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Role of Nutraceuticals in Modulation of Gut-Brain Axis in Elderly Persons

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<http://dx.doi.org/10.5772/intechopen.73005>

Abstract

A rather new and somewhat unusual concept connects brain functions to gut microbiota. It is called “gut-brain axis” (or “microbiota-gut-brain axis”) and states that probiotics consumption and a healthy gut microbiota positively influence brain functions related to behavior and cognition. Synergistic with a low chronic grade peripheral inflammation, this faulty barrier exposes the aged brain to negative extra-cerebral signals. Given the quasi-constant failure of pharmacological treatments in neurodegenerative diseases, increased interest is directed toward allopathic medicine, including dietary supplements. Interplay between gut microbiota and central nervous system by immune, neural and metabolic pathways is being explored as a possible modulator of cognitive impairment and behavior disorders. In elderly persons, this axis has been reported to be altered, contributing to systemic inflammation and was also indicated as a possible marker for early frailty in younger population. Currently, there are several clinical trials addressing the relationship between gut microbiota and central nervous system psychiatric disorders and at least one directly investigating whether there is a correlation between composition of gut microbiome, permeability of intestinal barrier and systemic inflammation in patients with dementia. This chapter discusses evidence-based data on positive modulation of gut-brain axis to alleviate behavior and cognition alterations in the elderly.

Keywords: nutraceuticals, gut-brain axis, microbiota, inflammaging, aging, neurodegeneration, anxiolytic

1. Introduction

In recent years, great progress has been made in characterizing bidirectional interactions between central nervous system (CNS), enteric nervous system and gastrointestinal tract. Dr Michael Gershon has defined the gut as “the second brain” [1] for several reasons: the enteric nervous system may function autonomously (it is capable of reflexes in the absence of CNS input), it can communicate with CNS through the parasympathetic (via vagal nerve) and sympathetic (via paravertebral ganglia) nervous system and is susceptible to neurotrophic and neuromodulators signaling.

The term gut-brain axis is often extended to include the role of intestinal flora in the system, in which case the axis is called microbiota-gut-brain axis. The microbiota is not limited to bacteria but also includes protozoa, fungi, nematodes and viruses, so that in the intestinal tract there are over 1000 species of bacteria out of a total of approximately 100 trillion organisms [2]. To maintain the homeostasis of such complex system, permanent correlation between the gut and the brain is essential.

The gastrointestinal microbiota has a symbiotic relationship with enteric cells and contributes to basic physiological processes such as digestion, growth and immune defense. The composition of an individual’s microbiota depends on the mode of delivery at birth, genetic predisposition, age, nutrition, physical activity, environmental factors, stress, infections, other diseases and the use of antibiotics [3].

Gut microbiota can influence the functioning of the CNS by the ability to synthesize or mimic some molecules such as host-signaling neuroactive molecules, for example, acetylcholine, catecholamine, γ -aminobutyric acid (GABA), histamine, melatonin and serotonin [4]. Conversely, the composition of the microbiota is influenced by emotional and psychological stress [5], resulting, for example, in the decrease in *Lactobacilli* species or the increase of *Clostridium* species [6, 7]. Although communication between the components of the microbiota-gut-brain axis has been well established by preclinical and clinical studies (excellently reviewed in [8–11]), the exact mechanisms by which this communication is made remains largely unknown. The interest in this research area began to consistently grow since the early 2000s, when one of the first papers to be published showed that germ-free (GF) mice exhibit an exaggerated hypothalamus-pituitary axis (HPA) response to stress compared to a normal mouse [12]. These results were later on confirmed by other studies on rodents grown in a germ-free (GF) environment that showed how gut microbiota influences the development of emotional behavior, stress and pain systems modulation, and the functioning of neurotransmitter systems in the brain [13, 14]. This communication between gut and brain was proven to be dependent on at least two elements such as vagus nerve signaling and specific bacterial species [15–18]. Further on, the influence of gut microbiota composition on high cognitive processes and brain chemistry [19] was demonstrated by its modulation with probiotics and antibiotics [10, 20].

Studies on GF mice also highlighted another surprising relationship between gut microbiota and aging and in the occurrence of aging-related-diseases. It has been shown that GF mice live significantly longer than normal animals, probably due to the reduction of pathological infections, with a first report back in the mid 1960s [21], followed by others in mice [22, 23] *Drosophila melanogaster* [24], *Caenorhabditis elegans* [25].

We shall further detail some topics related to the gut-brain axis in the elderly, like gut-brain alterations observed in preclinical and clinical studies, some data about neuro-nutraceuticals with a focus on mechanisms and gut-brain axis modulation with a final reference to clinical trials.

2. Evidence-based data of gut-brain axis alteration in aged laboratory animals

Aging is (so far) an irreversible process which impacts on all cell populations, with several common denominators such as genomic instability, epigenetic alterations and oxidative stress [26]. It equally affects gut lining and brain cells, but it also changes the gut microbiota composition [27, 28] which in turn is associated with behavioral and physiological modifications. An anxious behavioral phenotype was observed while transferring fecal microbiota between two strains of mice [10]. Also, fecal microbiota transplantation from depressed patients to microbiota-depleted rats may have the potential to provoke behavioral and physiological features specific to depression, including anhedonia, anxiety-like behaviors, as well as modifications in tryptophan metabolism, suggesting that gut microbiota could be an important player in neurobehavioral changes in the rat [29]. Reduced anxiety and depression-related compartment in mice were connected to dysregulated GABA signaling by metabolizing dietary glutamate through certain strains of *Lactobacillus* and *Bifidobacteria* [30]. Another study focused on the analysis of microbiota of aged mice. It is reported that, although composition differed significantly, there was only an insignificant overall increase in bacterial taxa, from that of young mice. At phylum level, the most common microbial taxa were *Bacteroidetes* and *Firmicutes*. A few statistically significant differences in bacterial groups were noticed in aged mice. At the phylum level, TM7 was significantly higher, while at family level abundance less than 1%, significant increases in *Porphyromonadaceae*, TM7 uncultured, *Clostridiaceae*, *Thermoanaerobacteraceae*, *Desulfovibrionaceae* and *Oxalobacteraceae* were seen in aged mice compared to young. Genera *Odoribacter* was much higher in the aged group whereas, other bacterial genera, including *Butyrivimonas*, TM7 uncultured, *Gelria*, *Anaerosporebacter*, *Clostridium* and *Oxalobacter* had significant increases in aged mice. The Chao 1 index (which estimates species richness), the number of observed species and the phylogenetic diversity, the Shannon Index (alpha diversity) and beta diversity were higher in the aged compared with young groups. Also, gut permeability in young and aged mice prior to and after 1 h of restraint stress was assessed, proved that aged mice had significantly greater basal intestinal permeability than young mice [31].

3. Evidence of gut-brain axis alteration in old patients

Each human organism hosts a widely diverse population of microbes that form a “metaorganism” (comprising 10 bacterial cells for every one of our own) [32]. This metaorganism, which is now studied thoroughly in major scientific endeavors such as Human Microbiome Project [33], impacts on its host as much as the human host changes it back throughout different life stages. Microbial diversity and intestinal microflora stability decrease with age [27, 28] and are accompanied by a reduction in brain function and a decrease in cognitive abilities [34, 35]. Furthermore, alteration of gut microbiota homeostasis, through dietary or environmental factors, can lead to an imbalance between symbionts and pathobionts, resulting in reduced intestinal barrier function such as a dysbiosis state can be related to subsequent metabolic and inflammatory disorders, visceral pain and even alterations in brain functioning [36]. Other studies have shown that while the microbial composition of the gut changes with age, it is not a linear process. The two dominant phyla in younger persons, *Bacteroides* and *Firmicutes*, remain prominent at older ages, but there are supposed to be changes in the percentage of these phyla, a fact still under discussion. Other studies support the prevalence of potentially pathogenic bacteria (e.g. proteobacteria) that are detrimental for symbiotic beneficial bacteria (e.g. species of *Bifidobacteria*) [37]. In this regard, there is an increased interest in the putative role of microbial gut in the fragility and vulnerability associated with the aging process.

Gut microbiota and extreme longevity are the main topics of several interesting studies. There are evidence that extreme aging might be supported by subdominant gut microbiota species, along with pro-inflammatory species and health-associated taxa [38]. Another study was focused on long-lived Chinese people and gut microbiota, with a special reference to the above-mentioned study. Significant differences in community membership and structures between the Italian and Chinese long-living groups were observed, attributed to many factors such as geography, genetics, diets and DNA-extraction methods [39].

These findings emphasize the importance of sampling a healthy population, both in terms of age, geographic and cultural traditions in order to identify features of gut microbiomes signatures related to age [40].

Age-associated alterations in gut microbiota are associated with subsequent decline with age in the functionality of the immune system (immunosenescence) and a chronic low-grade inflammatory status, partially due to increased intestinal permeability and increased colonic cytokine expression (inflammaging) [41]. The inflammaging process can undermine the homeostatic equilibrium and accelerate the changes in gut microbiota structure and composition that could be related to the progression of diseases and frailty in the elderly population [42].

Mabbott et al. in 2015 [43] provided an important advance in our understanding on the effects of aging on intestinal permeability and innate mucosal immune responsiveness in elderly patients. Using human terminal ileal biopsy tissues, they demonstrated that intestinal permeability to solutes, but not macromolecules, was significantly increased in the intestines of elderly humans. Tran and Greenwood-Van Meerveld in 2013 [44] showed for the first time a pivotal contributing factor to geriatric vulnerability to gastrointestinal dysfunction may increase colonic

permeability via age-associated remodeling of intestinal epithelial tight junction proteins. On the opposite side is a recent report by Valentini et al. that found no correlation between aging and increased intestinal permeability (or altered intestinal barrier), but mentioned low-grade inflammation as a possible favoring factor [45].

Age-related physiological modifications in the gastrointestinal tract undoubtedly affect the gut microbiota and high susceptibility to infections becomes an inevitable consequence. The gut microbiota homeostasis seem to play a crucial role for the gut well-being during the aging process and, in this perspective, dietary control of the gut microbiota of the elderly could be an important target for preserving a healthy gut microbiota community [42].

4. Neuro-nutraceuticals: definition, examples and mechanisms of action

Nutraceuticals are defined as “*food or food product that provides medical or health benefits including the prevention and treatment of diseases*” [46]. This concept is partially overlapping with the term “*bioactive compounds*” – “*secondary plant metabolites eliciting pharmacological or toxicological effects in man and animals*” [47]. Neuro-nutraceuticals are, by extrapolation, active compounds, obtained from food products or plants that exert effects on the CNS. They can be represented by vitamins, amino acids, minerals, trace elements, etc., with presumed health-promoting or disease-preventing effects. Oxidative stress, dysregulation of redox metals homeostasis and inflammation represent the main leading causes of brain aging and therefore the administration of antioxidant and anti-inflammatory molecules can be an important strategy for preventing brain aging and several brain age-related diseases such as Parkinson’s disease, Alzheimer’s disease, dementia and depression [48, 49].

However, the evaluation of nutraceutical efficacy and safety represents a big challenge due to the complex chemical compositions and multiple mode of actions [50]. Starting from chemical classification of bioactive compounds [47], several classes have been repeatedly associated with beneficial neurological effects. *Flavonoids* consist of a central three-ring structure and may occur as oligomers -*proanthocyanidins*. All compounds contain phenol groups with antioxidant effect. Many different polyphenols have been reported to retard age-related declines in CNS function, cognition and behavior. A polyphenol with the ability to modulate a multitude of signaling molecules and with antibacterial, anti-inflammatory and neuroprotective properties is *curcumin*, the active ingredient in the spice turmeric. Curcumin acting as an antioxidant, anti-inflammatory and lipophilic agent can improve the cognitive functions in animal models and patients with Alzheimer’s disease by several mechanisms. Short-term supplementation of curcumin to aged rats enhanced the frequency of polysialylated cells in the dentate infragranular zone and significantly improved both spatial learning and memory in adult and aged rats [51]. The long-term curcumin-supplemented diet had a important effects on hippocampal cellular proliferation, cognitive function and transcriptional responses in aged rats and this response is dependent of the length of curcumin treatment [52]. Curcumin administration supported the immune system to reduce beta-amyloid plaques, ensures the delayed degradation of neurons and decreased microglia activation resulting in the improvement of overall

memory [53]. Curcumin treatment could also improve the outcome of patients with traumatic brain injury by reducing acute activation of microglia/macrophages and neuronal apoptosis, demonstrated by *in vivo* experiments [54]. *Eugenol* (4-allyl-2-methoxyphenol), an antioxidant and anti-inflammatory molecule, found in various plants such as basil, cinnamon and other herbs is another nutraceutical with demonstrated roles in brain physiology. In the *Drosophila* model, eugenol manifests neuroprotective effects in acrylamide-induced neuropathy models. *In vitro* studies showed that eugenol enhanced the viability of neuroblastoma cell lines by reducing oxidative stress in experimental hyperglycemia. Moreover in diabetic rats, eugenol administration results in reduction of oxidative markers in brain with restoration of activities of mitochondrial complexes I, II and III [55, 56]. Other polyphenols (anthocyanin extract, pomegranate or resveratrol), exerted their anti-inflammatory effects by reducing TNF- α brain level and microgliosis or sirtuin activation in correlation with improving brain plasticity in non-transgenic AD animal models [57, 58]. *Resveratrol* positive effects were also related to the activation of AMP-activated kinase (AMPK) and the antioxidant transcription factor Nrf2 (nuclear factor (erythroid derived 2)-like 2) [59]. In a randomized, double-blind, placebo-controlled, phase II trial of resveratrol for patients with Alzheimer's disease, resveratrol was detected in cerebrospinal fluid with beneficial effects such as the alteration of Alzheimer's disease biomarker trajectories, the preservation of blood-brain barrier integrity and the modulation of the central nervous system immune response [60].

Methylxanthine alkaloids (found in coffee and cocoa) elicit stimulating neurological effects. Some *tropane alkaloids* are analgesics [61]. Aromatic compounds, terpenes/terpenoids and aliphatic molecules, particularly with low molecular weights, found in plant essential oils, were mentioned as free radicals scavengers and acetylcholine esterase inhibitors [62]. Some volatile oils were associated with anxiolytic and antidepressant effects, along with strong antioxidant effects [63].

Creatine is a nitrogenous organic acid found in animal tissues being involved in several critical processes in the brain such as the sustaining of energy supply, antioxidant processes and neuroprotection. Increased dietary intake of creatine can elevate brain creatine levels which can sustain cognitive function under oxidative and nitrosative stress. Several *in vitro* or even preclinical studies showed that creatine directly preserves mitochondrial function in adult neurodegenerative conditions [64, 65]. Clearly, mitochondrial impairment contributes directly and/or indirectly to the pathogenesis of numerous neurodegenerative disorders [66]. Exogenous creatine supplementation reduced neuronal cell loss in acute and chronic neurological diseases and promoted differentiation of neuronal precursor cells [67]. *In vivo* studies showed that maternal creatine supplementation during pregnancy protects the brain against the effects of severe birth asphyxia [68, 69].

A special class of food derivatives or food ingredients includes prebiotics and probiotics.

Prebiotics are defined as "nondigestible food ingredients that beneficially affect the host by selectively stimulating the growth or the activity of one or a limited number of bacteria (*Bifidobacteria* and *Lactobacilli*) in the colon" [70]. From chemical perspective, they are fructooligosaccharides, enzymatically processed in the colon with positive impact on commensal flora. Fermentation of prebiotics generates short-chain fatty acids [71], which exert positive effects on integrity of epithelial barrier, but also on brain metabolism, as discussed later.

Probiotics are “viable microorganisms, sufficient amounts of which reach the intestine in an active state and thus exert positive health effects” [72]. The most commonly used probiotics are bacterial species (frequently, *Lactobacillus* and *Bifidobacterium*, but also some *E. coli* and *Bacillus* species), but the yeast *Saccharomyces cerevisiae* and can also be employed [73].

Both types of nutraceuticals exert positive effects beyond local, intestinal environment. Prebiotics were demonstrated to exhibit triglycerides and cholesterol-lowering effects [70], with beneficial effect on blood-brain barrier integrity and brain lipid metabolism. Among many local effects, it is worth mentioning that, related to gut-brain axis, probiotics modify the gut microbiota, which is the main determinant of tryptophan levels, the serotonin precursor, hence the documented effect of these food supplements as anxiety alleviators.

Throughout the next sections, some evidence of modulation of gut-brain axis with nutraceuticals in the elderly will be discussed, in relationship with experimental results from preclinical and clinical studies.

5. Modulation of gut-brain axis with nutraceuticals in the elderly: evidence-based benefits in animal models

Diet and altered gut physiology, together with age-related changes in intestinal microbiome and a weakened immune system [74, 75] result in low-grade inflammation in the gut, that is associated with systemic release of pro-inflammatory metabolites. Finally, the inflammatory process is related to glial cells activation, neuroinflammation and to cognitive decline in the elderly [37, 41].

A useful model for the study of gut-brain axis is the germ-free (GF) mouse. GF mice have socially impaired behavior [12] and present an exaggerated stress response [76] that can be directly correlated with changes occurring in different regions of the brain [13], depressed neurogenesis [77] and prefrontal cortical hypermyelination [78]. However, preclinical studies reveal that oral administration of probiotics and/or nutraceuticals is sufficient to reduce anxiety-like and depressive-like behaviors and to induce changes in brain chemistry [10, 79]. For example, the impaired microglial function in GF animals was rescued by the oral treatment with short-chain fatty acids [80]. Also, Distrutti et al. [81], showed that a *probiotic* mixture (VSL#3) induced a significant change in the composition of gut microbiota of aged rats and increased brain tissue expression of genes associated with inflammation and neural plasticity such as BDNF and synapsin.

The gut microbiome is also essential to the bioavailability of *polyphenols*, *unsaturated fats* and *antioxidants*, all of which may help protect against neuronal and cell aging under normal circumstances [82]. For example, the diet supplemented with blueberries (rich in anthocyanin and flavanols) improved spatial working memory in aged animals [83]. This process is accompanied by increases in neural stem cells proliferation, extracellular receptor kinase activation and increase of insulin-like growth factor-1 (IGF-1) level, the key modulator of hippocampal neurogenesis [84]. Also, aged rats consuming berry diets exhibited enhanced motor performance and improved cognition, correlated with increased hippocampal neurogenesis and expression of IGF-1 [85].

Since short-chain fatty acids (SCFA) seem to play an important role in shaping the gut microbiota metabolism, it was necessary to study the effect of omega-3 polyunsaturated acids (n-3 PUFA) on cognitive decline in aging. Animal studies have shed light on their neuroprotective roles through pathways of synaptic plasticity, neuroinflammation and oxidative stress, evidencing also positive correlations between peripheral n-3 PUFA levels and regional gray matter [86]. Supplementation of n-3 PUFA increased hippocampal neurogenesis and the fatty acid docosahexaenoic acid (DHA – an intermediate molecule in the metabolism of eicosapentaenoic acid) was able to down regulate microglial activation [87]. Furthermore, age-related decline in c-Fos expression, that reflects neuronal response to extracellular signals such as growth factors and is triggered during action potentials, is attenuated by n-3 PUFA diet [88]. The protective role of n-3 PUFA supplementation in counteracting cognitive decline, emotional dysfunctions and brain atrophy is governed by antioxidant and anti-inflammatory mechanisms [86, 89]. Some evidence in animal models suggested that long-term consumption of fish oil (rich in n-3 PUFA) may predispose the brain to lipid oxidation. The enrichment of fish oil with quercetin significantly attenuated behavioral impairments, restored the ROT-induced oxidative markers, depleted dopamine levels in striatum and reduced mitochondrial dysfunction, offering a higher neuroprotection in animal model [90].

Phytosterols, a class of nutraceuticals derived from plant foods, have been demonstrated to possess cholesterol-lowering, antioxidant effects and recently neuroprotective role on cognitive deficit induced by a cholesterol-enriched diet in aged rats. The phytosterol ester (PSE) treatment maintained the body weight balance, reduced serum lipid levels and improved the cognitive performance of aged rats in the Morris water maze test. Importantly, histological and immunohistochemical results in the brain showed that PSE supplementation alleviates neuroinflammation by significantly increasing the number of pyramidal cells and decreasing the number of astrocytes. Furthermore, PSE improved cholinergic activities by restoring the acetylcholine (ACh) content and decreasing acetylcholinesterase (AChE) activity in the cerebral cortex, as well as by elevating choline acetyl transferase (ChAT) activity in the hippocampus and the cerebral cortex [91].

In conclusion, preclinical studies support the rationale of further clinical testing of nutritional strategies to improve aged brain function, including the use of bioactive compounds with antioxidant, anti-inflammatory or neuroprotective properties in the diet of the elderly.

6. Neuro-nutraceuticals/gut-brain axis targeting in clinical trials

The direct modulation of gut microbiome by targeted dietary and probiotic uptake seem to have a positive impact in treating particular age-related disorders and represent a promising therapeutic option for the aging process itself [28]. Well supported evidence came from findings from ELDERMET, a research consortium (<http://eldermet.ucc.ie>) which studied and characterized the gut microbiota in an Irish elderly population anti its relationship to mental health in aging [92]. As a consequence of a growing body of evidence regarding a positive correlation between the health of gut microbiota and brain health, funding for clinical research is also spent for study of modulation of gut-brain axis with impact on healthy aging and mental health.

No.	Clinical trial	Main objective	Status	Reference
1	Microbiome and the gut-brain axis	To examine the relationship between digestive tract microbes and mental health	Completed	https://clinicaltrials.gov/ct2/show/NCT02693327
2	Microbiome and dementia	To study the role of gut microbiome composition and gut permeability in the progression of dementia	Recruiting	https://clinicaltrials.gov/ct2/show/NCT03167983
3	Full4Health: understanding food-gut-brain axis across the life course	To examine how dietary manipulation influences the relationship between hunger/satiety/food preference and gut hormones, neural activation and energy metabolism	Completed	https://clinicaltrials.gov/ct2/show/NCT01597024
4	Oral fecal transplant in cirrhosis	To evaluate the safety and tolerability of oral fecal transplant in patients with cirrhosis and hepatic encephalopathy	Recruiting	https://clinicaltrials.gov/ct2/show/NCT03152188
5	Reduced appetite in Crohn's disease: the role of the brain in the control of food intake	To investigate the changes in activity in areas of the brain that control food intake	Recruiting	https://clinicaltrials.gov/ct2/show/NCT02772458
6	FMT treating constipation patients with depression and/or anxiety symptoms - clinical efficacy and potential mechanisms	To observe the clinical efficiency of fecal microbiota transplant and the role of the gut microbiome in treating patients with constipation, depression and/or anxiety	Recruiting	https://clinicaltrials.gov/ct2/show/NCT03233100
7	Prebiotic intake reduces the waking cortisol response and alters emotional bias in healthy volunteers	To investigate the effects of two prebiotics on the secretion of cortisol and emotional response in healthy individuals	Completed	[93]
8	A randomized, double-blind, placebo-controlled pilot study of a probiotic in emotional symptoms of chronic fatigue syndrome	To study how the administration of <i>Lactobacillus casei</i> strain Shirota affects the mood of patients with chronic fatigue syndrome	Completed	[94]
9	Assessment of psychotropic-like properties of a probiotic formulation (<i>Lactobacillus helveticus</i> R0052 and <i>Bifidobacterium longum</i> R0175) in rats and human subjects	To study the effects of probiotic formulations on stress, anxiety, depression and coping strategies in healthy volunteers	Completed	[95]
10	A randomized controlled trial to test the effect of multispecies probiotics on cognitive reactivity to sad mood	To evaluate whether a multispecies probiotic formulation can reduce cognitive reactivity in non-depressed individuals	Completed	[96]
11	Metabolic effect of new foods through gut-brain axis	To measure the effectiveness of coffee melanoidins, bread melanoidins, beta-glucans and a <i>Gentiana lutea</i> L. extract in decreasing energy intake and modifying the physiological markers of satiety in the short term	Recruiting	https://clinicaltrialbase.com/study/NCT01851304/

No.	Clinical trial	Main objective	Status	Reference
12	FMT for patients with IBS with fecal and mucosal microbiota assessment	To assess the efficiency of fecal microbiota transplant in treating irritable bowel syndrome	Recruiting	https://clinicaltrialsbase.com/study/NCT03125564/
13	Effects of green-MED diet via the gut-fat-brain axis	To investigate the effect of a Mediterranean diet low in processed meat on the gut microbiota and age-related declines (changes in adiposity, cognitive function and cardiometabolic risk)	Recruiting	https://clinicaltrialsbase.com/study/NCT03020186/
14	The clinical research on the relationship between circadian rhythm and gut microbiota in TBI patients	To examine whether the gut microbiota is involved in the modulation of sleep disorders in patients with brain traumatic injury	Recruiting	https://clinicaltrialsbase.com/study/NCT02849028/

Table 1. Clinical trials related to investigation of gut-brain axis in relationship with mental health.

Clinical trials targeting not only the cross-talk between the gut microbiota and the central nervous system focus on its association with various neuropsychiatric and neurodegenerative disorders (anxiety, depression, dementia, etc.), but also on its involvement in the regulation of hunger/satiety and in pathologies affecting the digestive tract (**Table 1**). The therapeutic solutions investigated these clinical trials involve the use of prebiotics and probiotics, dietary changes and fecal microbiota transplant.

Reports of already completed trials support the findings of preclinical trials, demonstrating that modulation of gut microbiota results in anxiolytic effect without a direct intervention on neurotransmitter circuitries. For example, the reported results of Schmidt et al. [93], after completion of trial, supported previous evidence that fructooligosaccharides, or Bimuno[®]-galactooligosaccharides supplementation lowered neuroendocrine stress response, measured by cortisol awakening response. Rao et al. [94] reported that supplementation with specific lactic acid probiotic bacteria for 8 weeks improved the anxiety scores of patients with chronic fatigue syndrome. A complex report by Messaoudi et al. [95], involving both laboratory rats as well as healthy human volunteers showed that supplementation with a combination of *Lactobacillus helveticus* and *Bifidobacterium longum* displayed beneficial psychological effect. Finally, a recent publication regarding the effect of “4-week multispecies probiotics intervention showed a significantly reduced overall cognitive reactivity to sad mood”, [96]. These results open a promising avenue not only for age-related mental disorders, but also for selected cases of psychiatric pathologies.

7. Conclusions

Gut-brain axis is a bidirectional chemical network sending information between the intestine and the brain via soluble, chemical messages as well as nervous sympathetic and parasympathetic

inputs. A third player with a determinant role in the health of both systems is the gut microbiota. Aging affects all players of the microbiota-gut-brain axis, leading to modified composition of bacterial taxa, chronic low-grade inflammation, modified intestinal metabolism, resulting in diminished availability of neurotransmitters or neurotransmitter precursors and short-chain fatty acids. Along with synaptic impairment, oxidative stress and neuroinflammation, aging leads to behavior alterations, anxiety and cognitive impairment. Interventions on gut-brain axis with nutraceuticals (food or food-derived products that have putative beneficial effects) alleviate some age-associated behavioral and cognitive alterations, as repeatedly demonstrated in animal models. Recently, clinical trials have begun to explore the beneficial effect of gut-brain axis modulation, in mood or cognition-associated disorders. Upon reports of positive results, gut-brain axis emerges as an important, easy to access target for promoting a healthy brain aging.

Acknowledgements

This work has been supported by National Authority for Scientific Research and Innovation (ANCSI), Program POC Axis 1 Action 1.2.3. Grant ID P_40_197, Contract No. 52/05.09.2016.

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