *FEBS J.* 279, 1356–1365. <https://doi.org/10.1111/j.1742-4658.2012.08485.x>.
- Häglin, L., Domellöf, M., Bäckman, L., Forsgren, L., 2020. Low plasma thiamine and phosphate in male patients with Parkinson's disease is associated with mild cognitive impairment. *Clin. Nutr. ESPEN* 37, 93–99. <https://doi.org/10.1016/j.clnesp.2020.03.012>.
- Han, B., Sivaramakrishnan, P., Lin, C.C.J., Neve, I.A.A., He, J., Tay, L.W.R., Sowa, J.N., Sizovs, A., Du, G., Wang, J., Herman, C., Wang, M.C., 2017. Microbial genetic composition tunes host longevity. *Cell* 169, 1249–1262. <https://doi.org/10.1016/j.cell.2017.05.036> (e13).
- Han, C., Ding, Z., Shi, H., Qian, W., Hou, X., Lin, R., 2016. The role of probiotics in lipopolysaccharide-induced autophagy in intestinal epithelial cells. *Cell. Physiol. Biochem.* 38, 2464–2478. <https://doi.org/10.1159/000445597>.
- Han, X., Holtzman, D.M., McKeel, D.W., Kelley, J., Morris, J.C., 2002. Substantial sulfatide deficiency and ceramide elevation in very early Alzheimer's disease: potential role in disease pathogenesis. *J. Neurochem.* 82, 809–818. <https://doi.org/10.1046/j.1471-4159.2002.00997.x>.

- Harris, H., Rubinsztein, D.C., 2012. Control of autophagy as a therapy for neurodegenerative disease. *Nat. Rev. Neurol.* 8, 108–117. <https://doi.org/10.1038/nrneurol.2011.200>.
- Hasegawa, S., Goto, S., Tsuji, H., Okuno, T., Asahara, T., Nomoto, K., Shibata, A., Fujisawa, Y., Minato, T., Okamoto, A., Ohno, K., Hirayama, M., 2015. Intestinal dysbiosis and lowered serum lipopolysaccharide-binding protein in Parkinson's disease. *PLoS One* 10, 1–15. <https://doi.org/10.1371/journal.pone.0142164>.
- Havelund, J.F., Andersen, A.D., Binzer, M., Blaabjerg, M., Heegaard, N.H.H., Stenager, E., Færgeman, N.J., Gramsbergen, J.B., 2017. Changes in kynureine pathway metabolism in Parkinson patients with L-DOPA-induced dyskinesia. *J. Neurochem.* 142, 756–766. <https://doi.org/10.1111/jnc.14104>.
- He, Z., Ma, Y., Yang, S., Zhang, S., Liu, S., Xiao, J., Wang, Y., Wang, W., Yang, H., Li, S., Cao, Z., 2022. Gut microbiota-derived ursodeoxycholic acid from neonatal dairy calves improves intestinal homeostasis and colitis to attenuate extended-spectrum β-lactamase-producing enterocaggregative *Escherichia coli* infection. *Microbiome* 10, 1–25. <https://doi.org/10.1186/s40168-022-01269-0>.
- Heilmann, P.L., Wang, E.W., Lewis, M.M., Krzyzanowski, S., Capan, C.D., Burmeister, A.R., Du, G., Escobar Galvis, M.L., Brundin, P., Huang, X., Brundin, L., 2020. Tryptophan metabolites are associated with symptoms and nigral pathology in Parkinson's disease. *Mov. Disord.* 35, 2028–2037. <https://doi.org/10.1002/mds.28202>.
- Heintz-Buschart, A., Pandey, U., Wicke, T., Sixel-Döring, F., Janzen, A., Sittig-Wiegand, E., Trenkwalder, C., Oertel, W.H., Mollenhauer, B., Wilmes, P., 2018. The nasal and gut microbiome in Parkinson's disease and idiopathic rapid eye movement sleep behavior disorder. *Mov. Disord.* 33, 88–98. <https://doi.org/10.1002/mds.27105>.
- Henjum, K., Watne, L.O., Godang, K., Halaas, N.B., Eldholm, R.S., Blennow, K., Zetterberg, H., Saltvedt, I., Bollerslev, J., Knapskog, A.B., 2022. Cerebrospinal fluid catecholamines in Alzheimer's disease patients with and without biological disease. *Transl. Psychiatry* 12, 1–9. <https://doi.org/10.1038/s41398-022-01901-5>.
- Hill-Burns, E.M., Debelius, J.W., Morton, J.T., Wissemann, W.T., Lewis, M.R., Wallen, Z.D., Peddada, S.D., Factor, S.A., Molho, E., Zabetian, C.P., Knight, R., Payami, H., 2017. Parkinson's disease and Parkinson's disease medications have distinct signatures of the gut microbiome. *Mov. Disord.* 32, 739–749. <https://doi.org/10.1002/mds.26942>.
- Hipp, M.S., Kasturi, P., Hartl, F.U., 2019. The proteostasis network and its decline in ageing. *Nat. Rev. Mol. Cell Biol.* 20, 421–435. <https://doi.org/10.1038/s41580-019-0101-y>.
- Hopfner, F., Künstner, A., Müller, S.H., Küntzel, S., Zeuner, K.E., Margraf, N.G., Deuschl, G., Baines, J.F., Kuhnenbäumer, G., 2017. Gut microbiota in Parkinson disease in a northern German cohort. *Brain Res.* 1667, 41–45. <https://doi.org/10.1016/j.brainres.2017.04.019>.
- Hou, Y., Lautrup, S., Cordonnier, S., Wang, Y., Croteau, D.L., Zavala, E., Zhang, Y., Moritoh, K., O'Connell, J.F., Baptiste, B.A., Stevensner, T.V., Mattson, M.P., Bohr, V.A., 2018. NAD⁺ supplementation normalizes key Alzheimer's features and DNA damage responses in a new AD mouse model with introduced DNA repair deficiency. *Proc. Natl. Acad. Sci. USA* 115, E1876–E1885. <https://doi.org/10.1073/pnas.1718819115>.
- Huy, P.D.Q., Yu, Y.C., Ngo, S.T., Thao, T.V., Chen, C.P., Li, M.S., Chen, Y.C., 2013. In silico and in vitro characterization of anti-amyloidogenic activity of vitamin K3 analogues for Alzheimer's disease. *Biochim. Biophys. Acta - Gen. Subj.* 1830, 2960–2969. <https://doi.org/10.1016/j.bbagen.2012.12.026>.
- International Institute for Population Sciences (IIPS), 2020. Longitudinal Ageing Study in India (LASI). An Investigation of Health, Economic, and Social Well-being of India's Growing Elderly Population. India Report.
- Iwaoka, K., Otsuka, C., Maeda, T., Yamahara, K., Kato, K., Takahashi, Kenta, Takahashi, Kai, Terayama, Y., 2020. Impaired metabolism of kynureine and its metabolites in CSF of parkinson's disease. *Neurosci. Lett.* 714, 134576. <https://doi.org/10.1016/j.neulet.2019.134576>.
- Jennings, D., Huntwork-Rodriguez, S., Henry, A.G., Sasaki, J.C., Meissner, R., Diaz, D., Solanoy, H., Wang, X., Negrou, E., Bondar, V.V., Ghosh, R., Maloney, M.T., Propson, N.E., Zhu, Y., Maciuca, R.D., Harris, L., Kay, A., LeWitt, P., King, T.A., Kern, D., Ellenbogen, A., Goodman, I., Siderowf, A., Aldred, J., Omidvar, O., Masoud, S.T., Davis, S.S., Arguello, A., Estrada, A.A., de Vicente, J., Sweeney, Z.K., Astarita, G., Borin, M.T., Wong, B.K., Wong, H., Nguyen, H., Scarce-Lievie, K., Ho, C., Troyer, M.D., 2022. Preclinical and clinical evaluation of the LRRK2 inhibitor DNL201 for Parkinson's disease. *Sci. Transl. Med.* 14, 1–18. <https://doi.org/10.1126/scitranslmed.abj2658>.
- Jiménez-Jiménez, F.J., Alonso-Navarro, H., García-Martín, E., Agúndez, J.A.G., 2020. Cerebrospinal and blood levels of amino acids as potential biomarkers for Parkinson's disease: review and meta-analysis. *Eur. J. Neurol.* 27, 2336–2347. <https://doi.org/10.1111/ene.14470>.
- Jiménez-Jiménez, F.J., Molina, J.A., Gómez, P., Vargas, C., De Bustos, F., Benito-León, J., Tallón-Barranco, A., Ortí-Pareja, M., Gasalla, T., Arenas, J., 1998. Neurotransmitter amino acids in cerebrospinal fluid of patients with Alzheimer's disease. *J. Neural Transm.* 105, 269–277. <https://doi.org/10.1007/s007020050056>.
- Jin, W., Pei, J., Rebecca, J., Jayaraman, S., Muthaiyan, R., Velliyur, G., Mironescu, M., Perumal, C., 2024. Comprehensive review on single-cell RNA sequencing: a new frontier in Alzheimer's disease research. *Ageing Res. Rev.* 100, 102454. <https://doi.org/10.1016/j.arr.2024.102454>.
- Kalecký, K., German, D.C., Montillo, A.A., Bottiglieri, T., 2022. Targeted metabolomic analysis in Alzheimer's disease plasma and brain tissue in non-hispanic whites. *J. Alzheimer's Dis.* 86, 1875–1895. <https://doi.org/10.3233/JAD-215448>.
- Kaur, H., Bose, C., Mande, S.S., 2019. Tryptophan metabolism by gut microbiome and gut-brain-axis: an in silico analysis. *Front. Neurosci.* 13, 1–17. <https://doi.org/10.3389/fnins.2019.01365>.
- Keshavarzian, A., Green, S.J., Engen, P.A., Voigt, R.M., Naqib, A., Forsyth, C.B., Mutlu, E., Shannon, K.M., 2015. Colonic bacterial composition in Parkinson's disease. *Mov. Disord.* 30, 1351–1360. <https://doi.org/10.1002/mds.26307>.
- Kim, C.H., Park, J., Kim, M., 2014. Gut microbiota-derived short-chain fatty acids, T cells, and inflammation. *Immune Netw.* 14, 277. <https://doi.org/10.4110/in.2014.14.6.277>.
- Kim, S., Kwon, S.H., Kam, T.I., Panicker, N., Karuppagounder, S.S., Lee, S., Lee, J.H., Kim, W.R., Kook, M., Foss, C.A., Shen, C., Lee, H., Kulkarni, S., Pasricha, P.J., Lee, G., Pomper, M.G., Dawson, V.L., Dawson, T.M., Ko, H.S., 2019. Transneuronal propagation of pathologic α-synuclein from the gut to the brain models Parkinson's disease. *Neuron* 103, 627–641. <https://doi.org/10.1016/j.neuron.2019.05.035> (e7).
- Kim, S., Sieburth, D., 2018. Sphingosine kinase regulates neuropeptide secretion during the oxidative stress-response through intertissue signaling. *J. Neurosci.* 38, 8160–8176. <https://doi.org/10.1523/JNEUROSCI.0536-18.2018>.
- Knudsen, K., Szwebs, M., Hansen, A.K., Borghammer, P., 2018. Gastric emptying in Parkinson's disease – a mini-review. *Park. Relat. Disord.* 55, 18–25. <https://doi.org/10.1016/j.parkreldis.2018.06.003>.
- Kolobaric, A., Andreescu, C., Jašarević, E., Hong, C.H., Roh, H.W., Cheong, J.Y., Kim, Y.K., Shin, T.S., Kang, C.S., Kwon, C.O., Yoon, S.Y., Hong, S.W., Aizenstein, H.J., Karim, H.T., Son, S.J., 2024. Gut microbiome predicts cognitive function and depressive symptoms in late life. *Mol. Psychiatry*. <https://doi.org/10.1038/s41380-024-02551-3>.
- Kondrikov, D., Elmansi, A., Shi, X., McGee-Lawrence, M., Fulzele, S., Hamrick, M., Isales, C., Hill, W., 2021. The kynureine pathway metabolites QA and KYNA induce senescence in bone marrow stem cells through the AhR pathway. *Innov. Aging* 5, 45–415. <https://doi.org/10.1093/geroni/igab046.171>.
- Kulkarni, A., Preeti, K., Tryphena, K.P., Srivastava, S., Singh, S.B., Khatri, D.K., 2023. Proteostasis in Parkinson's disease: recent development and possible implication in diagnosis and therapeutics. *Ageing Res. Rev.* 84, 101816. <https://doi.org/10.1016/j.arr.2022.101816>.
- Kumar, Adarsh M., Sevush, Steven, Kumar, Mahendra, Ruiz, Julio, E.C., 1995. Peripheral serotonin in Alzheimer's disease. *Neuropsychobiology* 32, 9–12. <https://doi.org/10.1159/000119205>.
- Labbadia, J., Morimoto, R.I., 2015. The biology of proteostasis in aging and disease. *Annu. Rev. Biochem.* 84, 435–464. <https://doi.org/10.1146/annurev-biochem-060614-033955>.
- Lee, J., Meijer, E., Langa, K.M., Ganguli, M., Varghese, M., Banerjee, J., Khobragade, P., Angrisani, M., Kurup, R., Chakrabarti, S.S., Gambhir, I.S., Koul, P.A., Goswami, D., Talukdar, A., Mohanty, R.R., Yadati, R.S., Padmaj, M., Sankhe, L., Rajguru, C., Gupta, M., Kumar, G., Dhar, M., Chatterjee, P., Singhal, S., Bansal, R., Bajpai, S., Desai, G., Rao, A.R., Sivakumar, P.T., Muliyala, K.P., Bhatnagar, S., Chattopadhyay, A., Govil, D., Pedgaonkar, S., Sekher, T.V., Bloom, D.E., Crimmins, E.M., Dey, A.B., 2023. Prevalence of dementia in India: national and state estimates from a nationwide study. *Alzheimer's Dement.* 2898–2912. <https://doi.org/10.1002/alz.12928>.
- Li, C., Cui, L., Yang, Y., Miao, J., Zhao, X., Zhang, J., Cui, G., Zhang, Y., 2019. Gut microbiota differs between parkinson's disease patients and healthy controls in northeast China. *Front. Mol. Neurosci.* 12, 1–13. <https://doi.org/10.3389/fnmol.2019.00171>.
- Li, F., Wang, P., Chen, Z., Sui, X., Xie, X., Zhang, J., 2019. Alteration of the fecal microbiota in North-Eastern Han Chinese population with sporadic Parkinson's disease. *Neurosci. Lett.* 707, 134297. <https://doi.org/10.1016/j.neulet.2019.134297>.
- Li, S., Zhao, L., Xiao, J., Guo, Y., Fu, R., Zhang, Y., Xu, S., 2023. The gut microbiome: an important role in neurodegenerative diseases and their therapeutic advances. *Mol. Cell. Biochem.* <https://doi.org/10.1007/s11010-023-04853-6>.
- Li, W., Wu, X., Hu, X., Wang, T., Liang, S., Duan, Y., Jin, F., Qin, B., 2017. Structural changes of gut microbiota in Parkinson's disease and its correlation with clinical features. *Sci. China Life Sci.* 60, 1223–1233. <https://doi.org/10.1007/s11427-016-9001-4>.
- Liang, J., Liu, B., Dong, X., Wang, Y., Cai, W., Zhang, N., Zhang, H., 2023. Decoding the role of gut microbiota in Alzheimer's pathogenesis and envisioning future therapeutic avenues. *Front. Neurosci.* 17, 1–17. <https://doi.org/10.3389/fnins.2023.1242254>.
- Lin, A., Zheng, W., He, Y., Tang, W., Wei, X., He, R., Huang, W., Su, Y., Huang, Y., Zhou, H., Xie, H., 2018. Gut microbiota in patients with Parkinson's disease in southern China. *Park. Relat. Disord.* 53, 82–88. <https://doi.org/10.1016/j.parkreldis.2018.05.007>.
- Lin, R., Jiang, Y., Zhao, X.Y., Guan, Y., Qian, W., Fu, X.C., Ren, H.Y., Hou, X.H., 2014. Four types of Bifidobacteria trigger autophagy response in intestinal epithelial cells. *J. Dig. Dis.* 15, 597–605. <https://doi.org/10.1111/1751-2980.12179>.
- Lin, S.Y., Lin, C.L., Wang, I.K., Lin, C.C., Lin, C.H., Hsu, W.H., Kao, C.H., 2018. Dementia and vagotomy in Taiwan: a population-based cohort study. *BMJ Open* 8, 1–7. <https://doi.org/10.1136/bmjopen-2017-019582>.
- Liska, D., Wolfe, Z., Norris, A., 2023. VISTA: visualizing the spatial transcriptome of the *C. elegans* nervous system. *David. BioRxiv.* <https://doi.org/10.1101/2023.04.28.538711>.
- Liu, B., Fang, F., Pedersen, N.L., Tillander, A., Ludvigsson, J.F., Ekbom, A., Svensson, P., Chen, H., Karin, W., 2017. Vagotomy and Parkinson disease A Swedish register-based matched-cohort study. *Neurology* 88, 1996–2002. <https://doi.org/10.1212/WNL.0000000000003961>.
- Liu, P., Wu, L., Peng, G., Han, Y., Tang, R., Ge, J., Zhang, L., Jia, L., Yue, S., Zhou, K., Li, L., Luo, B., Wang, B., 2019. Altered microbiomes distinguish Alzheimer's disease from amnestic mild cognitive impairment and health in a Chinese cohort. *Brain Behav. Immun.* 80, 633–643. <https://doi.org/10.1016/j.bbi.2019.05.008>.

- Liu, Y., Dai, M., 2020. Trimethylamine N-oxide generated by the gut microbiota is associated with vascular inflammation: new insights into atherosclerosis. *Mediat. Inflamm.* 2020 <https://doi.org/10.1155/2020/4634172>.
- Liu, Y., Hou, Y., Wang, G., Zheng, X., Hao, H., 2020. Gut microbial metabolites of aromatic amino acids as signals in host-microbe interplay. *Trends Endocrinol. Metab.* 31, 818–834. <https://doi.org/10.1016/j.tem.2020.02.012>.
- Lloréns-Rico, V., Simcock, J.A., Huys, G.R.B., Raes, J., 2022. Single-cell approaches in human microbiome research. *Cell* 185, 2725–2738. <https://doi.org/10.1016/j.cell.2022.06.040>.
- Lyon, L., 2018. “All disease begins in the gut”: was hippocrates right? *Brain* 141, 1–5. <https://doi.org/10.1093/brain/awy017>.
- Maheshwari, S., Singh, A., Ansari, V.A., Mahmood, T., Wasim, R., Akhtar, J., Verma, A., 2024. Navigating the dementia landscape: biomarkers and emerging therapies. *Ageing Res. Rev.* 94, 102193 <https://doi.org/10.1016/j.arr.2024.102193>.
- MahmoudianDehkordi, S., Arnold, M., Nho, K., Ahmad, S., Jia, W., Xie, G., Louie, G., Kueider-Paisley, A., Moseley, M.A., Thompson, J.W., St John Williams, L., Tenenbaum, J.D., Blach, C., Baillie, R., Han, X., Bhattacharyya, S., Toledo, J.B., Schafferer, S., Klein, S., Koal, T., Risacher, S.L., Kling, M.A., Motsinger-Reif, A., Rotroff, D.M., Jack, J., Hankemeier, T., Bennett, D.A., De Jager, P.L., Trojanowski, J.Q., Shaw, L.M., Weiner, M.W., Doraiswamy, P.M., van Duijn, C.M., Saykin, A.J., Kastenmüller, G., Kaddurah-Daouk, R., 2019. Altered bile acid profile associates with cognitive impairment in Alzheimer’s disease—an emerging role for gut microbiome. *Alzheimer’s Dement.* 15, 76–92. <https://doi.org/10.1016/j.jalz.2018.07.217>.
- Main, B.S., Minter, M.R., 2017. Microbial immuno-communication in neurodegenerative diseases. *Front. Neurosci.* 11, 1–8. <https://doi.org/10.3389/fnins.2017.00151>.
- Marizzoni, M., Cattaneo, A., Mirabelli, P., Festari, C., Lopizzo, N., Nicolosi, V., Mombelli, E., Mazzelli, M., Luongo, D., Naviglio, D., Coppola, L., Salvatore, M., Frisoni, G.B., 2020. Short-chain fatty acids and lipopolysaccharide as mediators between gut dysbiosis and amyloid pathology in Alzheimer’s disease. *J. Alzheimer’s Dis.* 78, 683–697. <https://doi.org/10.3233/JAD-200306>.
- Marksteiner, J., Blasko, I., Kemmler, G., Koal, T., Humpel, C., 2018. Bile acid quantification of 20 plasma metabolites identifies lithocholic acid as a putative biomarker in Alzheimer’s disease. *Metabolomics* 14, 1–10. <https://doi.org/10.1007/s11306-017-1297-5>.
- Martin, S., Battistini, C., Sun, J., 2022. A gut feeling in amyotrophic lateral sclerosis: microbiome of mice and men. *Front. Cell. Infect. Microbiol.* 12, 1–18. <https://doi.org/10.3389/fcimb.2022.839526>.
- Mayneris-Perxachs, J., Castells-Nobau, A., Arnriaga-Rodríguez, M., Martin, M., de la Vega-Correa, L., Zapata, C., Burokas, A., Blasco, G., Coll, C., Escribans, A., Biarnés, C., Moreno-Navarrete, J.M., Puig, J., Garre-Olmo, J., Ramos, R., Pedraza, S., Brugada, R., Vilanova, J.C., Serena, J., Gich, J., Ramíó-Torrentà, L., Pérez-Brocá, V., Moya, A., Pamplona, R., Sol, J., Jové, M., Ricart, W., Portero-Otín, M., Deco, G., Maldonado, R., Fernández-Real, J.M., 2022. Microbiota alterations in proline metabolism impact depression. *Cell Metab.* 34, 681–701.e10. <https://doi.org/10.1016/j.cmet.2022.04.001>.
- Meng, D., Ai, S., Spanos, M., Shi, X., Li, G., Cretoiu, D., Zhou, Q., Xiao, J., 2023. Exercise and microbiome: from big data to therapy. *Comput. Struct. Biotechnol. J.* 21, 5434–5445. <https://doi.org/10.1016/j.csbj.2023.10.034>.
- Metcalf, M.G., Monshtehadi, S., Sahay, A., Frakes, A.E., Durieux, J., Velichkovska, M., Mena, C., Farinas, A., Sanchez, M., Dillin, A., 2022. Cell non-autonomous control of autophagy and metabolism by glial cells 4. *BioRxiv*. <https://doi.org/10.1101/2022.12.15.520639>.
- Minnerly, J., Zhang, J., Parker, T., Kaul, T., Jia, K., 2017. The cell non-autonomous function of ATG-18 is essential for neuroendocrine regulation of *Caenorhabditis elegans* lifespan. *PLoS Genet.* 13, 1–23. <https://doi.org/10.1371/journal.pgen.1006764>.
- Miri, S., Yeo, J.D., Abubaker, S., Hammami, R., 2023. Neuromicrobiology, an emerging neurometabolic facet of the gut microbiome? *Front. Microbiol.* 14 <https://doi.org/10.3389/fmicb.2023.1098412>.
- Mittal, R., Debs, L.H., Patel, A.P., Nguyen, D., Patel, K., O’Connor, G., Grati, M., Mittal, J., Yan, D., Eshraghi, A.A., Deo, S.K., Daunert, S., Liu, X.Z., 2017. Neurotransmitters: the critical modulators regulating gut-brain axis. *J. Cell. Physiol.* 232, 2359–2372. <https://doi.org/10.1002/jcp.25518>.
- Moore, E., Mander, A., Ames, D., Carne, R., Sanders, K., Watters, D., 2012. Cognitive impairment and vitamin B12: a review. *Int. Psychogeriatr.* 24, 541–556. <https://doi.org/10.1017/S104610211002511>.
- Nakase, T., Tatewaki, Y., Thyreau, B., Mutoh, T., Tomita, N., Yamamoto, S., Takano, Y., Muranaka, M., Taki, Y., 2022. Impact of constipation on progression of Alzheimer’s disease: a retrospective study. *CNS Neurosci. Ther.* 28, 1964–1973. <https://doi.org/10.1111/cnts.13940>.
- Nargeh, H., Aliaabadi, F., Ajami, M., Pazoki-Toroudi, H., 2021. Role of polyphenols on gut microbiota and the ubiquitin-proteasome system in neurodegenerative diseases. *J. Agric. Food Chem.* 69, 6119–6144. <https://doi.org/10.1021/acs.jafc.1c00923>.
- Needham, B.D., Funabashi, M., Adame, M.D., Wang, Z., Boktor, J.C., Haney, J., Wu, W.-L., Rabut, C., Ladinsky, M.S., Hwang, S.-J., Guo, Y., Zhu, Q., Griffiths, J.A., Knight, R., Bjorkman, P.J., Shapiro, M.G., Geschwind, D.H., Holschneider, D.P., Fischbach, M.A., Mazmanian, S.K., 2022. A gut-derived metabolite alters brain activity and anxiety behaviour in mice. *Nature* 602. <https://doi.org/10.1038/s41586-022-04396-8>.
- Neish, A.S., Gewirtz, A.T., Zeng, H., Young, A.N., Hobert, M.E., Karmali, V., Rao, A.S., Madara, J.L., 2000. Prokaryotic regulation of epithelial responses by inhibition of IκB-α ubiquitination. *Science* 289 (80), 1560–1563. <https://doi.org/10.1126/science.289.5484.1560>.
- Nho, K., Kueider-Paisley, A., MahmoudianDehkordi, S., Arnold, M., Risacher, S.L., Louie, G., Blach, C., Baillie, R., Han, X., Kastenmüller, G., Jia, W., Xie, G., Ahmad, S., Hankemeier, T., van Duijn, C.M., Trojanowski, J.Q., Shaw, L.M., Weiner, M.W., Doraiswamy, P.M., Saykin, A.J., Kaddurah-Daouk, R., 2019. Altered bile acid profile in mild cognitive impairment and Alzheimer’s disease: relationship to neuroimaging and CSF biomarkers. *Alzheimer’s Dement.* 15, 232–244. <https://doi.org/10.1016/j.jalz.2018.08.012>.
- Nilchala, M., Bowyer, R.C.E., Moll, J.M., García, M.P., Wedge, S., Baleanu, A.F., Nessa, A., Sheedy, A., Akdag, G., Hart, D., Raffaele, G., Seed, P.T., Murphy, C., Harridge, S.D.R., Welch, A.A., Greig, C., Whelan, K., Steves, C.J., 2024. Effect of gut microbiome modulation on muscle function and cognition: the PROMOTE randomised controlled trial. *Nat. Commun.* 15 <https://doi.org/10.1038/s41467-024-1116-y>.
- Nicholson, K., Bjornevik, K., Abu-Ali, G., Chan, J., Cortese, M., Dedi, B., Jeon, M., Xavier, R., Huttenhower, C., Ascherio, A., Berry, J.D., 2021. The human gut microbiota in people with amyotrophic lateral sclerosis. *Amyotroph. Lateral Scler. Front. Degener.* 22, 186–194. <https://doi.org/10.1080/21678421.2020.1828475>.
- Nie, K., Li, Y., Zhang, J., Gao, Y., Qiu, Y., Gan, R., Zhang, Y., Wang, L., 2022. Distinct bile acid signature in Parkinson’s disease with mild cognitive impairment. *Front. Neurol.* 13, 1–7. <https://doi.org/10.3389/fneur.2022.897867>.
- Night, M., Al-Sadi, R., Guo, S., Rawat, M., Night, P., Watterson, M.D., Ma, T.Y., 2017. Lipopolysaccharide-induced increase in intestinal epithelial tight permeability is mediated by toll-like receptor 4/myeloid differentiation primary response 88 (MyD88) activation of myosin light chain kinase expression. *Am. J. Pathol.* <https://doi.org/10.1016/j.ajpath.2017.08.005>.
- Obeid, R., McCaddon, A., Herrmann, W., 2007. The role of hyperhomocysteineemia and B-vitamin deficiency in neurological and psychiatric diseases. *Clin. Chem. Lab. Med.* 45, 1590–1606. <https://doi.org/10.1515/CCLM.2007.356>.
- Ortiz de Ora, L., Bess, E.N., 2021. Emergence of *Caenorhabditis elegans* as a model organism for dissecting the gut-brain axis. *mSystems* 6, 1–5. <https://doi.org/10.1128/mSystems.00755-21>.
- Otaru, N., Ye, K., Mujezinovic, D., Berchtold, L., Constancias, F., Cornejo, F.A., Krzystek, A., de Wouters, T., Braegger, C., Lacroix, C., Pugin, B., 2021. GABA production by human intestinal *Bacteroides* spp.: prevalence, regulation, and role in acid stress tolerance. *Front. Microbiol.* 12 <https://doi.org/10.3389/fmicb.2021.656895>.
- OXenkrug, G., Hart, M., Van Der Roeser, J., Summergrad, P., Laboratories, R., Francisco, S.S., 2017. Peripheral Tryptophan – kynurenone metabolism associated with metabolic syndrome is different in Parkinson’s and Alzheimer’s diseases. *Endocrinol. Diabet. Metab. J.*, vol. 1, pp. 1–10. <https://doi.org/10.31038/edmj.2017141>.
- Paiva, I., Pinho, R., Pavlou, M.A., Hennion, M., Wales, P., Schütz, A.L., Rajput, A., Szego, É.M., Kerimoglu, C., Gerhardt, E., Rego, A.C., Fischer, A., Bonn, S., Outeiro, T.F., 2017. Sodium butyrate rescues dopaminergic cells from alpha-synuclein-induced transcriptional deregulation and DNA damage. *Hum. Mol. Genet.* 26, 2231–2246. <https://doi.org/10.1093/hmg/ddx114>.
- Pan, X., Fei, G., Lu, J., Jin, L., Pan, S., Chen, Z., Wang, C., Sang, S., Liu, H., Hu, W., Zhang, H., Wang, H., Wang, Z., Tan, Q., Qin, Y., Zhang, Q., Xie, X., Ji, Y., Cui, D., Gu, X., Xu, J., Yu, Y., Zhong, C., 2016. Measurement of blood thiamine metabolites for Alzheimer’s disease diagnosis. *EBioMedicine* 3, 155–162. <https://doi.org/10.1016/j.ebiom.2015.11.039>.
- Papuc, E., Rejdak, K., 2020. The role of myelin damage in Alzheimer’s disease pathology. *Arch. Med. Sci.* 16, 345–351. <https://doi.org/10.5114/aoms.2018.76863>.
- Park, S.H., Lee, J.H., Kim, J.S., Kim, T.J., Shin, J., Im, J.H., Cha, B., Lee, S., Kwon, K.S., Shin, Y.W., Ko, S.B., Choi, S.H., 2022. Fecal microbiota transplantation can improve cognition in patients with cognitive decline and Clostridioides difficile infection. *Aging* 14, 6449–6466. <https://doi.org/10.18632/aging.204230>.
- Parker, A., Fonseca, S., Carding, S.R., 2020. Gut microbes and metabolites as modulators of blood-brain barrier integrity and brain health. *Gut Microbes* 11, 135–157. <https://doi.org/10.1080/19490976.2019.1638722>.
- Parkinson, J., 2002. An essay on the shaking palsy. *J. Neuropsychiatry Clin. Neurosci.* <https://doi.org/10.1176/jnp.14.2.223>.
- Petrof, E.O., Kojima, K., Ropeleski, M.J., Musch, M.W., Tao, Y., De Simone, C., Chang, E.B., 2004. Probiotics inhibit nuclear factor-κB and induce heat shock proteins in colonic epithelial cells through proteasome inhibition. *Gastroenterology* 127, 1474–1487. <https://doi.org/10.1053/j.gastro.2004.09.001>.
- Philip Mani, A., Balasubramanian, B., Mali, L.A., Joseph, K.S., Meyyazhagan, A., Pappuswamy, M., Joseph, B.V., 2024. The role of the gut microbiota in neurodegenerative diseases. *Microbiol. Res.* 15, 489–507. <https://doi.org/10.3390/microbiolres15020033>.
- Pietracci, D., Cerroni, R., Unida, V., Farcomeni, A., Pierantozzi, M., Mercuri, N.B., Biocca, S., Stefani, A., Desideri, A., 2019. Dysbiosis of gut microbiota in a selected population of Parkinson’s patients. *Park. Relat. Disord.* 65, 124–130. <https://doi.org/10.1016/j.parkreldis.2019.06.003>.
- Pillet, L.E., Taccolla, C., Cotoni, J., Thiriez, H., André, K., Verpillot, R., 2020. Correlation between cognition and plasma noradrenaline level in Alzheimer’s disease: a potential new blood marker of disease evolution. *Transl. Psychiatry* 10. <https://doi.org/10.1038/s41398-020-0841-7>.
- Politis, M., Niccolini, F., 2015. Serotonin in Parkinson’s disease. *Behav. Brain Res.* 277, 136–145. <https://doi.org/10.1016/j.bbr.2014.07.037>.
- Pruss, K.M., Chen, H., Liu, Y., Van Treuren, W., Higginbottom, S.K., Jarman, J.B., Fischer, C.R., Mak, J., Wong, B., Cowan, T.M., Fischbach, M.A., Sonnenburg, J.L., Dodd, D., 2023. Host-microbe co-metabolism via MCAD generates circulating metabolites including hippuric acid. *Nat. Commun.* 14, 1–12. <https://doi.org/10.1038/s41467-023-36138-3>.
- Qi, H., Li, Y., Yun, H., Zhang, T., Huang, Y., Zhou, J., Yan, H., Wei, J., Liu, Y., Zhang, Z., Gao, Y., Che, Y., Su, X., Zhu, D., Zhang, Y., Zhong, J., Yang, R., 2019. Lactobacillus maintains healthy gut mucosa by producing L-Ornithine. *Commun. Biol.* 2 <https://doi.org/10.1038/s42003-019-0424-4>.

- Qi, Q., Zhang, H., Jin, Z., Wang, C., Xia, M., Chen, B., Lv, B., Peres Diaz, L., Li, X., Feng, R., Qiu, M., Li, Y., Meseguer, D., Zheng, X., Wang, W., Song, W., Huang, H., Wu, H., Chen, L., Schneeberger, M., Yu, X., 2024. Hydrogen sulfide produced by the gut microbiota impairs host metabolism via reducing GLP-1 levels in male mice. *Nat. Metab.* 1–15. <https://doi.org/10.1038/s42255-024-01068-x>.
- Qian, Y., Yang, X., Xu, S., Wu, C., Song, Y., Qin, N., Chen, S.D., Xiao, Q., 2018. Alteration of the fecal microbiota in Chinese patients with Parkinson's disease. *Brain Behav. Immun.* 70, 194–202. <https://doi.org/10.1016/j.bbi.2018.02.016>.
- Qiao, C.M., Sun, M.F., Jia, X.B., Li, Y., Zhang, B.P., Zhao, L.P., Shi, Y., Zhou, Z.L., Zhu, Y., Cui, C., Shen, Y.Q., 2020. Sodium butyrate exacerbates Parkinson's disease by aggravating neuroinflammation and colonic inflammation in MPTP-induced mice model. *Neurochem. Res.* 45, 2128–2142. <https://doi.org/10.1007/s11064-020-03074-3>.
- Quan, W., Qiao, C.M., Niu, G.Y., Wu, J., Zhao, L.P., Cui, C., Zhao, W.J., Shen, Y.Q., 2023. Trimethylamine-N-oxide exacerbates neuroinflammation and motor dysfunction in an acute MPTP mice model of Parkinson's disease. *Brain Sci.* 13 <https://doi.org/10.3390/brainsci13050790>.
- Rani, N., Alam, M.M., Jamal, A., Bin Ghaffar, U., Parvez, S., 2023. Caenorhabditis elegans: a transgenic model for studying age-associated neurodegenerative diseases. *Ageing Res. Rev.* 91, 102036 <https://doi.org/10.1016/j.arr.2023.102036>.
- Rao, M., Gershon, M.D., 2016. The bowel and beyond: the enteric nervous system in neurological disorders. *Nat. Rev. Gastroenterol. Hepatol.* 13, 517–528. <https://doi.org/10.1038/nrgastro.2016.107>.
- Ray Dorsey, E., Elbaz, A., Nichols, E., Abd-Allah, F., Abdelalim, A., Adsuar, J.C., Ansha, M.G., Brayne, C., Choi, J.Y.J., Collado-Mateo, D., Dahodwala, N., Do, H.P., Edessa, D., Endres, M., Fereshtehnejad, S.M., Foreman, K.J., Gankpe, F.G., Gupta, R., Hanky, G.J., Hay, S.I., Hegazy, M.I., Hibst, D.T., Kaseian, A., Khader, Y., Khalil, I., Khang, Y.H., Kim, Y.J., Kokubo, Y., Logroscino, G., Massano, J., Ibrahim, N.M., Mohammed, M.A., Mohammadi, A., Moradi-Lakeh, M., Naghavi, M., Nguyen, B.T., Niray, Y.L., Ogbo, F.A., Owolabi, M.O., Pereira, D.M., Postma, M.J., Qorbani, M., Rahman, M.A., Roba, K.T., Safari, H., Safiri, S., Satpathy, M., Sawhney, M., Shafeeetab, A., Shiferaw, M.S., Smith, M., Szoek, C.E.I., Tabarés-Seisdedos, R., Truong, N.T., Ukwaja, K.N., Venketasubramanian, N., Villafaina, S., Weldegeworgs, K.G., Westerman, R., Wijeratne, T., Winkler, A.S., Xuan, B.T., Yonemoto, N., Feigin, V.L., Vos, T., Murray, C.J.L., 2018. Global, regional, and national burden of Parkinson's disease, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol.* 17, 939–953. [https://doi.org/10.1016/S1474-4422\(18\)30295-3](https://doi.org/10.1016/S1474-4422(18)30295-3).
- Refsum, H., Smith, A.D., 2003. Low vitamin B-12 status in confirmed Alzheimer's disease as revealed by serum holotranscobalamin. *J. Neurol. Neurosurg. Psychiatry* 74, 959–961. <https://doi.org/10.1136/jnnp.74.7.959>.
- Richard, P., Kozlowski, L., Guillot, H., Garnier, P., McKnight, N.C., Danchin, A., Manière, X., 2021. Queuine, a bacterial-derived hypermodified nucleobase, shows protection in vitro models of neurodegeneration. *PLoS One* 16, 1–19. <https://doi.org/10.1371/journal.pone.0253216>.
- Riederer, F., 2022. Lecanemab in early Alzheimer's disease. *N. Engl. J. Med.* 388, 9–21. <https://doi.org/10.1056/nejmoa2212948>.
- Rosa, A.I., Duarte-Silva, S., Silva-Fernandes, A., Nunes, M.J., Carvalho, A.N., Rodrigues, E., Gama, M.J., Rodrigues, C.M.P., Maciel, P., Castro-Caldas, M., 2018. Tauroursodeoxycholic acid improves motor symptoms in a mouse model of Parkinson's disease. *Mol. Neurobiol.* 55, 9139–9155. <https://doi.org/10.1007/s12035-018-1062-4>.
- Rossi, M., Amaretti, A., Raimondi, S., 2011. Folate production by probiotic bacteria. *Nutrients* 3, 118–134. <https://doi.org/10.3390/nu3010118>.
- Rothhammer, V., Borucki, D.M., Tjon, E.C., Takenaka, M.C., Fabregat, A.A., Lima, K.A., De, Vazquez, C.G., Staszewski, O., Blain, M., Healy, L., Neziraj, T., Borio, M., Wheeler, M., Dragan, L.L., Laplaud, D.A., Antel, J., Alvarez, J.I., Prinz, M., Quintana, F.J., 2019. Microglial control of astrocytes in response to microbial metabolites, Microglial. vol. 557, pp. 724–8. <https://doi.org/10.1038/s41586-018-0119-x>.
- Rowin, J., Xia, Y., Jung, B., Sun, J., 2017. Gut inflammation and dysbiosis in human motor neuron disease. *Physiol. Rep.* 5, 1–6. <https://doi.org/10.1481/phy.123443>.
- Rusmini, P., Cortese, K., Crippa, V., Cristofani, R., Cicardi, M.E., Ferrari, V., Vezzoli, G., Tedesco, B., Meroni, M., Messi, E., Piccicella, M., Galbiati, M., Garré, M., Morelli, E., Vaccari, T., Poletti, A., 2019. Trehalose induces autophagy via lysosomal-mediated TFEB activation in models of motoneuron degeneration. *Autophagy* 15, 631–651. <https://doi.org/10.1080/15548627.2018.1535292>.
- Saito, Y., Sato, T., Nomoto, K., Tsuji, H., 2018. Identification of phenol- and p-cresol-producing intestinal bacteria by using media supplemented with tyrosine and its metabolites. *FEMS Microbiol. Ecol.* 94, 1–11. <https://doi.org/10.1093/femsec/fiy125>.
- Sampson, T.R., Debelius, J.W., Thron, T., Janssen, S., Shastri, G.G., Ilhan, Z.E., Challis, C., Schretter, C.E., Rocha, S., Grdinaru, V., Chesselet, M.F., Keshavarzian, A., Shannon, K.M., Krajmalnik-Brown, R., Wittung-Stafshede, P., Knight, R., Mazmanian, S.K., 2016. Gut microbiota regulate motor deficits and neuroinflammation in a model of Parkinson's disease. *Cell* 167, 1469–1480.e12. <https://doi.org/10.1016/j.cell.2016.11.018>.
- Sanchez-Mirasierra, I., Ghimire, S., Hernandez-Diaz, S., Soukup, S.F., 2022. Targeting macroautophagy as a therapeutic opportunity to treat Parkinson's disease. *Front. Cell Dev. Biol.* 10, 1–12. <https://doi.org/10.3389/fcell.2022.921314>.
- Sarkar, A., Nazir, A., 2022. Carrying excess baggage can slowdown life: protein clearance machineries that go awry during aging and the relevance of maintaining them. *Mol. Neurobiol.* 59, 821–840. <https://doi.org/10.1007/s12035-021-02640-2>.
- Scheperjans, F., Aho, V., Pereira, P.A.B., Koskinen, K., Paulin, L., Pekkonen, E., Haapaniemi, E., Kaakkola, S., Eerola-Rautio, J., Pohja, M., Kinnunen, E., Murros, K., Avuinen, P., 2015. Gut microbiota are related to Parkinson's disease and clinical phenotype. *Mov. Disord.* 30, 350–358. <https://doi.org/10.1002/mds.26069>.
- Schiess, N., Cataldi, R., Okun, M.S., Fothergill-Misbah, N., Dorsey, E.R., Bloem, B.R., Barreto, M., Bhidayasiri, R., Brown, R., Chishimba, L., Chowdhary, N., Coslov, M., Cubo, E., Di Rocca, A., Dolhun, R., Dowrick, C., Fung, V.S.C., Gershman, O.S., Gifford, L., Gordon, J., Khalil, H., Kühn, A.A., Lew, S., Lim, S.Y., Marano, M.M., Micalef, J., Mokaya, J., Moukheiber, E., Nwabuobi, L., Okubadejo, N., Pal, P.K., Shah, H., Shalash, A., Sherer, T., Siddiqui, B., Thompson, T., Ullrich, A., Walker, R., Dua, T., 2022. Six action steps to address global disparities in Parkinson disease: a World Health Organization priority. *JAMA Neurol.* 79, 929–936. <https://doi.org/10.1001/jamaneurol.2022.1783>.
- Schmit, K.J., Garcia, P., Sciotino, A., Aho, V.T.E., Pardo Rodriguez, B., Thomas, M.H., Gérardy, J.J., Bastero Acha, I., Halder, R., Cialini, C., Heurtaux, T., Ostahi, I., Busi, S., B., Grandmougin, L., Lowndes, T., Singh, Y., Martens, E.C., Mittelbronn, M., Buttini, M., Wilmes, P., 2023. Fiber deprivation and microbiome-borne curli shift gut bacterial populations and accelerate disease in a mouse model of Parkinson's disease. *Cell Rep.* 42 <https://doi.org/10.1016/j.celrep.2023.113071>.
- Scott, G.D., Lim, M.M., Drake, M.G., Woltjer, R., Quinn, J.F., 2021. Onset of skin, gut, and genitourinary prodromal Parkinson's disease: a study of 1.5 million veterans. *Mov. Disord.* 36, 2094–2103. <https://doi.org/10.1002/mds.28636>.
- Sealy, L., Chalkley, R., 1978. The effect of sodium butyrate on histone modification. *Cell* 14, 115–121. [https://doi.org/10.1016/0092-8674\(78\)90306-9](https://doi.org/10.1016/0092-8674(78)90306-9).
- Seo, D., oh, Holtzman, D.M., 2024. Current understanding of the Alzheimer's disease-associated microbiome and therapeutic strategies. *Exp. Mol. Med.* 56, 86–94. <https://doi.org/10.1038/s12276-023-01146-2>.
- Serger, E., Luengo-Gutierrez, L., Chadwick, J.S., Kong, G., Zhou, L., Crawford, G., Danzi, M.C., Myridakis, A., Brandis, A., Bello, A.T., Müller, F., Sanchez-Vassopoulos, A., De Virgiliis, F., Liddell, P., Dumas, M.E., Strid, J., Mani, S., Dodd, D., Di Giovanni, S., 2022. The gut metabolite indole-3 propionate promotes nerve regeneration and repair. *Nature* 607, 585–592. <https://doi.org/10.1038/s41586-022-04884-x>.
- Shao, Y., Gao, Z., Marks, P.A., Jiang, X., 2004. Apoptotic and autophagic cell death induced by histone deacetylase inhibitors. *Proc. Natl. Acad. Sci. USA* 101, 18030–18035. <https://doi.org/10.1073/pnas.0408345102>.
- Shao, Y., Li, T., Liu, Z., Wang, X., Xu, X., Li, S., Xu, G., Le, W., 2021. Comprehensive metabolic profiling of Parkinson's disease by liquid chromatography-mass spectrometry. *Mol. Neurodegener.* 16, 1–15. <https://doi.org/10.1186/s13024-021-00425-8>.
- Sharma, G., Biswas, S.S., Mishra, J., Navik, U., Kandimalla, R., Reddy, P.H., Bhatti, G.K., Bhatti, J.S., 2023. Gut microbiota dysbiosis and Huntington's disease: exploring the gut-brain axis and novel microbiota-based interventions. *Life Sci.* 328, 121882 <https://doi.org/10.1016/j.lfs.2023.121882>.
- Shen, K., Durieux, J., Mena, C.G., Webster, B.M., Tsui, C.K., Zhang, H., Joe, L., Berendzen, K.M., Dillin, A., 2024. The germline coordinates mitokine signaling. *Cell* 1–16. <https://doi.org/10.1016/j.cell.2024.06.010>.
- Shen, L., 2015. Associations between B vitamins and Parkinson's disease. *Nutrients* 7, 7197–7208. <https://doi.org/10.3390/nu7095333>.
- Shin, M.G., Lee, J.W., Han, J.S., Lee, B., Jeong, J.H., Park, S.H., Kim, J.H., Jang, S., Park, M., Kim, S.Y., Kim, S., Yang, Y.R., Kim, J.Y., Hoe, K.L., Park, C., Lee, K.P., Kwon, K.S., Kwon, E.S., 2020. Bacteria-derived metabolite, methylglyoxal, modulates the longevity of *C. elegans* through TORC2/SGK-1/ DAF-16 signaling. *Proc. Natl. Acad. Sci. USA* 117, 17142–17150. <https://doi.org/10.1073/pnas.1915719117>.
- Shou, J.W., Shaw, P.C., 2023. Berberine activates PPARδ and promotes gut microbiota-derived butyric acid to suppress hepatocellular carcinoma. *Phytomedicine* 115, 154842. <https://doi.org/10.1016/j.phymed.2023.154842>.
- Shum, A., Zaichick, S., McElroy, G.S., D'Alessandro, K., 2023. Octopamine metabolically reprograms astrocytes to confer neuroprotection against α-synuclein. *Proc. Natl. Acad. Sci.* 120, 1–10. <https://doi.org/10.1073/pnas.2217396120>.
- Sinha, R.A., Singh, B.K., Yen, P.M., 2017. Reciprocal crosstalk between autophagic and endocrine signaling in metabolite homeostasis. *Endocr. Rev.* 38, 69–102. <https://doi.org/10.1210/er.2016-1103>.
- Sorgdrager, F.J.H., Vermeiren, Y., Van Faassen, M., van der Ley, C., Nollen, E.A.A., Kema, I.P., De Deyn, P.P., 2019. Age- and disease-specific changes of the kynurenone pathway in Parkinson's and Alzheimer's disease. *J. Neurochem.* 151, 656–668. <https://doi.org/10.1111/jnc.14843>.
- Strandwitz, P., Kim, K.H., Terekhova, D., Liu, J.K., Sharma, A., Levering, J., McDonald, D., Dietrich, D., Ramadhar, T.R., Lekbua, A., Mroue, N., Liston, C., Stewart, E.J., Dubin, M.J., Zengler, K., Knight, R., Gilbert, J.A., Clardy, J., Lewis, K., 2019. GABA-modulating bacteria of the human gut microbiota. *Nat. Microbiol.* 4, 396–403. <https://doi.org/10.1038/s41564-018-0307-3>.
- Su, A., Gandhi, R., Barlow, C., Triadafilopoulos, G., 2017. Utility of the wireless motility capsule and lactulose breath testing in the evaluation of patients with Parkinson's disease who present with functional gastrointestinal symptoms. *BMJ Open Gastroenterol.* 4, 1–7. <https://doi.org/10.1136/bmjgast-2017-000132>.
- Sun, C.Y., Li, J.R., Wang, Y.Y., Lin, S.Y., Ou, Y.C., Lin, C.J., Wang, J.Der, Liao, S.L., Chen, C.J., 2020. P-cresol sulfate caused behavior disorders and neurodegeneration in mice with unilateral nephrectomy involving oxidative stress and neuroinflammation. *Int. J. Mol. Sci.* 21, 1–16. <https://doi.org/10.3390/ijms21186687>.
- Sun, M.F., Shen, Y.Q., 2018. Dysbiosis of gut microbiota and microbial metabolites in Parkinson's Disease. *Ageing Res. Rev.* 45, 53–61. <https://doi.org/10.1016/j.arr.2018.04.004>.
- Sun, Y., Zhang, H., Zhang, X., Wang, W., Chen, Y., Cai, Z., Wang, Q., Wang, J., Shi, Y., 2023. Promotion of astrocyte-neuron glutamate-glutamine shuttle by SCFA contributes to the alleviation of Alzheimer's disease. *Redox Biol.* 62, 102690 <https://doi.org/10.1016/j.redox.2023.102690>.

- Svensson, E., Horváth-Puhó, E., Thomsen, R.W., Djurhuus, J.C., Pedersen, L., Borghammer, P., Sorensen, H.T., 2015. Vagotomy and subsequent risk of Parkinson's disease. *Ann. Neurol.* 78, 522–529. <https://doi.org/10.1002/ana.24448>.
- Szabó, N., Kincses, Z.T., Toldi, J., Vécsai, L., 2011. Altered tryptophan metabolism in Parkinson's disease: a possible novel therapeutic approach. *J. Neurol. Sci.* 310, 256–260. <https://doi.org/10.1016/j.jns.2011.07.021>.
- Tan, A.H., Lim, S.Y., Lang, A.E., 2022. The microbiome–gut–brain axis in Parkinson disease — from basic research to the clinic. *Nat. Rev. Neurol.* 18, 476–495. <https://doi.org/10.1038/s41582-022-00681-2>.
- Teng, Y., Mu, J., Xu, F., Yan, J., Merchant, M.L., 2022. Article Gut bacterial isoamylamine promotes age-related cognitive dysfunction by promoting microglial cell death Article Gut bacterial isoamylamine promotes age-related cognitive dysfunction by promoting microglial cell death. *Cell Host Microbe* 1–17. <https://doi.org/10.1016/j.chom.2022.05.005>.
- Thangaraju, M., Cresci, G.A., Liu, K., Ananth, S., Gnanaprakasam, J.P., Browning, D.D., Mellinger, T.D., Smith, S.B., Digby, G.J., Lambert, N.A., Prasad, P.D., Ganapathy, V., 2009. GPR109A is a G-protein-coupled receptor for the bacterial fermentation product butyrate and functions as a tumor suppressor in colon. *Cancer Res.* 69, 2826–2832. <https://doi.org/10.1158/0008-5472.CAN-08-4466>.
- Thursby, E., Juge, N., 2017. Introduction to the human gut microbiota. *Biochem. J.* 474, 1823–1836. <https://doi.org/10.1042/BCJ20160510>.
- Timper, K., Paeger, L., Sánchez-Lasheras, C., Varela, L., Jais, A., Nolte, H., Vogt, M.C., Hausen, A.C., Heilinger, C., Evers, N., Pospisilik, J.A., Penninger, J.M., Taylor, E.B., Horvath, T.L., Kloppenburg, P., Brüning, J.C., 2018. Mild impairment of mitochondrial OXPHOS promotes fatty acid utilization in POMC neurons and improves glucose homeostasis in obesity. *Cell Rep.* 25, 383–397.e10. <https://doi.org/10.1016/j.celrep.2018.09.034>.
- Tohgi, H., Abe, T., Hashiguchi, K., Takahashi, S., Nozaki, Y., Kikuchi, T., 1991. A significant reduction of putative transmitter amino acids in cerebrospinal fluid of patients with Parkinson's disease and spinocerebellar degeneration. *Neurosci. Lett.* 126, 155–158. [https://doi.org/10.1016/0304-3940\(91\)90542-2](https://doi.org/10.1016/0304-3940(91)90542-2).
- Tong, Q., Xu, Q., Xia, Q., Yuan, Y., Zhang, L., Sun, H., Shan, H., Zhang, K., 2015. Correlations between plasma levels of amino acids and nonmotor symptoms in Parkinson's disease. *J. Neural Transm.* 122, 411–417. <https://doi.org/10.1007/s00702-014-1280-5>.
- Ulgherait, M., Rana, A., Rera, M., Graniel, J., Walker, D.W., 2014. AMPK modulates tissue and organismal aging in a non-cell-autonomous manner. *Cell Rep.* 8, 1767–1780. <https://doi.org/10.1016/j.celrep.2014.08.006>.
- Unger, M.M., Spiegel, J., Dillmann, K.U., Grundmann, D., Philippeit, H., Bürmann, J., Faßbender, K., Schwirtz, A., Schäfer, K.H., 2016. Short chain fatty acids and gut microbiota differ between patients with Parkinson's disease and age-matched controls. *Park. Relat. Disord.* 32, 66–72. <https://doi.org/10.1016/j.parkreldis.2016.08.019>.
- Urich, T., Lanzén, A., Qi, J., Huson, D.H., Schleper, C., Schuster, S.C., 2008. Simultaneous assessment of soil microbial community structure and function through analysis of the meta-transcriptome. *PLoS One* 3. <https://doi.org/10.1371/journal.pone.0002527>.
- van der Hee, B., Wells, J.M., 2021. Microbial regulation of host physiology by short-chain fatty acids. *Trends Microbiol.* 29, 700–712. <https://doi.org/10.1016/j.tim.2021.02.001>.
- van Kessel, S.P., Frye, A.K., El-Gendy, A.O., Castejon, M., Keshavarzian, A., van Dijk, G., El Aidy, S., 2019. Gut bacterial tyrosine decarboxylases restrict levels of levodopa in the treatment of Parkinson's disease. *Nat. Commun.* 10, 1–11. <https://doi.org/10.1038/s41467-019-08294-y>.
- Vascellari, S., Palmas, V., Melis, Marta, Pisani, S., Cusano, R., Uva, P., Perra, D., Madau, V., Sarchioto, M., Oppo, V., Simola, N., Morelli, M., Santoru, M.L., Atzori, L., Melis, Maurizio, Cossu, G., Manzin, A., 2020. Gut microbiota and metabolome alterations associated with Parkinson's disease. *mSystems* 5. <https://doi.org/10.1128/msystems.00561-20>.
- Venkatesh, M., Mukherjee, S., Wang, H., Li, H., Sun, K., Benechet, A.P., Qiu, Z., Maher, L., Redinbo, M.R., Phillips, R.S., Fleet, J.C., Kortagere, S., Mukherjee, P., Fasano, A., Le Ven, J., Nicholson, J.K., Dumas, M.E., Khanna, K.M., Mani, S., 2014. Symbiotic bacterial metabolites regulate gastrointestinal barrier function via the xenobiotic sensor PXR and toll-like receptor 4. *Immunity* 41, 296–310. <https://doi.org/10.1016/j.immuni.2014.06.014>.
- Vernocchi, P., Del Chierico, F., Putignani, L., 2016. Gut microbiota profiling: metabolomics based approach to unravel compounds affecting human health. *Front. Microbiol.* 7 <https://doi.org/10.3389/fmicb.2016.01144>.
- Vidal, B., Gulez, B., Cao, W.X., Leyva-Diaz, E., Reilly, M.B., Tekieli, T., Hobert, O., 2022. The enteric nervous system of the *C. elegans* pharynx is specified by the Sine oculis-like homeobox gene ceh-34. *Elife* 11. <https://doi.org/10.7554/elife.76003>.
- Visconti, A., Le Roy, C.I., Rosa, F., Rossi, N., Martin, T.C., Mohney, R.P., Li, W., de Rinaldis, E., Bell, J.T., Venter, J.C., Nelson, K.E., Spector, T.D., Falchi, M., 2019. Interplay between the human gut microbiome and host metabolism. *Nat. Commun.* 10 <https://doi.org/10.1038/s41467-019-12476-z>.
- Vogt, N.M., Kerby, R.L., Dill-McFarland, K.A., Harding, S.J., Merluzzi, A.P., Johnson, S.C., Carlsson, C.M., Asthana, S., Zetterberg, H., Blennow, K., Bendlin, B.B., Rey, F.E., 2017. Gut microbiome alterations in Alzheimer's disease. *Sci. Rep.* 7, 1–11. <https://doi.org/10.1038/s41598-017-13601-y>.
- Vogt, N.M., Romano, K.A., Darst, B.F., Engelman, C.D., Johnson, S.C., Carlsson, C.M., Asthana, S., Blennow, K., Zetterberg, H., Bendlin, B.B., Rey, F.E., 2018. The gut microbiota-derived metabolite trimethylamine N-oxide is elevated in Alzheimer's disease. *Alzheimer's Res. Ther.* 10, 1–8. <https://doi.org/10.1186/s13195-018-0451-2>.
- Vogt, R.M., Wang, Z., Brown, J.M., Engen, P.A., Naqib, A., Goetz, C.G., Hall, D.A., Metman, L.V., Shaikh, M., Forsyth, C.B., Keshavarzian, A., 2022. Gut microbial metabolites in Parkinson's disease: association with lifestyle, disease characteristics, and treatment status. *Neurobiol. Dis.* 170, 105780 <https://doi.org/10.1016/j.nbd.2022.105780>.
- Wakabayashi, K., Takahashi, H., Takeda, S., Ohama, E., Ikuta, F., 1988. Parkinson's disease: the presence of Lewy bodies in Auerbach's and Meissner's plexuses. *Acta Neuropathol.* 76, 217–221. <https://doi.org/10.1007/BF00687767>.
- Wakade, C., Chong, R., Bradley, E., Thomas, B., Morgan, J., 2014. Upregulation of GPR109A in Parkinson's disease. *PLoS One* 9, 1–10. <https://doi.org/10.1371/journal.pone.0109818>.
- Wan, Z., Zheng, J., Zhu, Z., Sang, L., Zhu, J., Luo, S., Zhao, Y., Wang, R., Zhang, Y., Hao, K., Chen, L., Du, J., Kan, J., He, H., 2022. Intermediate role of gut microbiota in vitamin B nutrition and its influences on human health. *Front. Nutr.* 9, 1–21. <https://doi.org/10.3389/fnut.2022.1031502>.
- Wang, C., Yang, M., Liu, D., Zheng, C., 2024. Metabolic rescue of α-synuclein-induced neurodegeneration through propionate supplementation and intestine-neuron signaling in *C. elegans*. *Cell Rep.* 43, 113865 <https://doi.org/10.1016/j.celrep.2024.113865>.
- Wang, F., Gu, Y., Xu, C., Du, K., Zhao, C., Zhao, Y., Liu, X., 2022. Transplantation of fecal microbiota from APP/PS1 mice and Alzheimer's disease patients enhanced endoplasmic reticulum stress in the cerebral cortex of wild-type mice. *Front. Aging Neurosci.* 14, 1–11. <https://doi.org/10.3389/fnagi.2022.858130>.
- Wang, G., Zhou, Y., Huang, F.J., Tang, H.D., Xu, X.H., Liu, J.J., Wang, Y., Deng, Y.L., Ren, R.J., Xu, W., Ma, J.F., Zhang, Y.N., Zhao, A.H., Chen, S.D., Jia, W., 2014. Plasma metabolite profiles of Alzheimer's disease and mild cognitive impairment. *J. Proteome Res.* 13, 2649–2658. <https://doi.org/10.1021/pr5000895>.
- Wang, Q., Song, Y., xiang, Wu, X., dong, Luo, Y., gen, Miao, R., Yu, X., meng, Guo, X., Wu, D., zhen, Rao, B., Mi, W., dong, Cao, J., bei, 2024. Gut microbiota and cognitive performance: a bidirectional two-sample Mendelian randomization. *J. Affect. Disord.* 353, 38–47. <https://doi.org/10.1016/j.jad.2024.02.083>.
- Wasser, C.I., Mercieca, E.C., Kong, G., Hannan, A.J., McKeown, S.J., Glikmann-Johnston, Y., Stout, J.C., 2020. Gut dysbiosis in Huntington's disease: associations among gut microbiota, cognitive performance and clinical outcomes. *Brain Commun.* 2, 1–13. <https://doi.org/10.1093/braincomms/fcaa110>.
- Wichit, P., Thanprasertsuk, S., Phokaewvarangkul, O., Bhidayasiri, R., Bongsebandhu-phubhakdi, S., 2021. Monoamine levels and Parkinson's disease progression: evidence from a high-performance liquid chromatography study. *Front. Neurosci.* 15, 1–8. <https://doi.org/10.3389/fnins.2021.605887>.
- Wilmes, P., Bond, P.L., 2004. The application of two-dimensional polyacrylamide gel electrophoresis and downstream analyses to a mixed community of prokaryotic microorganisms. *Environ. Microbiol.* 6, 911–920. <https://doi.org/10.1111/j.1462-2920.2004.00687.x>.
- Winblad, B., Kilander, L., Eriksson, S., Minthon, L., Bätsman, S., Wetterholm, A.L., Jansson-Blixt, C., Haglund, A., 2006. Donepezil in patients with severe Alzheimer's disease: double-blind, parallel-group, placebo-controlled study. *Lancet* 367, 1057–1065. [https://doi.org/10.1016/S0140-6736\(06\)68350-5](https://doi.org/10.1016/S0140-6736(06)68350-5).
- World Health Organisation, 2020. WHO reveals leading causes of death and disability worldwide: 2000–2019, 2020, pp. 1–5.
- World Health Organization, 2023. Parkinson Disease, pp. 1–5.
- World Health Organization, 2021. World failing to address dementia challenge, pp. 1–4.
- Wu, Y., Wang, B., Xu, H., Tang, L., Li, Y., Gong, L., Wang, Y., Li, W., 2019. Probiotic bacillus attenuates oxidative stress-induced intestinal injury via p38-mediated autophagy. *Front. Microbiol.* 10, 1–20. <https://doi.org/10.3389/fmicb.2019.02185>.
- Xiang, L., Moore, B.S., 2005. Biochemical characterization of a prokaryotic phenylalanine ammonia lyase. *J. Bacteriol.* 187, 4286–4289. <https://doi.org/10.1128/JB.187.12.4286-4289.2005>.
- Yakhine-Diop, S.M.S., Morales-García, J.A., Niso-Santano, M., González-Polo, R.A., Uribe-Carretero, E., Martínez-Chacón, G., Durand, S., Maiuri, M.C., Aistau, A., Zulaica, M., Ruiz-Martínez, J., de Munain, A.L., Pérez-Tur, J., Pérez-Castillo, A., Kroemer, G., Bravo-San Pedro, J.M., Fuentes, J.M., 2020. Metabolic alterations in plasma from patients with familial and idiopathic Parkinson's disease. *Aging* 12, 16690–16708. <https://doi.org/10.18632/AGING.103992>.
- Yilmaz, A., Geddes, T., Han, B., Bahado-Singh, R.O., Wilson, G.D., Imam, K., Maddens, M., Graham, S.F., 2017. Diagnostic biomarkers of Alzheimer's disease as identified in saliva using ¹H NMR-based metabolomics. *J. Alzheimer's Dis.* 58, 355–359. <https://doi.org/10.3233/JAD-161226>.
- Yokoyama, T., Miyazawa, K., Naito, M., Toyotake, J., Tauchi, T., Itoh, M., Yuo, A., Hayashi, Y., Georgescu, M.M., Kondo, Y., Kondo, S., Ohayashiki, K., 2008. Vitamin K2 induces autophagy and apoptosis simultaneously in leukemia cells. *Autophagy* 4, 629–640. <https://doi.org/10.4161/auto.5941>.
- Yu, Y., Yu, X., Cheng, Q., Tang, L., Shen, M., 2020. The association of serum vitamin K2 levels with Parkinson's disease: from basic case-control study to big data mining analysis Yan-Xia. *Aging* 12, 16410–16419. <https://doi.org/10.18632/aging.103691>.
- Zaylaa, M., Kassaa, A.I., Boutilier, J.A.I., Desramaut, V.P.D., Rosenstiel, J., Nguyen, P., Dabbousi, H.T.T., Pot, F., Grangette, C., 2019. Autophagy: a novel mechanism involved in the anti-inflammatory abilities of probiotics. *Cell. Physiol. Biochem.* 53, 774–793. <https://doi.org/10.33594/000000172>.
- Zeng, Q., Gong, Y., Zhu, N., Shi, Y., Zhang, C., Qin, L., 2024. Lipids and lipid metabolism in cellular senescence: Emerging targets for age-related diseases. *Ageing Res. Rev.* 97, 102294 <https://doi.org/10.1016/j.arr.2024.102294>.
- Zeng, Q., Shen, J., Chen, K., Zhou, J., Liao, Q., Lu, K., Yuan, J., Bi, F., 2020. The alteration of gut microbiome and metabolism in amyotrophic lateral sclerosis patients. *Sci. Rep.* 10, 1–12. <https://doi.org/10.1038/s41598-020-69845-8>.
- Zhang, F., Aschenbrenner, D., Yoo, J.Y., Zuo, T., 2022. The gut mycobiome in health, disease, and clinical applications in association with the gut bacterial microbiome assembly. *Lancet Microbe* 3, e969–e983. [https://doi.org/10.1016/S2666-5247\(22\)00203-8](https://doi.org/10.1016/S2666-5247(22)00203-8).

- Zhang, L., Yu, J., Pan, H., Hu, P., Hao, Y., Cai, W., Zhu, H., Yu, A.D., Xie, X., Ma, D., Yuan, J., 2007. Small molecule regulators of autophagy identified by an image-based high-throughput screen. *Proc. Natl. Acad. Sci. USA* 104, 19023–19028. <https://doi.org/10.1073/pnas.0709695104>.
- Zhang, Li, Yuan, Y., Tong, Q., Jiang, S., Xu, Q., Ding, J., Zhang, Lian, Zhang, R., Zhang, K., 2016. Reduced plasma taurine level in Parkinson's disease: association with motor severity and levodopa treatment. *Int. J. Neurosci.* 126, 630–636. <https://doi.org/10.3109/00207454.2015.1051046>.
- Zhang, T., Cheng, J. ke, Hu, Y. min, 2022. Gut microbiota as a promising therapeutic target for age-related sarcopenia. *Ageing Res. Rev.* 81, 101739 <https://doi.org/10.1016/j.arr.2022.101739>.
- Zhang, X., Bao, G., Liu, D., Yang, Y., Li, X., Cai, G., Liu, Y., Wu, Y., 2021. The association between folate and Alzheimer's disease: a systematic review and meta-analysis. *Front. Neurosci.* 15, 1–13. <https://doi.org/10.3389/fnins.2021.661198>.
- Zhou, C., Li, L., Li, T., Sun, L., Yin, J., Guan, H., Wang, L., Zhu, H., Xu, P., Fan, X., Sheng, B., Xiao, W., Qiu, Y., Yang, H., 2020. SCFAs induce autophagy in intestinal epithelial cells and relieve colitis by stabilizing HIF-1 α . *J. Mol. Med.* 98, 1189–1202. <https://doi.org/10.1007/s00109-020-01947-2>.
- Zhou, Z., Fan, Y., Zong, R., Tan, K., 2022. The mitochondrial unfolded protein response: a multitasking giant in the fight against human diseases. *Ageing Res. Rev.* 81, 101702 <https://doi.org/10.1016/j.arr.2022.101702>.
- Zhuang, Z.Q., Shen, L., Li, W.W., Fu, X., Zeng, F., Gui, L., Lü, Y., Cai, M., Zhu, C., Tan, Y.L., Zheng, P., Li, H.Y., Zhu, J., Zhou, H.D., Bu, X., Le, Wang, Y.J., 2018. Gut microbiota is altered in patients with Alzheimer's disease. *J. Alzheimer's Dis.* 63, 1337–1346. <https://doi.org/10.3233/JAD-180176>.