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GUT DYSBIOSIS AND AGE-RELATED NEUROLOGICAL DISEASES; AN INNOVATIVE APPROACH FOR THERAPEUTIC INTERVENTIONS

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Abstract

The gut microbiota is a complex ecosystem of bacteria, fungi, and viruses that acts as a critical regulator in microbial, metabolic, and immune responses in the host organism. Imbalances in the gut microbiota, termed “dysbiosis”, often induce aberrant immune responses, which in turn disrupt the local and systemic homeostasis of the host. Emerging evidence has highlighted the importance of gut microbiota in intestinal diseases, and more recently, in age-related central nervous systems diseases, e.g., stroke and Alzheimer’s disease. It is now generally recognized that gut microbiota significantly influences host behaviors and modulates the interaction between microbiota, gut, and brain, via the “microbiota-gut-brain axis”. Several approaches have been utilized to reduce age-related dysbiosis in experimental models and in clinical studies. These include strategies to manipulate the microbiome via fecal microbiota transplantation, administration of prebiotics and probiotics, and dietary interventions. In this review, we explore both clinical and pre-clinical therapies for treating age-related dysbiosis.

Keywords

Aging; gut microbiota; neurological disorders; microbiota-gut-brain axis; dysbiosis; fecal microbiota transplantation

INTRODUCTION

The microbiota represents a dynamic environment inhabited by a wide array of microorganisms encompassing bacteria, fungi, archaea, protozoans, and even viruses present ubiquitously on host tissues; their collective genomes are known as the microbiome (1). They reside both inside and outside of the host including on the skin, and in the mouth, pharynx, respiratory tract, urogenital tract, and gastrointestinal (GI) tract, and play critical

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roles in modulating host homeostasis (2). New molecular techniques have allowed for the rapid identification of microbiome components by sequencing of the 16S ribosomal RNA (rRNA)-encoding gene to identifying specific bacteria (3–5). Initiatives like the Human Microbiome Project (HMP), developed by the National Institutes of Health (NIH) are using genome sequencing to create a reference database of the healthy human microbiota composition (NIH HMP 2012) (6).

These microorganisms regulate many factors of host physiology, such as immunogenic and hormonal properties. They are profoundly attuned to the dynamic host mucosal environment. Changes to this environment, known as “dysbiosis”, especially within the gastrointestinal tract, have been associated with a vast array of neurological diseases such as in stroke and Alzheimer’s (AD), through the MGB axis (bottom-up signaling) (7–10). Studies have implicated this bottom-up signaling in the migration of pro-inflammatory mediators from the gut to the brain via several routes including circulating blood, the immune system, microbial metabolites, the vagus nerve, and the enteric nervous system (11). Over the past decade, numerous studies have shown that the microbiota within the gut plays an integral part in regulating brain development, function, and behavior. Furthermore, changes to the immune milieu orchestrating the bi-directional communication across the MGB axis is well documented, however, how this interaction influences the exacerbation of the disease, and its contribution to aging is still an emerging concept. Over 100 trillion microorganisms have been identified in the human GI tract encoding over three million genes, compared with the 23,000 genes within the human genome (12, 13). The microbiota produces thousands of diverse metabolites that play crucial functional roles in the host (12–14). Currently, more than 50 bacteria phyla have been detected in the GI tract of humans translating to a diversity of over 36,000 species of microorganisms (15).

Predominantly, the spike in the microbial load within the GI tract occurs during birth. The intestines of neonates are mostly sterile or have only trace levels of microbes (16). Although there are studies that suggest a placental microbiome may exist, which could influence the microbial flora within neonates, these studies are limited (17–20). During birth, as neonates pass through the birth canal, they are exposed to the microbial population of the mother’s vaginal canal. The principal genus are *Lactobacillus spp.* and *Bifidobacterium spp.* as indicated by the distinct metabolites present within the gut lumen (16, 20, 21). Interestingly, many population-based studies have shown that infants who are delivered by cesarean have a significantly reduced bacterial load in the gut at one month of age relative to neonates that were born by traditional vaginal delivery, suggesting that the host biome is programmed early in life (22).

The microbiome composition, at a genetic level, changes through the lifespan due to multiple external and physiological factors. During the first 3 years of life, the microbiome fluctuates dramatically until it reaches a more stable and unique signature at a genetic level resembling an adult microbiota, which can be relatively stable for decades (23–25). Under normal physiological conditions, the microbiome modulates the development of the immune system and immunogenic potential within the host (26–30). In particular, the intestinal microbiota regulates the differentiation and development of tissue-resident immune cells within the central nervous system, a hallmark classification for the microglial cell lineage

(31). In addition, it provides a stable source for several important nutrients and vitamins from well-established commensal bacteria, to facilitate proper metabolic homeostasis and function (26–30). Microbial diversity diminishes with aging, and elderly populations have differences in gut microbe composition compared to that of young adults (32, 33). However, understanding if the gut microbiota can itself influence aging is challenging, as the biome varies greatly between individuals and over time. Age-related changes in host physiology may shape the dysbiosis seen with aging, so it remains unknown if microbes themselves can drive the aging phenotype. Interestingly, work in simple model species, like the fruit fly, *Drosophila melanogaster*, have shown that changes in microbial composition precede intestinal and host aging, and manipulation of the microbiota can extend lifespan, suggesting that microbes can accelerate the aging process (34, 35). Age- or disease-related changes in microbiota composition can lead to a disruption in gut homeostasis in terms of integrity and overall physiology. This phenomenon is commonly referred to as dysbiosis, the term signifying the shift in the microbiota that is associated with a pathological state (36). Gut dysbiosis has been identified as a critical trigger for chronic low-grade inflammation, obesity, diabetes, cardiovascular disease, behavioral disorders, and neurodegenerative disease (37).

In this review, we will highlight the potential of 1) neurological disorders, e.g., stroke, AD, and 2) aging, to cause dysbiosis. Understanding the underlying mechanisms that lead to dysbiosis is imperative for the development of potential therapeutic interventions.

MICROBIOME: AN EMERGING KEY REGULATOR IN THE GUT-BRAIN AXIS

The microbes within the gut play a crucial role in human health. Biosynthesis of vitamins and amino acids using products of food breakdown/fermentation by microorganisms has been widely described (38). Moreover, it has been shown the microorganisms in the GI tract can provide a biochemical pathway for the metabolism of non-digestible carbohydrates, including more abundant polysaccharides (starches, cellulose, hemicellulose, pectins, and gums), oligosaccharides, non-absorbable sugars, and alcohols from the diet (39). The dietary consumption of these non-digestible molecules provides an avenue for the host to gain essential vitamins and minerals required for proper physiological function. Importantly, the gut microbiome also supports host protection. Commensal bacteria prevent pathogen invasion and growth by their crosstalk with the host intestinal epithelium and regulate protective mechanisms including secretory immunoglobulin A and mucous production for barrier protection (40). Beneficial bacteria in the gut help the host avoid colonization by pathogens through many competitive processes: nutrient metabolism, pH modification, antimicrobial peptide secretion, and effects on cell signaling pathways (41).

Recent studies demonstrate that the gut microbiome has an important role in connecting the brain and distant organs such as the gut, often referred to as the gut-brain axis or microbiota-gut-brain (MGB) axis (42). The MGB axis acts as a communication portal that integrates neural, hormonal, and immunological signaling in the host where microbial metabolites including short-chain fatty acids (SCFAs) and neurotransmitters play a key role inmodulating signaling cascades (7, 42, 43). The bidirectional communication within the brain and the gut is very intricate and dynamic allowing the central nervous system to

regulate proximal immune responses in the gut to maintain host homeostasis. Numerous studies have highlighted the complexity of this communicative interaction and have shed light on how neurological disorders have detrimental effects on gut morphology and integrity. Very recent findings highlight that the gut microbiota could be a therapeutic target in many neurological diseases such as stroke (8, 9).

Various studies have shown that stroke, AD, and even aging itself can lead to loss of gut barrier integrity (i.e., “leaky gut”), changes in gut microbiota composition, and altered microbial metabolite secretion of SCFAs and neurotransmitters that govern the pathogenic processes of the disease. As an example, in AD, the environment within the gut promotes the colonization of certain bacteria and fungi that secrete amyloid proteins, leading to an increase in amyloid proteins within the CNS and systemically (44–53). This continuous supply of amyloid shifts the dynamic equilibrium of Aβ production and clearance leading to its accumulation in the brain. Stroke leads to dysbiosis and activates inflammatory cascades within the gut, leading to exacerbated brain inflammation and poorer recovery after an ischemic event (7, (54–56). Stroke is responsible for 1 out of every 20 deaths in the United States (57, 58). A major contributor to mortality is post-stroke infection or sepsis. We investigated the effects of age and the role of bacterial translocation from the gut in young (2-3 months) and aged (18-20 months) C57BL/6 male mice following transient middle cerebral artery occlusion or sham surgery. Gut permeability was examined, and peripheral organs were assessed for the presence of gut-derived bacteria following stroke. We found that while stroke-induced gut permeability and bacterial translocation in both young and aged mice, only young mice were able to resolve the infection. Bacterial species seeding peripheral organs also differed between young (*Escherichia*) and aged (*Enterobacter*) mice. (59) Consequently, aged mice developed a septic response marked by persistent and exacerbated hypothermia, weight loss, and immune dysfunction compared to young mice following stroke. This suggests that bacteria that are present in aged mice, and the age-related dysbiosis well documented by others, can influence disease outcomes. Factors like aging, diet, environment, and genetics all have a crucial role in the promotion of gut dysbiosis (60) and increase both the risk of developing neurological disorders and impair recovery (61–67).

FACTORS THAT INFLUENCE THE MICROBIOME

The microbiome is a dynamic environment that coordinates with host physiology and is highly fine-tuned to protect the host against luminal antigens (5). In addition, the overall microbial population can change within the lifespan of the individual as well as with dietary and disease-related physiological alternations. However, based on certain factors such as genetics, certain individuals have a heightened predisposition or genetic susceptibility toward gut dysbiosis and neurological disorders (68–70). Several factors are involved in this alteration and with temporal changes in the microbiome, including host genetics, diet, medications (e.g., antibiotics), and aging (Fig. 1). The etiology of these factors are complicated and are often challenging in regards to identification of causative, rather than correlative variables. Do host changes (i.e. increased inflammation, immune/cellular senescence, gut motility/barrier impairment) drive age related dysbiosis, or does the dysbiosis change the host? Many of these questions remain to be answered but emerging

data from germ free mice or mice “rejuvenated” by young fecal transplants suggest that the microbial composition is a major contributor to changes in gut physiology, integrity, and overall host health with aging

a. Genetics

Large-scale population-based studies have shown that genetic interactions among the host and microbiota play an essential role in shaping the human microbiome composition. Predominantly, the genetic component is linked to the diversification of the microbiota during the progression of colonization within a wide range of gene transduction processes (71). Spontaneous mutations or lateral gene transfers within species of microbiota promote niche variations and maintain microbial diversity. Over the past decade, multiple studies have incorporated the use of integrated gene catalogs to incorporate and examine genetic sequencing data for most microbes (72, 73). Expanding the range of integrated gene analysis within the microbiome gene catalog will certainly aid in facilitating the quantitative characterization of metagenomics, metatranscriptomics, and metaproteomic on a genetic level to fully comprehend disease-specific differences within human pathological states (74).

Multiple studies have shown that host genetics have the potential to influence alpha-diversity or the degree of diversity within taxa (75, 76). Genome-wide association studies (GWAS) have made promising strides in predicting genetic variants and the association of population-based microbial phenotypes (77). However, modeling microbiome profiling datasets as heritable traits is still challenging due to the lack of a stable reference catalog. Additionally, sample sizes are too small under the criteria of Genome-wide association studies (GWAS) to accurately predict or validate significance individually, and comparative meta-analysis from cross-references are very distinct in their analytical methods of microbial profiling.

Modeling the transgenerational genetic composition of the microbiome as a diagnostic screen is crucial to highlight the heritability of microbe-induced diseases. Many studies have tried to elucidate how environmental factors, interactions among microbes, and host genetic differences shape the microbiome. It has been assumed that differing genetic backgrounds in the host contribute to differences in both the vulnerability to pathogens and the capacity to associate with symbionts. Several studies have shown that genetic differences between hosts influence the microbiome composition (78–80), while other studies have determined that the host plays a minor role, and it is mostly the environment that shapes the biome (81). Currently, it is difficult to separate genetic and environmental factors. Indeed, it is challenging to identify host effects as often environmental factors are not controlled for or taken into consideration in the course of analysis (82, 83).

b. Diet

Dietary intake is an essential factor that induces microbial shifts in the host to maintain immunogenic tolerance. The consumption of food is a major source of essential precursors for metabolite production required for homeostasis. Multiple studies have shown that dietary factors modulate the gut microbiota and have an impact on both the dynamic ecosystem, microbe-microbe interactions, and the overall microbiome profile (84, 85). Classification of certain diets (e.g., high fat, high carbohydrate intake, or high fiber) have the potential to

facilitate the colonization of certain bacterial phyla, including *Firmicutes, Actinobacteria*, and *Deltaproteobacteria* (fat) and *Prevotella* (carbohydrate, fiber) (86–88). High protein-based diets, such as meats, and synthetic-based proteins, have been correlated to the growth of bile tolerant microbes, which predominantly produce metabolites such as essential/non-essential amino acids required for maintaining proper gut health and harmful byproduct removal (89). On the other hand, high-fat diets (i.e., saturated fats) results in chronic regional gut inflammation due to increases in specific genus, i.e., *Clostridium*, and ultimately contribute to dysbiosis (90, 91).

Bacteroides are commonly found in diets dominated by abundant animal proteins, amino acids, and saturated fats like those consumed by US populations, and are potentially harmful to overall gut health (4, 92). Higher consumption of animal proteins has been linked to increased plasma concentrations of trimethylamine N-oxide (TMAO), a biologically active molecule produced by the microbiota from TMA. Elevated TMAO levels are associated with an increased risk of atherosclerosis and other chronic vascular diseases (93, 94). Studies have shown that alterations in dietary habits (vegan/vegetarian versus omnivore/carnivore) and changes in systemic TMAO concentrations correlate with changes in specific bacterial taxa (95).

All these findings indicate that diet may play a critical role in shaping the gut microbial signature in the elderly population (96).

c. Antibiotics

The discovery and use of antibiotics have helped treat many different types of diseases and infections over the past century. These drugs are given to patients to eradicate pathogenic bacteria, but some antibiotics can also kill mutualistic, commensal microbiota, and lead to long-term changes in the biome. Prolonged use of such antibodies has shown to have profound negative effects upon normal physiology and the composition of the biome (97). Multiple studies have shown that administration of antibiotics promotes gut dysbiosis (98), contributes to several gut-related diseases, and interestingly can affect behavioral outcomes (i.e., increased prevalence of depression and autism) (99).

In addition, extensive use of antibiotics gives rise to colonized bacteria that become resistant due to natural selection. For instance, in a longitudinal-based clinical study, healthy volunteers treated with 150 mg of clindamycin reported an upregulation of antibiotic resistance genes among *Bacteroides* that persisted six months to 2 years after completion of treatment (100). Further, a dramatic loss in gut microbial diversity as well as in the representation of specific taxa was evident. As not all antibiotics target the same bacteria, it is common to use a combination of different antibiotics, e.g., ampicillin, gentamycin, metronidazole, neomycin, and vancomycin, to widen the antimicrobial spectra for the treatment of severe bacterial infection, thus altering the microbiome. Currently, the usage of probiotics and fecal microbiota transplantation (FMT) are emerging therapies that can be a potential intervention to address the detrimental effects of antibiotic-induced gut dysbiosis (8).

d. Aging

Aging itself is not considered a disease, but is a critical risk factor for a wide array of neurological disorders. Aging comes with an increased risk of infection and chronic low-grade inflammation known as “inflamm-aging”. This phenotype is mainly due to the physiological changes that result in frailty and immunosenescence, which leads to increased infections in the elderly population (101). Changes in microbiota diversity have been observed over the lifespan of humans and during the progression of aging (102) (Fig. 2). Many studies (Table I) have shown dramatic changes within the microbiome composition and gut structure in the elderly population (103).

Gut epithelial layers are maintained by goblet cell-producing mucins and tight junctions (TJ), which form a paracellular barrier to regulate not only the flux of ions and solutes but also commensal flora. Studies have shown that aging leads to a breakdown of the epithelial barriers of the GI tract, which is prone to bacterial challenges such as infection, facilitating bacterial translocation and increasing infection rates and overall inflammation in the elderly (104) (Fig. 3). Loss of gut integrity induces pathological activation of the immune system, and “primes” a pro-inflammatory environment in the host (105). This is characterized by higher levels of inflammatory markers such as IL-6 and IL-S in the blood that have been linked to enhanced senescence (33).

A population-based study evaluated the microbiome diversity of individuals over 100 years of age (“the centenarians”) and compared this to 70-year-olds and young adults. As expected, centenarians showed a different pattern in their microbiome diversity compared with 70-year-olds and young adults, with a decrease in *Firmicutes* and enrichment in facultative anaerobes (33). A later study analyzed the bacterial metagenome in young (mean age: 38), adult (mean age: 66.4), and centenarian (mean age: 100.7) and demonstrated that an increase in genes related to tryptophan metabolism pathways correlated with a significant reduction in tryptophan levels in the serum in the centenarians, which was linked to cognitive deficits and dementia (106–108). Further analysis showed a reduction in genes involved in the production of SCFAs in centenarians and its correlation with overall health status. Butyrate is a key SCFA associated with improved intestinal structure and gut health. Butyrate has anti-inflammatory properties and suppresses nuclear factor-kappa B, signal transducer and activator of transcription 1 activation, and induces T_{reg} cell differentiation within the gut lamina propria (109). Higher levels of SCFA butyrate-producing bacteria were correlated with reduced inflammation and longevity in centenarians (33). These findings were supported by the publication of the ELDERMET project, which determined the composition of the intestinal microbiome of 500 elderly individuals (110).

GUT MICROBIOTA AS A THERAPEUTIC TARGET FOR AGING AND AGE-RELATED NEUROLOGICAL DISORDERS

Several studies have shown that the GI track and resident microbiota are susceptible to the progressive functional decline associated with aging and with neurological diseases such as stroke (Table II) and AD (Table III). Many of the pathological processes include the breakdown of the gut epithelial barrier, loss of enteric neurons, and altered mucosal immune

function resulting in excessive production of pro-inflammatory cytokines. Concomitant with changes in GI physiology, aging alone was associated with significant shifts in the makeup of the gut microbiota including altered microbial richness and diversity and a decrease in bacteria with anti-inflammatory properties (111). Through this communicative route or through the microbiota-gut-brain axis, the gut microbiota can regulate brain function of the host and even cognition and memory.

A few recent studies have attempted to manipulate the gut microbiome to eliminate this as a source of systemic inflammation in age-related neurological disorders. The crux of this emerging research is engaging the idea of the bidirectional communication between the brain and the gut. The gut or gut microbiota can communicate with the brain via the production of neurotransmitters, SCFAs, and other metabolites (7). These biochemical signals create a response in the brain, such as mood changes, behavioral changes, and changes in cognition. Different strategies have been tested in clinical trials to modify the microbiome, including fecal microbiota transplantation (FMT), administration of probiotics or antibiotics, or dietary interventions, which are non-invasive but may re-shape the host immune systems (Table IV). We summarize pre-clinical findings demonstrating the potential of manipulation of gut microbiota for therapeutic use in neurological disorders.

A. Fecal Microbiota Transplantation (FMT) in Aging and Age-related Neurological Disorders (Table V).

1. Aging—Studies using germ-free (GF) mice, which are devoid of all microbiota, have shown an increase in intestinal permeability and disturbed gut morphology as a consequence of aging. FMT using aged microbiome (17 months) transplanted into young GF mice (12-14 weeks) increased inflammation, and similarly, young mice given aged microbiota had features consistent with “inflamm-aging”. This was reflected by a reduction of the beneficial bacterial genus *Akkermansia* and increased gut permeability. This implies that the aged microbiome itself has a detrimental effect on inducing inflammation and dysfunction in the gut barrier (105). Understanding the role of dysbiosis with aging and age-related neurological disorders suggests there is potential to alter the gut microbiota to attenuate inflamm-aging. This becomes even more significant when the wide variety of diseases that primarily affect the elderly population are considered.

2. Alzheimer’s Disease (AD)—AD is the most common cause of dementia. AD is one of the most prevalent diseases of the elderly (112). It affects 16% of people between 65-74 years, 45% of people between 75-84 years, and 36% of people older than 85 years (113). The link between the gut microbiota and AD appears to be due in part to microbiome induced neuro-inflammation (114). Multiple studies have hypothesized that the onset of amyloid plaques is associated with the dysbiosis within the gut and is regulated via the bidirectional communication of the gut-brain axis (115, 116). In this regard, we recently found that gut inflammation and microbial dysbiosis precedes brain amyloid-beta accumulation using Tg2576 mice, a mouse model of AD (115). Further, researchers have investigated the concept of fecal microbial transplantation (FMT) to alleviate cognitive decline, enhance gut immune responses and promote anti-inflammatory cascades in a mouse model of AD (116). Using ADLP^{APT} (AD-like pathology with amyloid and neurofibrillary

tangles) transgenic mice (116), investigators found inflammation and microbial dysbiosis in the gut, compared with wild-type (WT) mice. Interestingly, ADLP^{APT} mice given a fecal transplant from WT donor mice had reduced amyloid and Tau pathology in the brain, enhanced cognition, and reduced gut and systemic inflammation. Using a different model of AD, APPswe/PSldE9 transgenic mice, FMT from healthy WT mice improved behavioral outcomes, decreased Aβ40 and Aβ42 levels and phosphorylation of Tau protein in the brain with reversed gut microbiota profiles in the recipient AD mice (117). Despite using three distinct animal models of AD, which could potentially have different gut microbiota profiles, manipulating the biome comprehensively could serve as an intervention to alleviate the effects of AD.

3. **Stroke—**Stroke is a major cause of mortality and morbidity in the United States (55). One of the major contributors to mortality is post-stroke infection. Recent studies demonstrated that stroke increases gut permeability and systemic bacterial translocation leading to lung infection, i.e., pneumonia in stroke patients (118). Brain injury also induces infection in a mouse model of ischemic stroke (54). Stroke-induced gut permeability and bacterial translocation were seen in both young and aged mice, but only young mice were able to resolve infection (54). The bacterial species colonizing peripheral organs also differed between young (Escherichia) and aged (Enterobacter) mice. Interestingly both are gut-originated bacteria (119), suggesting, as in humans, many stroke related infections arise from the gut.

Our recent study further emphasizes the translational potential of manipulating the microbiome (8). Using post-stroke FMT from young mice (young FMT), we reconstituted the biome of recipient aged mice (18-20 months). Compared with aged FMT as a control, young FMT had higher SCFA levels, improved behavioral outcomes, and enhanced gut integrity. In addition, mice with young FMT had 1) increased T_{reg} cells in both small intestines and the brain, 2) decreased microglial activation, and 3) decreased γν T cells in the brain, which secrete pro-inflammatory IL-17. We observed the same beneficial effect of young biome when we reconstituted the gut of aged mice with young biome before stroke (9). A summary of recent reviews and selected studies examining the microbiome in stroke can be found in Table II.

B. Probiotics and Prebiotics in Age-related Neurological Disorders (Table VI)

Probiotics are defined as live and beneficial bacteria (120). The most common probiotics used today are species of *Lactobacillus* and *Bifidobacterium* (121). The prebiotic is typically made up of carbohydrates such as galacto-oligosaccharides, fructo-oligosaccharides, and inulin to complement and foster the growth of the probiotic bacteria; usually, both agents are taken in combination for an ideal re-constitution (122). Studies have already shown that the use of this approach in elderly individuals leads to a decrease in circulating pro-inflammatory cytokines such as interleukin (IL)-6, IL-1β, and tumor necrosis factor-α (TNF- α) (122). An investigative review by Sharma et al. has recently compiled studies that used probiotics as therapeutic agents for the treatment of cellular senescence (123). They propose that probiotic supplementation can help improve age-related gut dysbiosis, suppress age-associated inflammatory stress, and possibly enhance lifespan as seen in model

organisms (124). The use of probiotics and prebiotics have been shown to be helpful to treat metabolic conditions (125–135). A new perspective within this therapeutic intervention is the incorporation of probiotics to treat the cognitive dysfunction that is linked with these diseases as well (124, 136). However, most of these studies are still in the pre-clinical phase as the effect of metabolic disease on cognitive decline is still inconclusive in human studies (137).

1. Probiotics in AD—More recently, research has examined the effects of probiotics on age-induced cognitive decline and other neurodegenerative diseases of aging via the bidirectional communication of the MBA axis (138). Administration of a probiotic to AD model mice improved glucose uptake in the brain by restoring expression levels of glucose transporter (GLUT) 3 and GLUT1, key glucose transporters (139). A reduction in the expression of these glucose transporters is seen in AD patients and is believed to contribute to the cognitive decline seen in the disease phenotype. With the daily administration of a probiotic, an improvement in cognition in treated mice compared to that of non-treated mice was seen. Based on these findings, although the cognitive symptoms of AD may not develop until later in disease progression, the use of probiotics could be both a preventative and a symptomatic therapy for the cognitive dysfunction seen with AD and possibly other neurodegenerative diseases as well (139).

2. Probiotics and prebiotics in stroke—Studies examining the use of probiotics to treat stroke are limited. One study found that oral ingestion of *Bifidobacterium breve, Lactobacillus casei, Lactobacillus bulgaricus*, and *Lactobacillus acidophilus* reduced ischemic injury after an experimental stroke in mice (140), but confirmation of changes in the microbial levels was not performed, and no behavioral benefits were seen. Administration of *Clostridium butyricum* by oral gavage two weeks prior to bilateral common carotid artery occlusion (BCCAO) reduced brain injury, but again, changes in the microbiome were not assessed directly. Levels of SCFAs (e.g., acetate, butyrate, and propionate) in young biome are higher than aged biome (8). For more refined and targeted microbial therapy, we selected bacterial strains that produce SCFAs (SCFA-producers) based on microbial and metagenomic sequencing. Transplanting selected SCFA-producers (*Bifidobacterium longum, Clostridium symbiosum, Faecalibacterium prausnitzii*, and *Lactobacillus fermentum*) improved stroke outcomes in aged stroke mice by decreasing brain IL-17 levels secreted by $\gamma\nu$ T cells (141).

C. Dietary interventions (Table VII)—It is well known that a change in diet can influence the microbiota composition in the gut. Instead of adding beneficial bacteria to the gut, changes in diet aim to promote the growth of beneficial bacteria already present in the gut. A seminal study done by Claesson et al. showed that dietary changes in older individuals living in nursing facilities vs. communityd-welling elders had a significant effect on microbiota diversity (32). Previous data show that microbiome divergence is greater among older people compared to younger adults. Claesson hypothesized that the elderly had greater variance environmentally, and devised this study to specifically look at how much the environment affects diet and the aging microbiome. The variability in microbiota in the elderly, their diets, and their overall health was examined in community-dwelling groups and

groups that were transitioning into a long-term nursing facility. The community-dwelling group that had a more balanced and diverse diet had a more diverse microbiome whereas the nursing facility group that had a more fixed diet that was higher in glucose, glycine, and lipids had a less diverse microbiome. The nursing facility group also had increased levels of circulating cytokines, were more frail and depressed, and had poorer overall nutrition. Given their results, they concluded that although other factors contributed to the decline in the health of these individuals, there was an association of diet with microbiota composition. Therefore, supporting dietary interventions could be a strategy to modulate the microbiota and, as a result, promote healthier aging. That said, changes in diet would be most effective as a preventative approach or used in conjunction with probiotics and prebiotics to essentially revert the aged dysbiotic microbiome to a ‘younger’ healthier composition.

CONCLUSION

It is becoming apparent that the gut microbiota play a pivotal role both in health and in age related diseases. In this review, we highlighted some of the ways that alterations of the gut microbiota could be both detrimental and beneficial in terms of aging and neurological diseases. Currently research using microbiota-based therapies for age-related diseases is in its infancy, but the research in this area has been growing exponentially over the past decade. The concept of manipulating the host gut microbiome, using FMT, dietary interventions, or pro/prebiotics as a therapeutic approach to address neurological diseases is gaining traction. As we begin to gain a better understanding of host-microbiota interactions, there are opportunities to produce a better approach to treat these diseases with more refined and targeted approaches.

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Abbreviations:

AD	Alzheimer’s disease
CNS	central nervous system
FMT	fecal microbiota transplantation
GF	germ-free
GI	gastrointestinal
GLUT	glucose transporter
HMP	human genome project
IFN	interferon
IL	interleukin
MGB	microbiota-gut-brain

PAMP	pathogen-associated molecular pattern
PRR	pattern-recognition receptor
SCFA	short-chain fatty acid
TJ	tight junction
TLR	toll-like receptor
TMAO	trimethylamine N-oxide
TNF-α	tumor necrosis factor-α
T_{reg}	regulatory T cell

REFERENCES

1. Heintz-Buschart A & Wilmes P (2018) Human Gut Microbiome: Function Matters. Trends Microbiol 26(7):563–574. [PubMed: 29173869]
2. Dominguez-Bello MG, Godoy-Vitorino F, Knight R, & Blaser MJ (2019) Role of the microbiome in human development. Gut 68(6):1108–1114. [PubMed: 30670574]
3. Zoetendal EG, Collier CT, Koike S, Mackie RI, & Gaskins HR (2004) Molecular ecological analysis of the gastrointestinal microbiota: a review. J Nutr 134(2):465–472. [PubMed: 14747690]
4. Arumugam M, et al. (2011) Enterotypes of the human gut microbiome. Nature 473(7346):174–180. [PubMed: 21508958]
5. Shreiner AB, Kao JY, & Young VB (2015) The gut microbiome in health and in disease. Curr Opin Gastroenterol 31(1):69–75. [PubMed: 25394236]
6. Anonymous (2019) A review of 10 years of human microbiome research activities at the US National Institutes of Health, Fiscal Years 2007–2016. Microbiome 7(1):31. [PubMed: 30808411]
7. Durgan DJ, Lee J, McCullough LD, & Bryan RM Jr. (2019) Examining the Role of the Microbiota-Gut-Brain Axis in Stroke. Stroke 50(8):2270–2277. [PubMed: 31272315]
8. Lee J, et al. (2020) Gut Microbiota-Derived Short-Chain Fatty Acids Promote Post-Stroke Recovery in Aged Mice. Circ Res.
9. Spychala MS, et al. (2018) Age-related changes in the gut microbiota influence systemic inflammation and stroke outcome. Ann Neurol 84(1):23–36. [PubMed: 29733457]
10. Tyler Patterson T & Grandhi R (2020) Gut Microbiota and Neurologic Diseases and Injuries. Adv Exp Med Biol 1238:73–91. [PubMed: 32323181]
11. Rodenbach R, et al. (2020) Coaching Palliative Care Conversations: Evaluating the Impact on Resident Preparedness and Goals-of-Care Conversations. J Palliat Med 23(2):220–225. [PubMed: 31460823]
12. Bull MJ & Plummer NT (2014) Part 1: The Human Gut Microbiome in Health and Disease. Integr Med (Encinitas) 13(6):17–22. [PubMed: 26770121]
13. Rath CM & Dorrestein PC (2012) The bacterial chemical repertoire mediates metabolic exchange within gut microbiomes. Curr Opin Microbiol 15(2):147–154. [PubMed: 22209085]
14. Vyas U & Ranganathan N (2012) Probiotics, prebiotics, and synbiotics: gut and beyond. Gastroenterol Res Pract 2012:872716. [PubMed: 23049548]
15. Rinninella E, et al. (2019) What is the Healthy Gut Microbiota Composition? A Changing Ecosystem across Age, Environment, Diet, and Diseases. Microorganisms 7(1).
16. Biasucci G, et al. (2010) Mode of delivery affects the bacterial community in the newborn gut. Early Hum Dev 86 Suppl 1:13–15.
17. Aagaard K, et al. (2014) The placenta harbors a unique microbiome. Sci Transl Med 6(237):237ra265.

18. Dudley DJ (2020) The placental microbiome: yea, nay or maybe? Bjog 127(2):170. [PubMed: 31628695]
19. de Goffau MC, et al. (2019) Human placenta has no microbiome but can contain potential pathogens. Nature 572(7769):329–334. [PubMed: 31367035]
20. Theis KR, et al. (2019) Does the human placenta delivered at term have a microbiota? Results of cultivation, quantitative real-time PCR, 16S rRNA gene sequencing, and metagenomics. Am J Obstet Gynecol 220(3):267.e261–267.e239. [PubMed: 30832984]
21. Escobar MF, Hincapie MA, & Barona JS (2020) Immunological Role of the Maternal Uterine Microbiota in Postpartum Hemorrhage. Front Immunol 11:504. [PubMed: 32296425]
22. Huurre A, et al. (2008) Mode of delivery - effects on gut microbiota and humoral immunity. Neonatology 93(4):236–240. [PubMed: 18025796]
23. Smith LG Jr., et al. (1989) High hepatitis B carrier rate among non-Oriental patients with acute salpingitis. Am J Obstet Gynecol 161(4):879–880. [PubMed: 2801832]
24. Tanaka M & Nakayama J (2017) Development of the gut microbiota in infancy and its impact on health in later life. Allergol Int 66(4):515–522. [PubMed: 28826938]
25. Bäckhed F, et al. (2015) Dynamics and Stabilization of the Human Gut Microbiome during the First Year of Life. Cell Host Microbe 17(5):690–703. [PubMed: 25974306]
26. Karasov WH, Martínez del Rio C, & Caviedes-Vidal E (2011) Ecological physiology of diet and digestive systems. Annu Rev Physiol 73:69–93. [PubMed: 21314432]
27. LeBlanc JG, et al. (2013) Bacteria as vitamin suppliers to their host: a gut microbiota perspective. Curr Opin Biotechnol 24(2):160–168. [PubMed: 22940212]
28. Kamada N, Seo SU, Chen GY, & Núñez G (2013) Role of the gut microbiota in immunity and inflammatory disease. Nat Rev Immunol 13(5):321–335. [PubMed: 23618829]
29. Abreu MT (2010) Toll-like receptor signalling in the intestinal epithelium: how bacterial recognition shapes intestinal function. Nat Rev Immunol 10(2):131–144. [PubMed: 20098461]
30. Sommer F & Bäckhed F (2013) The gut microbiota--masters of host development and physiology. Nat Rev Microbiol 11(4):227–238. [PubMed: 23435359]
31. Erny D & Prinz M (2020) How microbiota shape microglial phenotypes and epigenetics. Glia 68(8):1655–1672. [PubMed: 32181523]
32. Claesson MJ, et al. (2012) Gut microbiota composition correlates with diet and health in the elderly. Nature 488(7410):178–184. [PubMed: 22797518]
33. Biagi E, et al. (2010) Through ageing, and beyond: gut microbiota and inflammatory status in seniors and centenarians. PLoS One 5(5):e10667. [PubMed: 20498852]
34. Broderick NA, Buchon N, & Lemaitre B (2014) Microbiota-induced changes in drosophila melanogaster host gene expression and gut morphology. mBio 5(3):e01117–01114.
35. Broderick NA & Lemaitre B (2012) Gut-associated microbes of Drosophila melanogaster. Gut Microbes 3(4):307–321. [PubMed: 22572876]
36. Kim S & Jazwinski SM (2018) The Gut Microbiota and Healthy Aging: A Mini-Review. Gerontology 64(6):513–520. [PubMed: 30025401]
37. Durack J & Lynch SV (2019) The gut microbiome: Relationships with disease and opportunities for therapy. J Exp Med 216(1):20–40. [PubMed: 30322864]
38. Rowland I, et al. (2018) Gut microbiota functions: metabolism of nutrients and other food components. Eur J Nutr 57(1):1–24.
39. Cummings JH, Pomare EW, Branch WJ, Naylor CP, & Macfarlane GT (1987) Short chain fatty acids in human large intestine, portal, hepatic and venous blood. Gut 28(10):1221–1227. [PubMed: 3678950]
40. Wells JM, Rossi O, Meijerink M, & van Baarlen P (2011) Epithelial crosstalk at the microbiotamucosal interface. Proc Natl Acad Sci U S A 108 Suppl 1:4607–4614. [PubMed: 20826446]
41. Guarner F & Malagelada JR (2003) Gut flora in health and disease. Lancet 361(9356):512–519. [PubMed: 12583961]
42. De Vadder F, et al. (2014) Microbiota-generated metabolites promote metabolic benefits via gut-brain neural circuits. Cell 156(1–2):84–96. [PubMed: 24412651]

43. Johnson KV & Foster KR (2018) Why does the microbiome affect behaviour? Nat Rev Microbiol 16(10):647–655. [PubMed: 29691482]
44. Giau VV, et al. (2018) Gut Microbiota and Their Neuroinflammatory Implications in Alzheimer's Disease. Nutrients 10(11):1765.
45. Hill JM & Lukiw WJ (2015) Microbial-generated amyloids and Alzheimer's disease (AD). Front Aging Neurosci 7:9. [PubMed: 25713531]
46. Roubaud-Baudron C, Krolak-Salmon P, Quadrio I, Mégraud F, & Salles N (2012) Impact of chronic Helicobacter pylori infection on Alzheimer's disease: preliminary results. Neurobiol Aging 33(5):1009e1011–1009.
47. Gérard HC, et al. (2006) Chlamydophila (Chlamydia) pneumoniae in the Alzheimer's brain. FEMS Immunol Med Microbiol 48(3):355–366. [PubMed: 17052268]
48. Kountouras J, et al. (2007) Alzheimer's disease and Helicobacter pylori infection: Defective immune regulation and apoptosis as proposed common links. Med Hypotheses 68(2):378–388. [PubMed: 16979298]
49. Prandota J (2014) Possible link between Toxoplasma gondii and the anosmia associated with neurodegenerative diseases. Am J Alzheimers Dis Other Demen 29(3):205–214. [PubMed: 24413543]
50. Ball MJ (1982) "Limbic predilection in Alzheimer dementia: is reactivated herpesvirus involved?". Can J Neurol Sci 9(3):303–306. [PubMed: 7116237]
51. Lurain NS, et al. (2013) Virological and immunological characteristics of human cytomegalovirus infection associated with Alzheimer disease. J Infect Dis 208(4):564–572. [PubMed: 23661800]
52. Chiu WC, et al. (2014) Hepatitis C viral infection and the risk of dementia. Eur J Neurol 21(8):1068–e1059. [PubMed: 24313931]
53. Kong Y, Jiang B, & Luo X (2018) Gut microbiota influences Alzheimer's disease pathogenesis by regulating acetate in Drosophila model. Future Microbiol 13:1117–1128. [PubMed: 30043649]
54. Crapser J, et al. (2016) Ischemic stroke induces gut permeability and enhances bacterial translocation leading to sepsis in aged mice. Aging (Albany NY) 8(5):1049–1063. [PubMed: 27115295]
55. Virani SS, et al. (2020) Heart Disease and Stroke Statistics-2020 Update: A Report From the American Heart Association. Circulation 141(9):e139–e596. [PubMed: 31992061]
56. Meisel C, Schwab JM, Prass K, Meisel A, & Dirnagl U (2005) Central nervous system injury-induced immune deficiency syndrome. Nat Rev Neurosci 6(10):775–786. [PubMed: 16163382]
57. Miller MC (1995) ECT and mania. Am J Psychiatry 152(4):654. [PubMed: 7694934]
58. Rashid MH, Kabir A, Waris MU, Salman U, & Zain S (2020) Role of Prophylactic Antibiotics in Critical Care of Stroke Patients - A Preventive Approach to Post-stroke Infections? Cureus 12(3):e7158. [PubMed: 32257701]
59. Crapser J, et al. (2016) Ischemic stroke induces gut permeability and enhances bacterial translocation leading to sepsis in aged mice. Aging 8(5):1049–1063. [PubMed: 27115295]
60. Hasan N & Yang H (2019) Factors affecting the composition of the gut microbiota, and its modulation. PeerJ 7:e7502. [PubMed: 31440436]
61. Vendrik KEW, et al. (2020) Fecal Microbiota Transplantation in Neurological Disorders. Front Cell Infect Microbiol 10:98. [PubMed: 32266160]
62. Du Y, Gao XR, Peng L, & Ge JF (2020) Crosstalk between the microbiota-gut-brain axis and depression. Heliyon 6(6):e04097. [PubMed: 32529075]
63. Tilocca B, et al. (2020) Gut-Brain Axis and Neurodegeneration: State-of-the-Art of Meta-Omics Sciences for Microbiota Characterization. Int J Mol Sci 21(11).
64. Kaur G, et al. (2020) Dysregulation of the Gut-Brain Axis, Dysbiosis and Influence of numerous factors on Gut Microbiota associated Parkinson's Disease. Curr Neuropharmacol.
65. Pusceddu MM & Del Bas JM (2020) The role of the gut microbiota in the pathophysiology of mental and neurological disorders. Psychiatr Genet.
66. Obrenovich M, et al. (2020) The Role of the Microbiota-Gut-Brain Axis and Antibiotics in ALS and Neurodegenerative Diseases. Microorganisms 8(5).

67. Vuotto C, Battistini L, Caltagirone C, & Borsellino G (2020) Gut Microbiota and Disorders of the Central Nervous System. Neuroscientist:1073858420918826.
68. Dicksved J, et al. (2008) Molecular analysis of the gut microbiota of identical twins with Crohn's disease. Isme j 2(7):716–727. [PubMed: 18401439]
69. Turnbaugh PJ, et al. (2009) A core gut microbiome in obese and lean twins. Nature 457(7228):480–484. [PubMed: 19043404]
70. Li K, et al. (2020) Host Genetic and Environmental Factors Shape the Composition and Function of Gut Microbiota in Populations Living at High Altitude. Biomed Res Int 2020:1482109. [PubMed: 32190648]
71. Lerner A, Matthias T, & Aminov R (2017) Potential Effects of Horizontal Gene Exchange in the Human Gut. Frontiers in immunology 8:1630–1630. [PubMed: 29230215]
72. Joice R, Yasuda K, Shafquat A, Morgan XC, & Huttenhower C (2014) Determining microbial products and identifying molecular targets in the human microbiome. Cell Metab 20(5):731–741. [PubMed: 25440055]
73. Li J, et al. (2014) An integrated catalog of reference genes in the human gut microbiome. Nature Biotechnology 32(8):834–841.
74. Aguiar-Pulido V, et al. (2016) Metagenomics, Metatranscriptomics, and Metabolomics Approaches for Microbiome Analysis. Evolutionary bioinformatics online 12(Suppl 1):5–16. [PubMed: 27199545]
75. Tabrett A & Horton MW (2020) The influence of host genetics on the microbiome. *F1000Research 9*:F1000 Faculty Rev-1084.
76. Goodrich JK, Davenport ER, Clark AG, & Ley RE (2017) The Relationship Between the Human Genome and Microbiome Comes into View. Annual review of genetics 51:413–433.
77. Goodrich JK, Davenport ER, Waters JL, Clark AG, & Ley RE (2016) Cross-species comparisons of host genetic associations with the microbiome. Science (New York, N.Y.) 352(6285):532–535.
78. Benson AK, et al. (2010) Individuality in gut microbiota composition is a complex polygenic trait shaped by multiple environmental and host genetic factors. Proc Natl Acad Sci U S A 107(44):18933–18938. [PubMed: 20937875]
79. Bonder MJ, et al. (2016) The effect of host genetics on the gut microbiome. Nat Genet 48(11):1407–1412. [PubMed: 27694959]
80. Goodrich JK, et al. (2016) Genetic Determinants of the Gut Microbiome in UK Twins. Cell Host Microbe 19(5):731–743. [PubMed: 27173935]
81. Rothschild D, et al. (2018) Environment dominates over host genetics in shaping human gut microbiota. Nature 555(7695):210–215. [PubMed: 29489753]
82. Wang J, et al. (2016) Genome-wide association analysis identifies variation in vitamin D receptor and other host factors influencing the gut microbiota. Nat Genet 48(11):1396–1406. [PubMed: 27723756]
83. Peiffer JA, et al. (2013) Diversity and heritability of the maize rhizosphere microbiome under field conditions. Proc Natl Acad Sci U S A 110(16):6548–6553. [PubMed: 23576752]
84. Zmora N, Suez J, & Elinav E (2019) You are what you eat: diet, health and the gut microbiota. Nat Rev Gastroenterol Hepatol 16(1):35–56. [PubMed: 30262901]
85. Clements SJ & S RC (2018) Diet, the intestinal microbiota, and immune health in aging. Crit Rev Food Sci Nutr 58(4):651–661. [PubMed: 27712080]
86. Clarke SF, et al. (2012) The gut microbiota and its relationship to diet and obesity: new insights. Gut microbes 3(3):186–202. [PubMed: 22572830]
87. Turnbaugh PJ, Backhed F, Fulton L, & Gordon JI (2008) Diet-induced obesity is linked to marked but reversible alterations in the mouse distal gut microbiome. Cell Host Microbe 3(4):213–223. [PubMed: 18407065]
88. De Filippo C, et al. (2010) Impact of diet in shaping gut microbiota revealed by a comparative study in children from Europe and rural Africa. Proceedings of the National Academy of Sciences 107(33):14691.

89. Madsen L, Myrmel LS, Fĵre E, Liaset B, & Kristiansen K (2017) Links between Dietary Protein Sources, the Gut Microbiota, and Obesity. Frontiers in physiology 8:1047–1047. [PubMed: 29311977]

90. Murphy EA, Velazquez KT, & Herbert KM (2015) Influence of high-fat diet on gut microbiota: a driving force for chronic disease risk. Current opinion in clinical nutrition and metabolic care 18(5):515–520. [PubMed: 26154278]

91. Munukka E, et al. (2012) Women with and without metabolic disorder differ in their gut microbiota composition. Obesity (Silver Spring) 20(5):1082–1087. [PubMed: 22293842]

92. Yatsunenko T, et al. (2012) Human gut microbiome viewed across age and geography. Nature 486(7402):222–227. [PubMed: 22699611]

93. Zeisel SH & Warrier M (2017) Trimethylamine N-Oxide, the Microbiome, and Heart and Kidney Disease. Annu Rev Nutr 37:157–181. [PubMed: 28715991]

94. Shi X, et al. (2015) Simultaneous quantification of naproxcinod and its active metabolite naproxen in rat plasma using LC-MS/MS: application to a pharmacokinetic study. J Chromatogr B Analyt Technol Biomed Life Sci 978-979:157–162.

95. Koeth RA, et al. (2013) Intestinal microbiota metabolism of L-carnitine, a nutrient in red meat, promotes atherosclerosis. Nat Med 19(5):576–585. [PubMed: 23563705]

96. Salazar N, Valdes-Varela L, Gonzalez S, Gueimonde M, & de Los Reyes-Gavilan CG (2017) Nutrition and the gut microbiome in the elderly. Gut Microbes 8(2):82–97. [PubMed: 27808595]

97. Rizzatti G, Ianiro G, & Gasbarrini A (2018) Antibiotic and Modulation of Microbiota: A New Paradigm? J Clin Gastroenterol 52 Suppl 1, Proceedings from the 9th Probiotics, Prebiotics and New Foods, Nutraceuticals and Botanicals for Nutrition & Human and Microbiota Health Meeting, held in Rome, Italy from September 10 to 12, 2017:S74–S77.

98. Neuman H, Forsythe P, Uzan A, Avni O, & Koren O (2018) Antibiotics in early life: dysbiosis and the damage done. FEMS Microbiol Rev 42(4):489–499. [PubMed: 29945240]

99. Clapp M, et al. (2017) Gut microbiota's effect on mental health: The gut-brain axis. Clinics and practice 7(4):987–987. [PubMed: 29071061]

100. Card RM, et al. (2015) Impact of Ciprofloxacin and Clindamycin Administration on GramNegative Bacteria Isolated from Healthy Volunteers and Characterization of the Resistance Genes They Harbor. Antimicrobial agents and chemotherapy 59(8):4410–4416. [PubMed: 25987611]

101. Inoue S, Saito M, & Kotani J (2018) Immunosenescence in neurocritical care. J Intensive Care 6:65. [PubMed: 30349725]

102. Nagpal R, et al. (2018) Gut microbiome and aging: Physiological and mechanistic insights. Nutrition and healthy aging 4(4):267–285. [PubMed: 29951588]

103. Kohler CA, et al. (2016) The Gut-Brain Axis, Including the Microbiome, Leaky Gut and Bacterial Translocation: Mechanisms and Pathophysiological Role in Alzheimer's Disease. Curr Pharm Des 22(40):6152–6166. [PubMed: 27604604]

104. Ahmadi S, et al. (2020) A human-origin probiotic cocktail ameliorates aging-related leaky gut and inflammation via modulating the microbiota/taurine/tight junction axis. JCI Insight 5(9).

105. Fransen F, et al. (2017) Aged Gut Microbiota Contributes to Systemical Inflammaging after Transfer to Germ-Free Mice. Front Immunol 8:1385. [PubMed: 29163474]

106. Rampelli S, et al. (2013) Functional metagenomic profiling of intestinal microbiome in extreme ageing. Aging (Albany NY) 5(12):902–912. [PubMed: 24334635]

107. Collino S, et al. (2013) Metabolic signatures of extreme longevity in northern Italian centenarians reveal a complex remodeling of lipids, amino acids, and gut microbiota metabolism. PLoS One 8(3):e56564. [PubMed: 23483888]

108. Mace JL, Porter RJ, Dalrymple-Alford JC, Wesnes KA, & Anderson TJ (2010) Effects of acute tryptophan depletion on neuropsychological and motor function in Parkinson's disease. J Psychopharmacol 24(10):1465–1472. [PubMed: 19460872]

109. Qin Y & Wade PA (2018) Crosstalk between the microbiome and epigenome: messages from bugs. J Biochem 163(2):105–112. [PubMed: 29161429]

110. Cusack S, O'Toole PW, & consortium E (2013) Challenges and implications for biomedical research and intervention studies in older populations: insights from the ELDERMET study. Gerontology 59(2):114–121. [PubMed: 23146954]
111. Xu C, Zhu H, & Qiu P (2019) Aging progression of human gut microbiota. BMC Microbiology 19(1):236. [PubMed: 31660868]
112. Kawas CH & Corrada MM (2006) Alzheimer's and dementia in the oldest-old: a century of challenges. Current Alzheimer research 3(5):411–419. [PubMed: 17168640]
113. Association As (2019) Alzheimer's Disease Facts and Figures. Alzheimers Dement 15(3):321–387.
114. Maccioni RB, et al. (2020) Inflammation: A Major Target for Compounds to Control Alzheimer's Disease. J Alzheimers Dis.
115. Honarpisheh P, et al. (2020) Dysregulated Gut Homeostasis Observed Prior to the Accumulation of the Brain Amyloid-β in Tg2576 Mice. IntJ Mol Sci 21(5).
116. Kim MS, et al. (2020) Transfer of a healthy microbiota reduces amyloid and tau pathology in an Alzheimer's disease animal model. Gut 69(2):283–294. [PubMed: 31471351]
117. Sun J, et al. (2019) Fecal microbiota transplantation alleviated Alzheimer's disease-like pathogenesis in APP/PS1 transgenic mice. Transl Psychiatry 9(1):189. [PubMed: 31383855]
118. Stanley D, et al. (2016) Translocation and dissemination of commensal bacteria in post-stroke infection. Nat Med 22(11):1277–1284. [PubMed: 27694934]
119. Wen SW, et al. (2019) Advanced age promotes colonic dysfunction and gut-derived lung infection after stroke. Aging Cell 18(5):e12980. [PubMed: 31199577]
120. Sánchez B, et al. (2017) Probiotics, gut microbiota, and their influence on host health and disease. Molecular Nutrition & Food Research 61(1):1600240.
121. López-Moreno A, Suárez A, Avanzi C, Monteoliva-Sánchez M, & Aguilera M (2020) Probiotic Strains and Intervention Total Doses for Modulating Obesity-Related Microbiota Dysbiosis: A Systematic Review and Meta-analysis. Nutrients 12(7).
122. Toward R, Montandon S, Walton G, & Gibson GR (2012) Effect of prebiotics on the human gut microbiota of elderly persons. Gut Microbes 3(l):57–60. [PubMed: 22555548]
123. Ebrahimzadeh Leylabadlo H, Sanaie S, Sadeghpour Heravi F, Ahmadian Z, & Ghotaslou R (2020) From role of gut microbiota to microbial-based therapies in type 2-diabetes. Infect Genet Evol 81:104268. [PubMed: 32126303]
124. Paiva IHR, Duarte-Silva E, & Peixoto CA (2020) The role of prebiotics in cognition, anxiety, and depression. Eur Neuropsychopharmacol 34:1–18. [PubMed: 32241688]
125. He M & Shi B (2017) Gut microbiota as a potential target of metabolic syndrome: the role of probiotics and prebiotics. Cell Biosci 7:54. [PubMed: 29090088]
126. Takemura N, Okubo T, & Sonoyama K (2010) Lactobacillus plantarum strain No. 14 reduces adipocyte size in mice fed high-fat diet. Exp Biol Med (Maywood) 235(7):849–856. [PubMed: 20558839]
127. Chen Z, et al. (2014) Incorporation of therapeutically modified bacteria into gut microbiota inhibits obesity. J Clin Invest 124(8):3391–3406. [PubMed: 24960158]
128. Kadooka Y, et al. (2010) Regulation of abdominal adiposity by probiotics (Lactobacillus gasseri SBT2055) in adults with obese tendencies in a randomized controlled trial. Eur J Clin Nutr 64(6):636–643. [PubMed: 20216555]
129. Genta S, et al. (2009) Yacon syrup: beneficial effects on obesity and insulin resistance in humans. Clin Nutr 28(2):182–187. [PubMed: 19254816]
130. Parnell JA & Reimer RA (2009) Weight loss during oligofructose supplementation is associated with decreased ghrelin and increased peptide YY in overweight and obese adults. Am J Clin Nutr 89(6):1751–1759. [PubMed: 19386741]
131. Liong MT, Dunshea FR, & Shah NP (2007) Effects of a synbiotic containing Lactobacillus acidophilus ATCC 4962 on plasma lipid profiles and morphology of erythrocytes in hypercholesterolaemic pigs on high- and low-fat diets. Br J Nutr 98(4):736–744. [PubMed: 17490507]

132. Ataie-Jafari A, Larijani B, Alavi Majd H, & Tahbaz F (2009) Cholesterol-lowering effect of probiotic yogurt in comparison with ordinary yogurt in mildly to moderately hypercholesterolemic subjects. Ann Nutr Metab 54(l):22–27. [PubMed: 19229114]
133. Akash MSH, Fiayyaz F, Rehman K, Sabir S, & Rasool MFI (2019) Gut Microbiota and Metabolic Disorders: Advances in Therapeutic Interventions. Crit Rev Immunol 39(4):223–237. [PubMed: 32421966]
134. Sivamaruthi BS, Fern LA, Rashidah Pg Hj Ismail DSN, & Chaiyasut C (2020) The influence of probiotics on bile acids in diseases and aging. Biomed Pharmacother 128:110310. [PubMed: 32504921]
135. Cerdo T, Garcia-Santos JA, M GB, & Campoy C (2019) The Role of Probiotics and Prebiotics in the Prevention and Treatment of Obesity. Nutrients 11(3).
136. Romo-Araiza A & Ibarra A (2020) Prebiotics and probiotics as potential therapy for cognitive impairment. Med Hypotheses 134:109410. [PubMed: 31627123]
137. Assuncao N, Sudo FK, Drummond C, de Felice FG, & Mattos P (2018) Metabolic Syndrome and cognitive decline in the elderly: A systematic review. PLoS One 13(3):e0194990. [PubMed: 29579115]
138. Carabotti M, Scirocco A, Maselli MA, & Severi C (2015) The gut-brain axis: interactions between enteric microbiota, central and enteric nervous systems. Ann Gastroenterol 28(2):203–209. [PubMed: 25830558]
139. Bonfili L, et al. (2020) Gut microbiota manipulation through probiotics oral administration restores glucose homeostasis in a mouse model of Alzheimer's disease. Neurobiol Aging 87:35–43. [PubMed: 31813629]
140. Akhoundzadeh K, Vakili A, Shadnoush M, & Sadeghzadeh J (2018) Effects of the Oral Ingestion of Probiotics on Brain Damage in a Transient Model of Focal Cerebral Ischemia in Mice. Iran J Med Sci 43(1):32–40. [PubMed: 29398750]
141. Sun J, et al. (2016) Clostridium butyricum pretreatment attenuates cerebral ischemia/reperfusion injury in mice via anti-oxidation and anti-apoptosis. Neurosci Lett 613:30–35. [PubMed: 26733300]
142. Lif Holgerson P, Esberg A, Sjodin A, West CE, & Johansson I (2020) A longitudinal study of the development of the saliva microbiome in infants 2 days to 5 years compared to the microbiome in adolescents. Sci Rep 10(1):9629. [PubMed: 32541791]
143. Yahfoufi N, Matar C, & Ismail N (2020) Adolescence and Aging: Impact of Adolescence Inflammatory Stress and Microbiota Alterations on Brain Development, Aging, and Neurodegeneration. J Gerontol A Biol Sci Med Sci 75(7):1251–1257. [PubMed: 31917834]
144. Dillon SM, et al. (2020) Age-related alterations in human gut CD4 T cell phenotype, T helper cell frequencies, and functional responses to enteric bacteria. J Leukoc Biol 107(1):119–132. [PubMed: 31573727]
145. Zhang X, et al. (2020) Age-related compositional changes and correlations of gut microbiome, serum metabolome, and immune factor in rats. Geroscience.
146. Adriansjach J, et al. (2020) Age-Related Differences in the Gut Microbiome of Rhesus Macaques. J Gerontol A Biol Sci Med Sci 75(7):1293–1298. [PubMed: 32052009]
147. Wu L, et al. (2020) Age-Related Variation of Bacterial and Fungal Communities in Different Body Habitats across the Young, Elderly, and Centenarians in Sardinia. mSphere 5(1).
148. Cox LM, et al. (2019) Calorie restriction slows age-related microbiota changes in an Alzheimer's disease model in female mice. Sci Rep 9(1):17904. [PubMed: 31784610]
149. Vlachos GS & Scarmeas N (2019) Dietary interventions in mild cognitive impairment and dementia. Dialogues Clin Neurosci 21(l):69–82. [PubMed: 31607782]
150. Lee C & Longo V (2016) Dietary restriction with and without caloric restriction for healthy aging. F1000Res 5.
151. Fernandes MF, de Oliveira S, Portovedo M, Rodrigues PB, & Vinolo MAR (2020) Effect of Short Chain Fatty Acids on Age-Related Disorders. Adv Exp Med Biol 1260:85–105. [PubMed: 32304031]
152. Lee JVV, Durgan DJ., McCullough LD, Bryan RM (2020) Effects of the Gut Microbiome on Aged-Related Cognitive Decline and Inflammation. The FASEB Journal 34(S1).

153. Singh H, et al. (2019) Gastro-intestinal and oral microbiome signatures associated with healthy aging. Geroscience 41(6):907–921. [PubMed: 31620923]

154. Picca A, et al. (2019) Gut Microbial, Inflammatory and Metabolic Signatures in Older People with Physical Frailty and Sarcopenia: Results from the BIOSPHERE Study. Nutrients 12(1).

155. Ctoi AF, et al. (2020) Gut microbiota and aging-A focus on centenarians. Biochim Biophys Acta Mol Basis Dis 1866(7):165765. [PubMed: 32169505]

156. Ticinesi A, Nouvenne A, Tana C, Prati B, & Meschi T (2019) Gut Microbiota and Microbiota-Related Metabolites as Possible Biomarkers of Cognitive Aging. Adv Exp Med Biol 1178:129–154. [PubMed: 31493226]

157. Luo D, et al. (2020) Gut microbiota combined with metabolomics reveals the metabolic profile of the normal aging process and the anti-aging effect of FuFang Zhenshu TiaoZhi(FTZ) in mice. Biomed Pharmacother 121:109550. [PubMed: 31704617]

158. Shimizu Y (2018) Gut microbiota in common elderly diseases affecting activities of daily living. World J Gastroenterol 24(42):4750–4758. [PubMed: 30479462]

159. Ang QY, et al. (2020) Ketogenic Diets Alter the Gut Microbiome Resulting in Decreased Intestinal Th17 Cells. Cell 181(6):1263–1275 e1216. [PubMed: 32437658]

160. Zhang DI, Li C, Shi R, Zhao F, & Yang Z (2020) Lactobacillus fermentum JX306 Restrain D-galactose-induced Oxidative Stress of Mice through its Antioxidant Activity. Pol J Microbiol 69(2):205–215. [PubMed: 32548989]

161. Hor YY, et al. (2019) Lactobacillus sp. improved microbiota and metabolite profiles of aging rats. Pharmacol Res 146:104312. [PubMed: 31207344]

162. Donaldson DS, Pollock J, Vohra P, Stevens MP, & Mabbott NA (2020) Microbial Stimulation Reverses the Age-Related Decline in M Cells in Aged Mice. iScience 23(6):101147. [PubMed: 32454449]

163. Lye HS, et al. (2018) Modifying progression of aging and reducing the risk of neurodegenerative diseases by probiotics and synbiotics. Front Biosci (Elite Ed) 10:344–351. [PubMed: 29293462]

164. Romo-Araiza A, et al. (2018) Probiotics and Prebiotics as a Therapeutic Strategy to Improve Memory in a Model of Middle-Aged Rats. Front Aging Neurosci 10:416. [PubMed: 30618722]

165. Piggott DA & Tuddenham S (2020) The gut microbiome and frailty. Transl Res 221:23–43. [PubMed: 32360945]

166. Magrone T & Jirillo E (2013) The interaction between gut microbiota and age-related changes in immune function and inflammation. Immun Ageing 10(1):31. [PubMed: 23915308]

167. Bana B & Cabreiro F (2019) The Microbiome and Aging. Annu Rev Genet 53:239–261. [PubMed: 31487470]

168. Hor YY, et al. (2020) The molecular mechanisms of probiotic strains in improving aging bone and muscle of D-galactose-induced aging rats. J Appl Microbiol.

169. O'Toole PW & Shiels PG (2020) The role of the microbiota in sedentary lifestyle disorders and ageing: lessons from the animal kingdom. J Intern Med 287(3):271–282. [PubMed: 31957113]

170. Chen Y, et al. (2020) Transplant of microbiota from long-living people to mice reduces aging-related indices and transfers beneficial bacteria. Aging (Albany NY) 12(6):4778–4793. [PubMed: 32176868]

171. Bonsack B, Jiang RH, & Borlongan CV (2020) A gut feeling about stroke reveals gut-brain axis' active role in homeostasis and dysbiosis. J Cereb Blood Flow Metab 40(5):1132–1134. [PubMed: 32063084]

172. Benakis C, et al. (2020) Distinct Commensal Bacterial Signature in the Gut Is Associated With Acute and Long-Term Protection From Ischemic Stroke. Stroke 51(6):1844–1854. [PubMed: 32404038]

173. Xu XD & Shao F (2015) Enteral ecoimmunonutrition reduced enteral permeability and serum ghrelin activity in severe cerebral stroke patients with lung infection. Cell Biochem Biophys 71(1):195–198. [PubMed: 25142270]

174. Yamashiro K, et al. (2017) Gut dysbiosis is associated with metabolism and systemic inflammation in patients with ischemic stroke. PLoS One 12(2):e0171521. [PubMed: 28166278]

175. Tan BYQ, Paliwal PR, & Sharma VK (2020) Gut Microbiota and Stroke. Ann Indian Acad Neurol 23(2):155–158. [PubMed: 32189854]
176. Prame Kumar K & Wong CH (2020) Imbalance in the force: the dark side of the microbiota on stroke risk and progression. Curr Opin Neurobiol 62:10–16. [PubMed: 31809996]
177. Xia GH, et al. (2019) Stroke Dysbiosis Index (SDI) in Gut Microbiome Are Associated With Brain Injury and Prognosis of Stroke. Front Neurol 10:397. [PubMed: 31068891]
178. Liu Y, et al. (2020) The Association of Post-Stroke Cognitive Impairment and Gut Microbiota and its Corresponding Metabolites. J Alzheimers Dis 73(4):1455–1466. [PubMed: 31929168]
179. Singh V, et al. (2018) The gut microbiome primes a cerebroprotective immune response after stroke. J Cereb Blood Flow Metab 38(8):1293–1298. [PubMed: 29846130]
180. Singh V, et al. (2016) Microbiota Dysbiosis Controls the Neuroinflammatory Response after Stroke. J Neurosci 36(28):7428–7440. [PubMed: 27413153]
181. Angelucci F, Cechova K, Amlerova J, & Hort J (2019) Antibiotics, gut microbiota, and Alzheimer's disease. J Neuroinflammation 16(1):108. [PubMed: 31118068]
182. Vogt NM, et al. (2017) Gut microbiome alterations in Alzheimer's disease. Sci Rep 7(1):13537. [PubMed: 29051531]
183. Pluta R, Ulamek-Koziol M, Januszewski S, & Czuczwar SJ (2020) Gut microbiota and pro/prebiotics in Alzheimer's disease. Aging (Albany NY) 12(6):5539–5550. [PubMed: 32191919]
184. Zhuang ZQ, et al. (2018) Gut Microbiota is Altered in Patients with Alzheimer's Disease. J Alzheimers Dis 63(4):1337–1346. [PubMed: 29758946]
185. Park JY, et al. (2017) Metagenome Analysis of Bodily Microbiota in a Mouse Model of Alzheimer Disease Using Bacteria-derived Membrane Vesicles in Blood. Exp Neurobiol 26(6):369–379. [PubMed: 29302204]
186. Li B, et al. (2019) Mild cognitive impairment has similar alterations as Alzheimer's disease in gut microbiota. Alzheimers Dement 15(10):1357–1366. [PubMed: 31434623]
187. Kruger JF, Hillesheim E, Pereira A, Camargo CQ, & Rabito EI (2020) Probiotics for dementia: a systematic review and meta-analysis of randomized controlled trials. Nutr Rev.
188. Saji N, et al. (2020) Relationship between dementia and gut microbiome-associated metabolites: a cross-sectional study in Japan. Sci Rep 10(1):8088. [PubMed: 32424166]
189. Sun Y, et al. (2020) The Gut Microbiome as a Therapeutic Target for Cognitive Impairment. J Gerontol A Biol Sci Med Sci 75(7):1242–1250. [PubMed: 31811292]
190. Panza F, Lozupone M, Solfrizzi V, Watling M, & Imbimbo BP (2019) Time to test antibacterial therapy in Alzheimer's disease. Brain 142(10):2905–2929. [PubMed: 31532495]
191. Stebegg M, et al. (2019) Heterochronic faecal transplantation boosts gut germinal centres in aged mice. Nat Commun 10(1):2443. [PubMed: 31164642]
192. Benakis C, et al. (2016) Commensal microbiota affects ischemic stroke outcome by regulating intestinal gammadelta T cells. Nat Med 22(5):516–523. [PubMed: 27019327]
193. Zeng X, et al. (2019) Higher Risk of Stroke Is Correlated With Increased Opportunistic Pathogen Load and Reduced Levels of Butyrate-Producing Bacteria in the Gut. Front Cell Infect Microbiol 9:4. [PubMed: 30778376]
194. Chen R, et al. (2019) Transplantation of fecal microbiota rich in short chain fatty acids and butyric acid treat cerebral ischemic stroke by regulating gut microbiota. Pharmacol Res 148:104403. [PubMed: 31425750]
195. Liu P, et al. (2019) Altered microbiomes distinguish Alzheimer's disease from amnestic mild cognitive impairment and health in a Chinese cohort. Brain Behav Immun 80:633–643. [PubMed: 31063846]
196. Fujii Y, et al. (2019) Fecal metabolite of a gnotobiotic mouse transplanted with gut microbiota from a patient with Alzheimer's disease. Biosci Biotechnol Biochem 83(11):2144–2152. [PubMed: 31327302]
197. Dodiya HB, et al. (2019) Sex-specific effects of microbiome perturbations on cerebral Abeta amyloidosis and microglia phenotypes. J Exp Med 216(7):1542–1560. [PubMed: 31097468]

198. Matsumoto M, Kurihara S, Kibe R, Ashida H, & Benno Y (2011) Longevity in mice is promoted by probiotic-induced suppression of colonic senescence dependent on upregulation of gut bacterial polyamine production. PLoS One 6(8):e23652. [PubMed: 21858192]

199. Sun T, et al. (2020) Association of Gut Microbiota-Dependent Metabolite Trimethylamine N-Oxide with First Ischemic Stroke. J Atheroscler Thromb.

200. Tan C, et al. (2020) Dysbiosis of Gut Microbiota and Short-Chain Fatty Acids in Acute Ischemic Stroke and the Subsequent Risk for Poor Functional Outcomes. JPEN J Parenter Enteral Nutr.

201. Sadler R, et al. (2020) Short-Chain Fatty Acids Improve Poststroke Recovery via Immunological Mechanisms. J Neurosci 40(5):1162–1173. [PubMed: 31889008]

202. Kaur H, et al. (2020) Effects of Probiotic Supplementation on Short Chain Fatty Acids in the AppNL-G-F Mouse Model of Alzheimer's Disease. J Alzheimers Dis.

203. Kaur H, et al. (2020) Probiotics ameliorate intestinal pathophysiology in a mouse model of Alzheimer's disease. Neurobiol Aging 92:114–134. [PubMed: 32417748]

204. Yang X, Yu D, Xue L, Li H, & Du J (2020) Probiotics modulate the microbiota-gut-brain axis and improve memory deficits in aged SAMP8 mice. Acta Pharm Sin B 10(3):475–487. [PubMed: 32140393]

205. van de Wouw M, et al. (2018) Short-chain fatty acids: microbial metabolites that alleviate stress-induced brain-gut axis alterations. J Physiol 596(20):4923–4944. [PubMed: 30066368]

206. Rodriguez-Campello A, et al. (2014) Dietary habits in patients with ischemic stroke: a case-control study. PLoS One 9(12):e114716. [PubMed: 25506934]

207. Syeda T, et al. (2018) Bioactive Food Abates Metabolic and Synaptic Alterations by Modulation of Gut Microbiota in a Mouse Model of Alzheimer's Disease. J Alzheimers Dis 66(4):1657–1682. [PubMed: 30475761]

208. Sun J, et al. (2019) Fructooligosaccharides Ameliorating Cognitive Deficits and Neurodegeneration in APP/PS1 Transgenic Mice through Modulating Gut Microbiota. J Agric Food Chem 67(10):3006–3017. [PubMed: 30816709]

209. Nagpal R, Neth BJ, Wang S, Craft S, & Yadav H (2019) Modified Mediterranean-ketogenic diet modulates gut microbiome and short-chain fatty acids in association with Alzheimer's disease markers in subjects with mild cognitive impairment. EBioMedicine 47:529–542. [PubMed: 31477562]

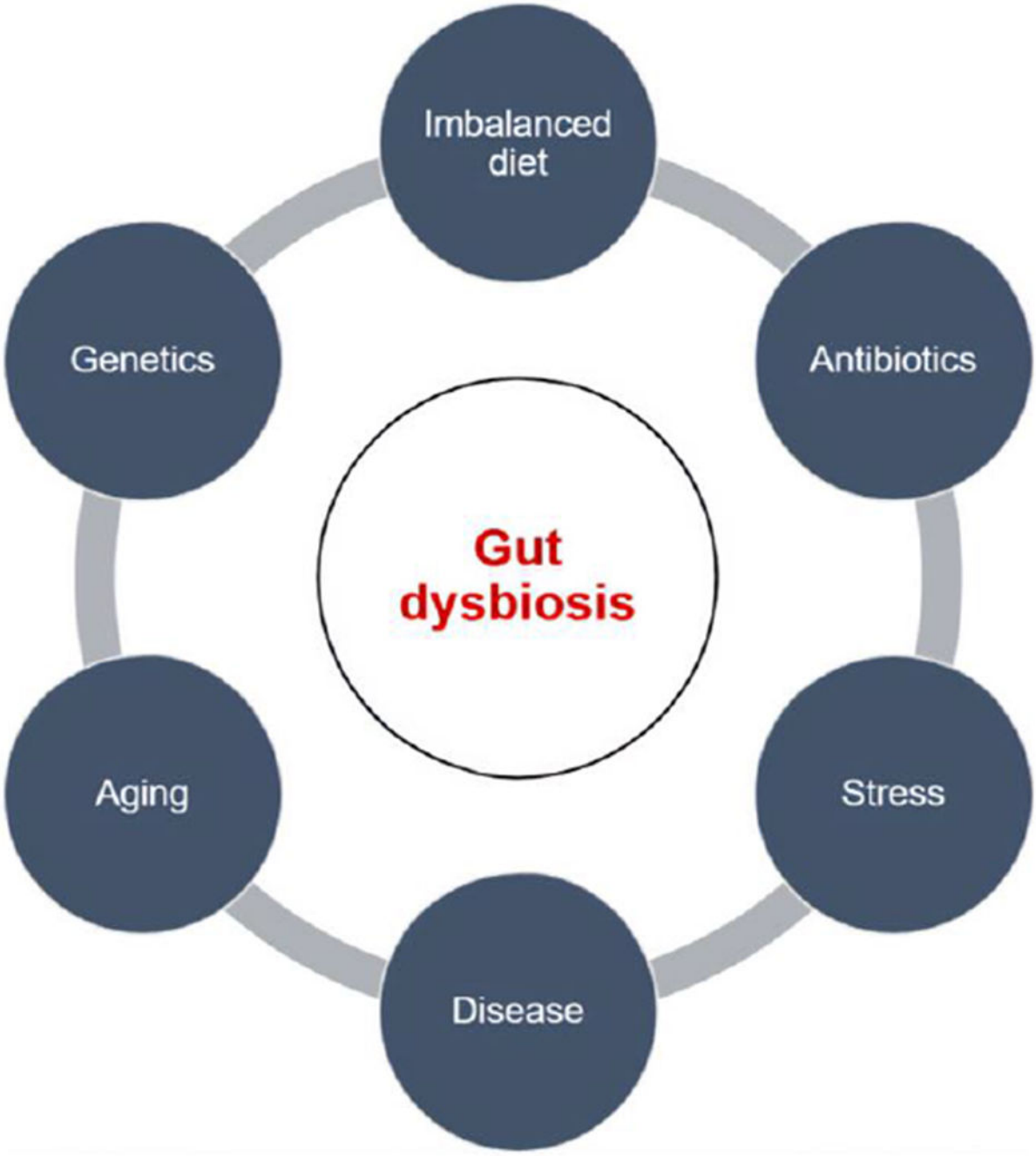

Fig 1.
Factors that can influence gut microbiota composition and cause gut dysbiosis

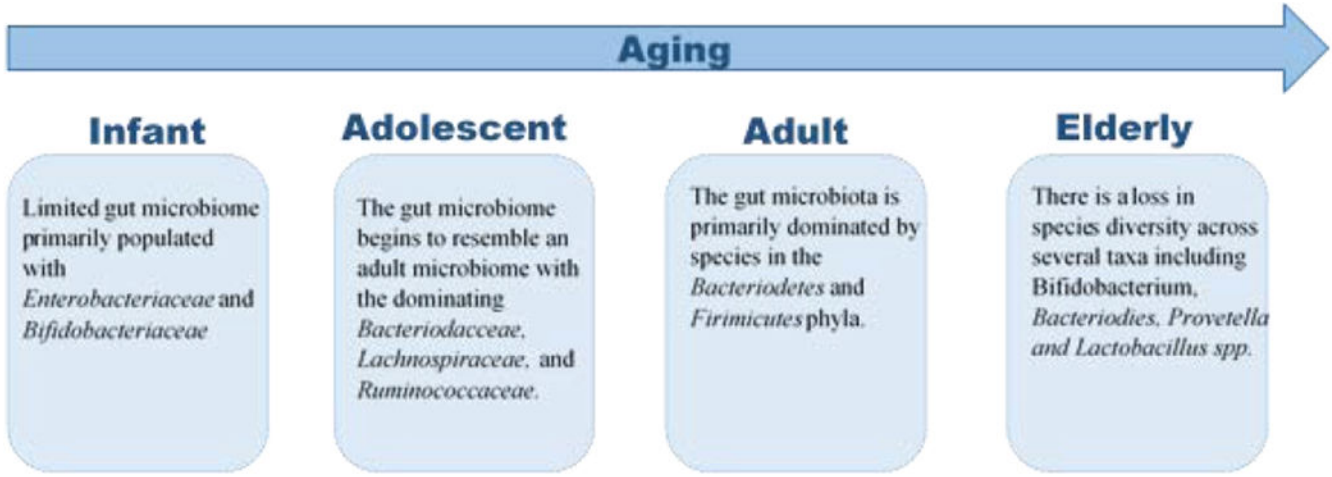

Fig 2.

Changes in gut microbiota with aging. Examples of the dominant bacterial species found human intestinal tract during different stages of human development from birth. As aging occurs, there is a decrease in microbial diversity and significant shifts in the microbiome that can lead to gut dysbiosis.

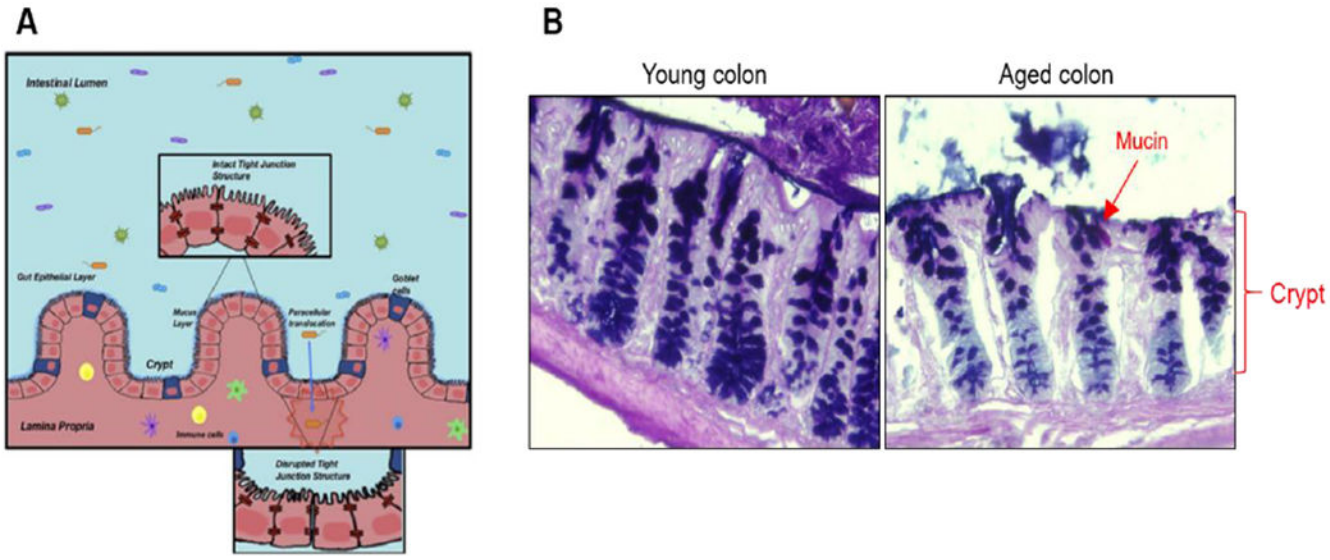

Fig 3.

(A) Disruption in gut epithelial structure may allow the translocation of commensal bacteria and toxic signals into the host which cause both inflammation and infection. **(B)** Age-associated impairment of the histological architecture and the mucin production in the colon. Colonic tissues were collected from young (2-3 months) and aged (18-20 months) mice and stained with Alcian-blue and periodic acid-Schiff staining to examine the global structure and mucins.

Table I.

CHANGES IN THE MICROBIOME IN AGING

Disease	Study Title	Reference
Aging	A Human-Origin Probiotic Cocktail Ameliorates Aging-Related Leaky Gut And Inflammation Via Modulating The Microbiota/Taurine/Tight Junction Axis	(104)
Aging	A Longitudinal Study Of The Development Of The Saliva Microbiome In Infants 2 Days To 5 Years Compared To The Microbiome In Adolescents	(142)
Aging	Adolescence And Aging: Impact Of Adolescence Inflammatory Stress And Microbiota Alterations On Brain Development, Aging, And Neurodegeneration	(143)
Aging	Age-Related Alterations In Human Gut Cd4 T Cell Phenotype, T Helper Cell Frequencies, And Functional Responses To Enteric Bacteria	(144)
Aging	Age-Related Compositional Changes And Correlations Of Gut Microbiome, Serum Metabolome, And Immune Factor In Rats	(145)
Aging	Age-Related Differences In The Gut Microbiome Of Rhesus Macaques	(146)
Aging	Age-Related Variation Of Bacterial And Fungal Communities In Different Body Habitats Across The Young, Elderly, And Centenarians In Sardinia	(147)
Aging	Calorie Restriction Slows Age-Related Microbiota Changes In An Alzheimer's Disease Model In Female Mice	(148)
Aging	Dietary Interventions In Mild Cognitive Impairment And Dementia	(149)
Aging	Dietary Restriction With And Without Caloric Restriction For Healthy Aging	(150)
Aging	Effect Of Short Chain Fatty Acids On Age-Related Disorders	(151)
Aging	Effects Of The Gut Microbiome On Aged-Related Cognitive Decline And Inflammation	(152)
Aging	Gastro-Intestinal And Oral Microbiome Signatures Associated With Healthy Aging	(153)
Aging	Gut Microbial, Inflammatory And Metabolic Signatures In Older People With Physical Frailty And Sarcopenia: Results From The Biosphere Study	(154)
Aging	Gut Microbiota And Aging-A Focus On Centenarians	(155)
Aging	Gut Microbiota And Microbiota-Related Metabolites As Possible Biomarkers Of Cognitive Aging	(156)
Aging	Gut Microbiota Combined With Metabolomics Reveals The Metabolic Profile Of The Normal Aging Process And The Anti-Aging Effect Of Fufang Zhenshu Tiaozhi(FTZ) In Mice	(157)
Aging	Gut Microbiota In Common Elderly Diseases Affecting Activities Of Daily Living	(158)
Aging	Ketogenic Diets Alter The Gut Microbiome Resulting In Decreased Intestinal Th17 Cells	(159)
Aging	*Lactobacillus Fermentum* JX306 Restrain D-Galactose-Induced Oxidative Stress Of Mice Through Its Antioxidant Activity	(160)
Aging	Lactobacillus Sp. Improved Microbiota And Metabolite Profiles Of Aging Rats	(161)
Aging	Microbial Stimulation Reverses The Age-Related Decline In M Cells In Aged Mice	(162)
Aging	Modifying Progression Of Aging And Reducing The Risk Of Neurodegenerative Diseases By Probiotics And Symbiotic	(163)
Aging	Probiotics And Prebiotics As A Therapeutic Strategy To Improve Memory In A Model Of Middle-Aged Rats	(164)
Aging	The Gut Microbiome And Frailty	(165)
Aging	The Interaction Between Gut Microbiota And Age-Related Changes In Immune Function And Inflammation	(166)
Aging	The Microbiome And Aging	(167)
Aging	The Molecular Mechanisms Of Probiotic Strains In Improving Aging Bone And Muscle Of D-Galactose-Induced Aging Rats	(168)
Aging	The Role Of The Microbiota In Sedentary Lifestyle Disorders And Ageing: Lessons From The Animal Kingdom	(169)
Aging	Transplant Of Microbiota From Long-Living People To Mice Reduces Aging-Related Indices And Transfers Beneficial Bacteria	(170)

Table II.

CHANGES IN THE MICROBIOME IN STROKE

Disease	Study Title	Reference
Stroke	A Gut Feeling About Stroke Reveals Gut-Brain Axis' Active Role In Homeostasis And Dysbiosis	(171)
Stroke	Age-Related Changes In The Gut Microbiota Influence Systemic Inflammation And Stroke Outcome	(9)
Stroke	Distinct Commensal Bacterial Signature In The Gut Is Associated With Acute And Long-Term Protection From Ischemic Stroke	(172)
Stroke	Enteral Eco-Immuno-Nutrition Reduced Enteral Permeability And Serum Ghrelin Activity In Severe Cerebral Stroke Patients With Lung Infection	(173)
Stroke	Examining The Role Of The Microbiota-Gut-Brain Axis In Stroke	(7)
Stroke	Gut Dysbiosis Is Associated With Metabolism And Systemic Inflammation In Patients With Ischemic Stroke	(174)
Stroke	Gut Microbiota And Stroke	(175)
Stroke	Imbalance In The Force: The Dark Side Of The Microbiota On Stroke Risk And Progression	(176)
Stroke	Stroke Dysbiosis Index (Sdi) In Gut Microbiome Are Associated With Brain Injury And Prognosis Of Stroke	(177)
Stroke	The Association Of Post-Stroke Cognitive Impairment And Gut Microbiota And Its Corresponding Metabolites	(178)
Stroke	The Gut Microbiome Primes A Cerebro-Protective Immune Response After Stroke	(179)
Stroke	Microbiota Dysbiosis Controls the Neuro-inflammatory Response after Stroke.	(180)
Stroke	Age-related changes in the gut microbiota influence systemic inflammation and stroke outcome.	(9)
Stroke	Gut dysbiosis is associated with metabolism and systemic Inflammation in patients with ischemic stroke.	(174)

Table III.

CHANGES IN THE MICROBIOME IN ALZHEIMER'S DISEASE

Disease	Study Title	Reference
Alzheimer's	Antibiotics, Gut Microbiota, And Alzheimer's Disease	(181)
Alzheimer's	Gut Microbiome Alterations In Alzheimer's Disease	(182)
Alzheimer's	Gut Microbiota And Pro/Prebiotics In Alzheimer's Disease	(183)
Alzheimer's	Gut Microbiota is Altered In Patients With Alzheimer's Disease	(184)
Alzheimer's	Metagenome Analysis Of Bodily Microbiota In A Mouse Model Of Alzheimer Disease Using Bacteria-Derived Membrane Vesicles In Blood	(185)
Alzheimer's	Mild Cognitive Impairment Has Similar Alterations As Alzheimer's Disease In Gut Microbiota	(186)
Alzheimer's	Modifying Progression Of Aging And Reducing The Risk Of Neurodegenerative Diseases By Probiotics And Symbiotic	(163)
Alzheimer's	Probiotics For Dementia: A Systematic Review And Meta-Analysis Of Randomized Controlled Trials	(187)
Alzheimer's	Relationship Between Dementia And Gut Microbiome-Associated Metabolites: A Cross-Sectional Study In Japan	(188)
Alzheimer's	The Gut Microbiome As A Therapeutic Target For Cognitive Impairment	(189)
Alzheimer's	Time To Test Antibacterial Therapy In Alzheimer's Disease	(190)

Table IV.

Interventional microbiome-based therapeutic approaches in clinical trials for Aging, Stroke, and Alzheimer's. Additional Information on Clinical trials can be found at the website of NIH clinical trials (https://clinicaltrials.gov/).

Condition	Study Title	Drug	Intervention	Trial ID
Stroke	Cognition and Gut Microbiome Associated Study of Shanghai People With Acute Ischemic Stroke	Probiotics	Diet Supplement	NCT03812445
Stroke	Gut Microbiota in Acute Stroke Patients	Fecal Sample Collection	Observational	NCT03934021
Stroke	The Effectiveness of Oral Health Promotion on Pneumonia Complicating Stroke		Behavioral	NCT04095780
Condition	**Study Title**	**Drug**	**Intervention**	**Trial ID**
Alzheimer's Disease	Taxonomic and Functional Composition of the Intestinal Microbiome: a Predictor of Rapid Cognitive Decline in Patients With Alzheimer's Disease	Fecal Sample Collection	Observational	NCT03487380
Alzheimer's Disease	The PREVENTION Trial: Precision Recommendations to Optimize Neurocognition (PREVENTION)		Behavioral	NCT04082611
Alzheimer's Disease	Study: Diet and Exercise Study to Improve Brain Blood Flow: Blood Flow Improvement Trial	Diet and Exercise	Behavioral	NCT03117829
Alzheimer's Disease	Oral Fecal Microbiota Transplant Feasibility Study in Alzheimer's Disease	Fecal Microbiota Transplant	Diet Supplement	NCT03998423
Condition	**Study Title**	**Drug**	**Intervention**	**Trial ID**
Aging, and Cognitive Decline	The Impact of Cranberries On the Microbiome and the Brain in Healthy Ageing sTudy (COMBAT)	Freeze-Dried Cranberry	Dietary Supplement	NCT03679533
Aging	Acarbose Anti-aging Effects in Geriatric Subjects (Substudy B & C)	Acarbose	n α-Glucosidase Inhibitor	NCT02865499
Aging	Study of Acarbose in Longevity	Acarbose	Drug	NCT02953093
Aging	Age-associated Arterial Dysfunction, Western Diet, and Aerobic Exercise: Role of the Gut Microbiome	Western Diet	Diet	NCT03334201
Aging	Resistant Starch and Nonstarch Polysaccharide (Dietary Fibre) Intake and the Colonic Microbiome in Older People	Dietary Fiber/ Resistant Starch	Diet Supplement	NCT02384174
Aging	Accelerated Genital Tract Aging in HIV: Estradiol Clinical Trial	Estradiol Vaginal Insert	Drug	NCT04079218
Aging	Synbiotic Use Effect Gut Bacteria and the Immune Response in Older People	Synbiotic	Dietary Supplement	NCT01226212
Aging	Low Sugar Protein Pacing, Intermittent Fasting Diet in Men and Women	intermittent fasting; Heart Healthy Diet	Diet	NCT04327141
Microbiome, Aging, Immune, and Inflammation	The RAMP Study-Rejuvenation of the Aging Microbiota With Prebiotics	Prebiotic	Dietary Supplement	NCT03690999
Microbiota, and Aging	Impact of Okara and Bio-okara Food Product on Gut and Glycaemic Health in Middle-aged and Older Adults in Singapore	Okara/Bio-Okara	Dietary Supplement	NCT03978104
Aging	Probiotic on Psychological and Cognitive Effects	Probiotic	Dietary Supplement	NCT03080818
Aging	Nutritional Strategies for Metabolic Health in Aging	Supplements	Behavioral	NCT04282603
Aging	Investigating the Effects of Daily Consumption of Blueberry (Poly)Phenols on Vascular Function and Cognitive Performance	Wild-Blueberry Powder	Dietary Supplement	NCT04084457

Condition	Study Title	Drug	Intervention	Trial ID
Aging	Effects of Aronia Berries on Vascular Endothelial Function and the Gut Microbiota in Middle-Aged/Older Adults	Aronia	Dietary Supplement	NCT03824041
Aging, and Cognitive Decline	Dietary Reduction of AGEs to Prevent Cognitive Decline in Elderly Diabetics	Low AGEs Diet	Behavioral	NCT02739971

Table V.

FECAL TRANSFER AS THERAPEUTIC APPROACH FOR AGING, STROKE, AND AD.

Disease	Study title	Treatment	Reference
Aging	Microbial Stimulation Reverses The Age-Related Decline In M Cells In Aged Mice	FMT	(162)
Aging	Heterochronic Fecal Transplantation Boosts Gut Germinal Centers In Aged Mice	FMT	(191)
Aging	Transplant Of Microbiota From Long-Living People To Mice Reduces Aging-Related Indices And Transfers Beneficial Bacteria	FMT	(170)
Stroke	Age-Related Changes In The Gut Microbiota Influence Systemic Inflammation And Stroke Outcome.	FMT	(9)
Stroke	Commensal Microbiota Affects Ischemic Stroke Outcome By Regulating Intestinal Γδ T Cells	FMT	(192)
Stroke	Higher Risk Of Stroke Is Correlated With Increased Opportunistic Pathogen Load And Reduced Levels Of Butyrate-Producing Bacteria In The Gut	FMT	(193)
Stroke	Microbiota Dysbiosis Controls The Neuro-lnflammatory Response After Stroke	FMT	(180)
Stroke	Transplantation Of Fecal Microbiota Rich In Short-Chain Fatty Acids And Butyric Acid Treat Cerebral Ischemic Stroke By Regulating Gut Microbiota	FMT	(194)
Alzheimer's	Altered Microbiomes Distinguish Alzheimer's Disease From Amnestic Mild Cognitive Impairment And Health In A Chinese Cohort	FMT	(195)
Alzheimer's	Fecal Metabolite Of A Gnotobiotic Mouse Transplanted With Gut Microbiota From A Patient With Alzheimer's Disease	FMT	(196)
Alzheimer's	Fecal Microbiota Transplantation Alleviated Alzheimer's Disease-Like Pathogenesis In APP/PS1 Transgenic Mice	FMT	(117)
Alzheimer's	Sex-Specific Effects Of Microbiome Perturbations On Cerebral Aβ Amyloidosis And Microglia Phenotypes	FMT	(197)
Alzheimer's	Transfer Of A Healthy Microbiota Reduces Amyloid And Tau Pathology In An Alzheimer's Disease Animal Model	FMT	(116)
Alzheimer's	Transplant Of Microbiota From Long-Living People To Mice Reduces Aging-Related Indices And Transfers Beneficial Bacteria	FMT	(170)
Alzheimer's	Transplantation Of Fecal Microbiota Rich In Short-Chain Fatty Acids And Butyric Acid Treat Cerebral Ischemic Stroke By Regulating Gut Microbiota	FMT	(194)

Table VI.

PROBIOTICS AS THERAPEUTIC APPROACH FOR AGING, STROKE, AND AD.

Disease	Study title	Treatment	Reference
Aging	Lactobacillus Sp. Improved Microbiota And Metabolite Profiles Of Aging Rats	Probiotics	(161)
Aging	The Molecular Mechanisms Of Probiotic Strains In Improving Aging Bone And Muscle Of D-Galactose-Induced Aging Rats	Probiotics	(168)
Aging	*Lactobacillus Fermentum* JX306 Restrain D-Galactose-Induced Oxidative Stress Of Mice Through Its Antioxidant Activity	Probiotics	(160)
Aging	A Human-Origin Probiotic Cocktail Ameliorates Aging-Related Leaky Gut And Inflammation Via Modulating The Microbiota/Taurine/Tight Junction Axis	Probiotics	(104)
Aging	Probiotics And Prebiotics As A Therapeutic Strategy To Improve Memory In A Model Of Middle-Aged Rats	Probiotics	(164)
Aging	Longevity In Mice Is Promoted By Probiotic-Induced Suppression Of Colonic Senescence Dependent On Upregulation Of Gut Bacterial Polyamine Production	Probiotics	(198)
Stroke	Association Of Gut Microbiota-Dependent Metabolite Trimethylamine N-Oxide With First Ischemic Stroke	Probiotics	(199)
Stroke	Clostridium Butyricum Pretreatment Attenuates Cerebral Ischemia/Reperfusion Injury In Mice Via Anti-Oxidation And Anti-Apoptosis	Probiotics	(141)
Stroke	Dysbiosis Of Gut Microbiota And Short-Chain Fatty Acids In Acute Ischemic Stroke And The Subsequent Risk For Poor Functional Outcomes	Probiotics	(200)
Stroke	Effects Of The Oral Ingestion Of Probiotics On Brain Damage In A Transient Model Of Focal Cerebral Ischemia In Mice	Probiotics	(140)
Stroke	Gut Microbiota-Derived Short-Chain Fatty Acids Promote Post-Stroke Recovery In Aged Mice	Probiotics	(8)
Stroke	Short-Chain Fatty Acids Improve Post-Stroke Recovery Via Immunological Mechanisms	Probiotics	(201)
Alzheimer's	Effects Of Probiotic Supplementation On Short Chain Fatty Acids In The Appnl-G-F Mouse Model Of Alzheimer's Disease	Probiotics	(202)
Alzheimer's	Probiotics Ameliorate Intestinal Pathophysiology In A Mouse Model Of Alzheimer's Disease	Probiotics	(203)
Alzheimer's	Probiotics Ameliorate Intestinal Pathophysiology In A Mouse Model Of Alzheimer's Disease.	Probiotics	(203)
Alzheimer's	Probiotics Modulate The Microbiota-Gut-Brain Axis And Improve Memory Deficits In Aged SAMP8 Mice	Probiotics	(204)
Alzheimer's	Short-Chain Fatty Acids: Microbial Metabolites That Alleviate Stress-Induced Brain-Gut Axis Alterations	Probiotics	(205)

Table VII.

DIATERY INTERVENTIONS AS THERAPEUTIC APPROACH FOR AGING, STROKE, AND AD.

Disease	Study Title	Treatment	Reference
Aging	Ketogenic Diets Alter The Gut Microbiome Resulting In Decreased Intestinal Th17 Cells	Dietary Intervention	(159)
Aging	Gut Microbiota Combined With Metabolomics Reveals The Metabolic Profile Of The Normal Aging Process And The Anti-Aging Effect Of Fufang Zhenshu Tiaozhi(FTZ) In Mice	Dietary Intervention	(157)
Stroke	Dietary Habits In Patients With Ischemic Stroke: A Case-Control Study	Dietary Intervention	(206)
Alzheimer's	Bioactive Food Abates Metabolic And Synaptic Alterations By Modulation Of Gut Microbiota In A Mouse Model Of Alzheimer's Disease.	Dietary Intervention	(207)
Alzheimer's	Fructo-Oligo-Saccharides Ameliorating Cognitive Deficits And Neurodegeneration In APP/PS1 Transgenic Mice Through Modulating Gut Microbiota	Dietary Intervention	(208)
Alzheimer's	Modified Mediterranean-Ketogenic Diet Modulates Gut Microbiome And Short-Chain Fatty Acids In Association With Alzheimer's Disease Markers In Subjects With Mild Cognitive Impairment	Dietary Intervention	(209)
Alzheimer's	Modified Mediterranean-Ketogenic Diet Modulates Gut Microbiome And Short-Chain Fatty Acids In Association With Alzheimer's Disease Markers In Subjects With Mild Cognitive Impairment	Dietary Intervention	(209)