**Supplementary Material**

**Table 4.** Selected Human Studies Examining Gut Biotics in Neurocognitive and Mental Health Conditions

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| --- | --- | --- | --- |
| **Condition** | **Study** | **Gut Biotic** | **Outcome** |
| Dementia | Akbari et al, 2016 [83]Placebo: n = 30Probiotic: n = 30 | Probiotic: *Lactobacillus acidophilus*, *Lactobacillus casei*, *Bifdobacterium bifidum*, and *Lactobacillus fermentum*  | After a 12-week treatment, patients with Alzheimer’s dementia treated with probiotics showed a significant improvement in MMSE scores (P < 0.001).  |
| Tillisch et al, 2013 [157]Total: 36 healthy females FMP: N = 12Non-FMP: N = 11No treatment: N = 13 | Probiotic: *B. animalis* subsp*. lactis, S. thermophilus, L. bulgaricus, L. lactis subsp. lactis* | Findings suggested that supplementation with the FMP activated specific areas of the brain linked to control of emotion and sensation. Intake of FMP reduced task-related response of a distributed functional network (P < 0.004).  |
| Eskelinen et al, 2009 [245]Total: 1,409 individuals aged 65 - 79) | Prebiotic: coffee | Individuals who drank 3 - 5 cups of coffee per day at midlife showed a 65-70% reduced risk of dementia and 62-64% lower risk of AD compared to those who drank less than 2.  |
| Kobayashi et al, 2019 [80]Total: 121 older adults (50 - 80 years old) with subjective memory complaints.Placebo: N = 60Probiotic: N = 61 | Probiotic: *Bifidobacterium breve* A1 | Patients receiving the probiotic supplement showed a beneficial effect on cognitive function compared to placebo group.  |
| Hwang et al, 2019 [82]Total: 100 individuals with MCIPlacebo: N = 50Probiotic: N = 50 | Probiotic: *L. plantarum* C29 - fermented soybean  | The study showed that the probiotic can be safely given and helps enhance cognitive function (P for interaction = 0.02) and attention domain (P for interaction = 0.02) in individuals with MCI.  |
| Leblhuber et al, 2018 [246]Total: 20 individuals with AD | Probiotic: *L. casei W56, L. lactis W19, L. acidophilus W22, B. lactis W52, L. paracasei W20, L. plantarum W62, B. lactis W51, B. bifidum W23 and L. salivarius W24* | AD patients treated with a multispecies probiotic showed alterations to the gut microbiome and tryptophan metabolism and increased serum kyurenine concentrations (P < 0.05).  |
| Tamtaji et al, 2019 [84]Total: 79 patients with ADPlacebo: N = 26Probiotic: N = 27Selenium: N = 26 | Probiotic: *L. acidophilus, B. bifidum,* and *B. longum* | Probiotic and selenium co-supplementation for 12 weeks to patients with AD improved cognitive function in MMSE scores (P < 0.001) compared to only selenium and placebo.  |
| Agahi et al, 2018 [247] Total: 48 patients with ADPlacebo: N = 23Probiotic: N = 25 | Probiotic: *L. fermentum, L.* *plantarum, B. lactis L. acidophilus,* *B. bifidum, B. longum* | No significant change in cognitive and biochemical indications was found in patients with severe AD treated with probiotic supplementation.  |
| Anxiety | Takada et al, 2016 [248]Total: 140 healthy students Placebo: n = 70Probiotic: n = 70 | Probiotic: *L. casei* Shirota YIT 9029 | Cold/flu symptoms and abdominal symptoms associated with stress were significantly lower (P < 0.05) in the probiotic group compared to controls.  |
| Mohammadi et al, 2015 [77]Total: 70 petrochemical workersProbiotic yogurt and placebo capsule: n = 25Conventional yogurt and probiotic capsule: n = 25Conventional yogurt and placebo capsule: n = 20 | Probiotic yogurt: *Lacidophulus* LA5 + B lactic Bb12)Conventional yogurt: *S. thermophilus* and *L. bulgaricus*Probiotic capsule: *L. casei, L acidophilus, L. rhamnosus, L. bulgaricus, B. breve, B. longum, S. thermophilus* | Significant improvements were seen in GHQ (P = 0.007) and DASS (P = 0.02) in the probiotic yogurt group. In the probiotic capsule groups, significant improvement in the GHQ (P = 0.001) and DASS (P = 0.006). No significant change in the conventional yogurt group.  |
| Messaoudi et al, 2011(a) [239] Total: 55 healthy volunteersPlacebo: N = 29Probiotic: N = 26 | Probiotic: *L. helveticus* R0052, *B. longum* R0175 | Individuals taking the probiotic formulation showed less psychological distress with the HSCL-90 (P < 0.05), HADS (P < 0.05) and CCL (P < 0.05).  |
| Schmidt et al, 2015 [180]Total: 45 health volunteers FOS: N = 15B-GOS: N = 15Placebo: N = 15 | Prebiotic: fructooligosaccharides (FOS) or bimuno-galactooligosarccharides (B-GOS) | No effects were seen after the administration of FOS. Those receiving the B-GOS had significantly lower salivary cortisol (P < 0.05) awakening response and decreases attentional vigilance (P = 0.014).  |
| Rao et al, 2009 [249]Total: 35 patients with chronic fatigue syndrome.Placebo: N = 16Probiotic: N = 19 | Probiotic: *L. casei* Shirota | Patients receiving the probiotic showed a reduction in anxiety symptoms (P = 0.01) compared to the control group.  |
| Depression  | Kazemi et al, 2019 [89]Total: 81 patients with MDDPlacebo: N = 26Probiotic: N = 28Prebiotic: N = 26 | Probiotic: *L. helveticus* R0052 and *B. longum* R0175Prebiotic: galactooligosaccharide | Patients in the probiotic group showed a significant decrease in Beck Depression Index scores (P = 0.042) compared to placebo and prebiotic supplementation. No significant results were seen with the prebiotic group (P = 0.001) |
| Akkasheh et al, 2016 [88]Placebo: N = 20Probiotic: N = 20 | Probiotic: *L. acidophilus, L. casei,* and *B. bifidum*  | Patients receiving the probiotic supplements showed decreases Beck Depression Inventory total scores (P = 0.001).  |
| Majeed et al, 2018 [250]Placebo: N = 20Probiotic: N = 20 | Probiotic: *Bacillus coagulans* MTCC 5856 | Patients treated with *B. coagulans* MTCC 5856 showed improvement in the HAM-D, MADRS, and CES-D scores (P = 0.01).  |
| Benton et al, 2006 [251]Total: 124 healthy volunteersPlacebo: NA Probiotic: NA | Probiotic: *L. casei* Shirota (containing milk)  | Those consuming the probiotic-containing yogurt showed improved mood symptoms (P < 0.05) compared to placebo. |
| Steenbergen et al, 2015 [252]Placebo: N = 20Probiotic: N = 20 | Probiotic: *B. bifidum* W23, *B. lactis* W52, *L. acidophilus* W37, *L. brevis* W63, *L. casei* W56, *L. salivarius* W24, and *L. lactiz* W19 and W58 | Those who received the probiotic intervention showed a significant reduced cognitive reactivity to sad mood through reduced rumination (P < 0.001) and aggressive thoughts (P = 0.004) compared to placebo group.  |
| Smith et al, 2015 [101]Total: 47 healthy volunteersCross-over design, each participant was treated with inulin and placebo throughout the study | Prebiotic: FOS-enriched inulin  | The days the inulin was consumed, participants were happier (P < 0.05) and had less indigestion (P < 0.05) and hunger (P < 0.072) compared to when they consumed the placebo. When consuming inulin there was a great accuracy in recognition memory (P = 0.05) and recall (P < 0.05).  |
| PTSD | Gocan et al, 2012 [190]N = 11 totalN = 10 analyzed | Prebiotic: germented soy product  | Reduction in anxiety, derealization/detachment, and insomnia.  |
| Brenner et al, 2020 [253]Placebo: N = 15Probiotic: N = 16 | Probiotic: *Lactobacillus reuteri* DSM 17938 | Decreased plasma CRP compared to placebo group, thought not statistically significant (P = 0.056). No significant difference in subjective measure of stress responsivity.  |
| OCD | Messaoudi et al, 2011 [194]Total: 25 health volunteersProbiotic: N = 10Placebo: N = 15 | Probiotic: *L. helveticus* R0052 | Volunteers treated with a probiotic formulation showed decreased obsessive-compulsive scores.  |
| Schizophrenia or schizoaffective  | Dickerson et al, 2014 [204]Total: 65 schizophrenia patientsPlacebo: N = 27Probiotic: N = 31 | Probiotic: *L. rhamnosus* strain GG and *B. animalis* subsp. Lactis Bb12 | No significant difference in PANSS total scores between groups. Patients in probiotic group had less bowel difficulty.  |
| Severance et al, 2017 [202]Placebo: N = 27Probiotic: N = 31 | Probiotic: *L. rhamnosus* strain GG and *B. animalis* subsp. Lactis Bb12 | Probiotics help to normalize *C. albincans* antibody levels (P < 0.001) and *C. albicans*-associated gut discomfort in male schizophrenia patients (P < 0.04) compared to placebo group.  |
| Tomasik et al, 2015 [203]Placebo: N = 27Probiotic: N = 31 | Probiotic: *L. rhamnosus* strain GG and *B. animalis* subsp. Lactis Bb12 | Probiotics significantly lowered vWF levels (P = 0.047) and increased levels of MCP-1 (P = 0.054), BDNF (P = 0.063), RANTES (P = 0.069), and MIP-1 (P = 0.080) in schizophrenia patients. |
| Bipolar disorder  | Dickerson et al, 2018 [212]Placebo: N = 33Probiotic: N = 33 | Probiotic: *L. rhamnosus* strain GG and *B. animalis* subsp. Lactis Bb12 crystalline cellulose | Patients treated with probiotics showed decreased levels of rehospitalization (P = 0.007) after an episode of acute mania. Probiotic treatment also showed fewer days hospitalized (P = 0.017). |
| Reininghaus et al, 2018 [213]Total: N = 20 | Probiotic supplement | With probiotic supplement, bipolar patients improved in psychomotor processing with digital symbol test (P < 0.01) and with TMT-B over 3 months (P < 0.05). |

OCD: obsessive-compulsive disorder; GHQ: general health questionnaire; DASS: Depression Anxiety and Stress Scale; BDNF: brain-derived neurotrophic factor; CES-D: Center for Epidemiological Studies Depression Scale; CCL: Coping Checklist; FMP: fermented milk product; HAM-D: Hamilton Rating Scale for Depression; HSL-90: Hopkins Symptom Checklist; HADS: Hospital Anxiety and Depression Scale; MCP-1: monocyte chemotactic protein-1; MIP-1: macrophage inflammatory protein-1; MADRS: Montgomery-Asberg Depression Rating Scale; MCI: mild cognitive impairment; PANSS: Positive and Negative Syndrome Scale; RANTES: regulated upon activation, normal T-cell expressed and secreted; vWF: von Willebrand factor; MMSE: mini-mental status exam; PTSD: post-traumatic stress disorder.

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