Review Article

A Minireview Exploring the Interplay of the Muscle-Gut-Brain (MGB) Axis to Improve Knowledge on Mental Disorders: Implications for Clinical Neuroscience Research and Therapeutics

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What benefit might emerge from connecting clinical neuroscience with microbiology and exercise science? What about the influence of the muscle-gut-brain (MGB) axis on mental health? The gut microbiota colonizes the intestinal tract and plays a pivotal role in digestion, production of vitamins and immune system development, but it is also able to exert a particular effect on psychological well-being and appears to play a critical role in regulating several muscle metabolic pathways. Endogenous and exogenous factors may cause dysbiosis, with relevant consequences on the composition and function of the gut microbiota that may also modulate muscle responses to exercise. The capacity of specific psychobiotics in ameliorating mental health as complementary strategies has been recently suggested as a novel treatment for some neuropsychiatric diseases. Moreover, physical exercise can modify qualitative and quantitative composition of the gut microbiota and alleviate certain psychopathological symptoms. In this minireview, we documented evidence about the impact of the MGB axis on mental health, which currently appears to be a possible target in the context of a multidimensional intervention mainly including pharmacological and psychotherapeutic treatments, especially for depressive mood.

1. Introduction

From a historical point of view, the pivotal role of the gut microbiota on an individual’s health was first conceived by the Russian biologist E. Metchnikoff, who described some health benefits in a population of poor Bulgarians connected to the consumption of lactic acid bacteria in fermented milk [1].

On one side, microbiota refers to a specific population of organisms (i.e., bacteria, yeasts, and parasites) colonizing the skin, the respiratory, the uro-genital, and the gastrointestinal tract, where the majority of the population lives. The human gut is a complex, dynamic, and heterogeneous system which exert a marked influence on the host during homeostasis and disease. It contains $10^{13}$-$10^{14}$ microorganisms, and its weight is about one kilogram in the adult, with the majority of bacteria residing in the colon [2]. Through physiological functions, the microbiota can offer specific benefits to the host, such as strengthening gut integrity or shaping the intestinal epithelium, harvesting energy, protecting against pathogens, and regulating immunity [3]. In healthy adults, two bacterial phyla, Bacteroidetes and Firmicutes, dominate the gut bacterial composition, with smaller amounts of Actinobacteria, Proteobacteria, and Verrucomicrobia [2].
Alterations that affect the commensal flora impair microbial homeostasis and generate a condition called “dysbiosis”; particularly, gut dysbiosis is characterized by a significant decrease of Bacteroidetes and Lactobacilli [4]. In a similar way, Lactobacillus abundance is predominant in other body districts, including vagina and endometrium [5], and even in the latter, eubiosis exists if the percentage of endometrial Lactobacilli is greater than 90% [6].

On the other side, the microbiome consists of the genes that microbial cells harbor [7]. It comprises all the genetic material within a microbiota, the whole collection of microorganisms in a definite situs, in such a case, the human gut. This has been defined by some researchers as the “metagenome of the microbiota”, too [8].

Evidence from literature documented that the alteration of the native microbial intestinal florae is being invoked in nutrition, human metabolism, direct host defense, immunological development, physiological and pathological aging, and even psychiatric disorders [9]. Starting from this assumption, microbiota manipulation may represent a promising tool as adjunct therapy for treating specific mental illnesses and their associated symptoms [10].

Moreover, the impact of the gut microbiota on skeletal muscle function and quality in terms of energy, neuromuscular connectivity, mitochondrial function, and endocrine and insulin resistance, has recently been the focus of some research attempts [11]. The gut microbiota may represent a challenging new therapeutic opportunity and advances in the field of exercise science may enrich the heritage of clinical neuroscience applied to psychiatric disorders. Studies reporting experiments on the gut microbiota intervention documented that specific probiotics have the potential to interact with the brain and exert a positive bacteria-mental functioning relationship [12]. Altered gut microbial profiles have been described in several psychiatric disorders and psychobiotics are currently employed as adjunct treatment to pharmacological and psychotherapeutic interventions. Many of these effects appear to be specific, suggesting a potential role of certain probiotic strains. Further, physical exercise inducing microbial changes with release of neuroendocrine factors may lower inflammatory and oxidative stress of the brain [13].

This mini-review briefly summarizes the progress of research on the muscle-gut-brain (MGB) axis highlighting the role of psychobiotics and physical activity in modulating the response of the microbiota and its effects on mental health, and discusses implications for clinical neuroscience research and therapeutics.

2. The MGB Axis: Communication Links and Role of Physical Activity in the Mutual Relationship between the Gut and the Skeletal Muscles

As well as regulating brain functions, the gut microbiota affects the skeletal muscle functioning. The graphical representation (Figure 1) depicts gut eubiosis and dysbiosis. In particular, intestinal eubiosis, conceived as the balance of the intestinal microbial ecosystem, favors the integrity of the gut barrier and prevents the translocation of lipopolysaccharides (LPS) and other harmful products in the bloodstream, with positive effects on systemic inflammation which could alter muscle metabolism [14–16]. On the other hand, intestinal dysbiosis, an ecosystem where “good” and “bad” bacteria do not live in mutual harmony, [1] is also responsible for a decreased activation of AMPK (i.e., AMP-activated protein kinase) and PGC-1α (i.e., proliferator-activated receptor coactivator-1) signaling pathways, which are at the basis of autophagy mechanisms. Autophagy, in fact, is fundamental for the skeletal muscles to remove older organelles and myocytes and to preserve muscle functions [17]. Moreover, an impaired autophagy stimulates inflammation and oxidative stress that negatively affects muscle vitality [18].

An altered gut microbiota also affects insulin-like growth factor-1 (i.e., IGF-1) release. IGF-1 usually activates phosphatidylinositol 3-kinase (i.e., PI3K-AKT) signaling pathway that inhibits mRNA transcription and muscle protein synthesis [19]. In murine models, the lack of a gut microbiota decreases levels of IGF-1 reducing the transcription of genes fundamental for efficient mitochondrial functions within the skeletal muscles [20]. Therefore, intestinal dysbiosis promotes inflammation, oxidative stress, and alters muscle anabolism and mitochondria impairing muscle vitality [11].

In recent years, the interaction between the gut microbiota and the muscles has been receiving considerable attention from the scientific community [21]. It is now well established that the integrity of the muscular system correlates with regular physical activity. On the basis of such evidence, an attempt has been made to establish how the intestinal microbiota may influence the muscular system, or whether physical activity may lead to intestinal eubiosis or dysbiosis.

The positive interaction between physical activity and the gut microbiota is highlighted by the studies of Santacroce et al. [22] and Manders et al. [23], in which it is observed that a low amount of physical activity can induce a reduction in the risk of colon cancer, diverticulosis, and irritable bowel syndrome (IBS). These results are confirmed in the study of Monda et al. [24] documenting how regular physical activity reduces inflammation in the intestine. In their studies, Petersen et al. [25] and Scheiman et al. [26] showed that athletes have a greater biodiversity of the fecal microbiota and also a presence of mycobacterium correlated with the health status. Physical exercise modulates not only the expression of the gut microbiota in terms of microorganisms, but also the production of immunoglobulin A (i.e., IgA) and the reduction of B-cells and T-CD4 in murine models. Such modifications suggest that the gut microbiota also has immunomodulatory functions [27]. However, prolonged and strenuous exercise increases intestinal permeability. Such a mechanism causes a passage of the bacteria from the colon with the consequent risk of gastrointestinal problems [28]. When analyzing the scientific literature, it is always difficult to understand which type of physical activity (e.g., endurance exercise, resistance training exercise, acute or chronic exercise sessions, etc.) induces better changes [29]. Endurance exercise, that is a kind of cardiovascular exercise performed over a prolonged
period of time [30], induces a number of major adaptations such as capillary neogenesis, mitochondrial biogenesis, and increased cardiofitness. In addition, endurance training increases *Lactobacillus, Bifidobacterium,* and *Blautia cocoides-Eubacterium rectale* species, while a decrease of *Clostridium* and *Enterococcus* has been found in a rat model [31].

Clarke et al. [32] showed that athletes (i.e., rugby players) had greater variability of the gut microbiota than sedentary individuals. The greater variability is the basis for an improved overall health. *Firmicutes* and *Lactobacillales* are two classes of microbes that seem to be affected by positive changes induced by endurance exercise (i.e., ability to last) [33]. Few studies pointing out the relationship between resistance training (i.e., all exercises in which a force is required to overcome a resistance) and the composition of the gut microbiota are present in literature [34]. In a recent study by Castro et al. [35], it was observed that 12 weeks of resistance training promoted the diversity and the composition of the gut microbiota in rats. In the trained group, an abundance of *Pseudomonas* and, in contrast, a decrease in *Serratia* and *Comamonas* were observed. Subsequently, in a study conducted in a human model by Moore et al. [36], it was observed that 6 weeks of resistance training can improve the integrity of the intestinal barrier in a group of elderly subjects by modulating the population of intestinal microbes. In conclusion, it should be noted that the relationship between physical activity and microbiota is inverse. In fact, some studies have shown that a correct composition of the intestinal microbiota (or *eubiosis*) improves athletic performance [37–39]. Indeed, it was observed that sport performance (i.e. endurance swimming) was better in specific pathogens (SPF) and *Bacteroides fragilis* mice than in germ-free mice. This result suggests that the composition of the gut microbiota may be crucial for athletic performance. Moreover, the study also showed a possible improvement of antioxidant systems in SPF mice, linked to an increased plasmatic levels of glutathione peroxidase and catalase [40]. In this regard, it has to be considered that intestinal microbiota exerts beneficial effects on the oxidative stress status; several microorganisms have antioxidant properties since they are able to improve the expression of antioxidant enzymes as well as controlling the release of proinflammatory cytokines [41].

With the aim of completing the MBG axis description, it has to be noted that the gut-brain axis includes the vagus nerve (VN), a mixed nerve composed of 80% afferent and 20% efferent fibers with anti-inflammatory properties and the circumventricular organs (CO), the gut hormone signaling, the immune system, the serotonin, and the tryptophan metabolism and microbial metabolites such as short-chain fatty acids (SCFAs) [46]. The neuroactive compounds released by bacteria, such as the γ-aminobutyric acid (GABA), the serotonin, the dopamine, and the acetylcholine locally acting within the
enteric nervous system also reaches the brain by blood [47]. Other bacterial metabolites exerting neuroactive functions include long and SCFAs [2] such as acetate, propionate, and butyrate that are important metabolites in intestinal homeostasis maintenance. The existence of a gut-brain axis has been demonstrated in Alzheimer’s disease (AD). In a murine model, gut inflammation, enteric dysmotility, and intestinal AD-related protein deposition were found in early stages of the disease [48]. Similarly, Palmitolethanolamide (PEA), a lipid mediator, has proven to counteract intestinal dysmotility associated to AD. Specifically, PEA is able to prevent glial hyperactivation and the enteric deposition of AD-related proteins, with a decreased inflammatory status [49].

3. Psychobiotics and Physical Exercise in Mental Disorders

With regard to psychological well-being, some gastrointestinal diseases have been recognized as triggered by biopsychosocial factors, such as the IBS, often accompanied by depression and anxiety [50], and the inflammatory bowel disease (IBD). These syndromes are influenced by an individual’s stress response because of the stimulation of the sympathetic nervous system and the inhibition of the vagus [2]. Stress, anxiety, and depressed mood may be manipulated by the gut microbiome [51]. Accordingly, a double-blind randomized controlled trial (RCT) on volunteers receiving a probiotic (i.e., Probio-Stick) containing Lactobacillus acidophilus and Bifidobacterium longum during a 3-week period significantly reduced stress-induced gastrointestinal symptoms (i.e., abdominal pain and nausea/vomiting). Another RCT documented multiple benefits of Lactobacillus plantarum assumed 1 × 10⁹ cfu/day for 12 weeks in terms of reduced stress and anxiety [52]. The use of 24 billion cfu Lactobacillus casei strain Shirota (LcS) for 2 months was also shown to reduce anxiety symptoms in patients with chronic fatigue syndrome [53].

Altered gut microbial profiles have been found in some medical conditions, including psychiatric disorders [9]. Differently from healthy subjects, an increased bacterial diversity in feces of autistic children consisting of Bacteroidetes, Proteobacteria, Actinobacteria, and Firmicutes has been found [54]. A recent systematic review concluded that major depressive disorder, bipolar disorder, and schizophrenia were not characterized by differences in the number or distribution (i.e., α-diversity) of gut bacteria but display compositional differences compared to controls (i.e., β-diversity) [55]. Further, dysbiotic alterations of the gut microbiota may lead to local inflammation and increased permeability of the gastrointestinal wall leading to an augment of lipopolysaccharides (LPS) circulation. They activate the production of systemic inflammation mediators (i.e., IL-1β, IL-6, IL-8 and TNF-α) that have been found to be higher in psychiatric patients, such as those suffering from schizophrenia [56]. High levels of IL-6 and TNF-α were also found in patients with bipolar disorder during both mood alterations and euthymic phases [56]. The phenomenon known as “leaky gut” has been proposed to shed light on major depressive disorder (MDD), too, as a proinflammatory response induced by external and internal stressors and by an increased translocation of the LPS from gram-negative bacteria [57].

Psychobiotics include a range of substances that may affect the gut-brain axis signaling, including probiotics (i.e., living microorganisms contained in food products or supplements), prebiotics (i.e., the substrate used by the host organism conferring health benefits), synbiotics (i.e., a combination of probiotics and prebiotics), and postbiotics (i.e., metabolites of bacterial fermentation and bioactive compounds) [58]. Specifically, probiotics have some effects in ameliorating certain psychopathological symptoms by improving intestinal homeostasis. Their supplementation may serve in adaptation to exercise as aiding muscle recovery and supporting skeletal muscle [59]. Akkasheh et al. [60] found a decreased Beck Depression Inventory (BDI) total score after complementary treatment with probiotic administration (i.e., Lactobacillus acidophilus, Lactobacillus casei, and Bifidobacterium bifidum, 2 × 10⁹ cfu/g) for 8 weeks in patients with MDD. Similar results on the same psychodiagnostic scale were reached by Kazemi et al. [61] by using a formula containing freeze-dried Lactobacillus helveticus and Bifidobacterium longum at a dosage of ten billion colony-forming units (i.e., ≥10 × 10⁹ CFU) per 5 g. sachet on an 8-week treatment. Further, a change in the 17-item Hamilton Depression Rating Scale score and BDI score from baseline to week 8 were found after an adjunctive therapy of Clostridium butyricum MIYAIRI 588 in patients with treatment-resistant MDD [62]. Finally, substantial shifts to the microbial community in response to dietary patterns may cause important health implications, as reported in attention deficit hyperactivity disorder [63].

Beyond probiotics assumption, physical exercise has been shown to be a significant factor causing changes in qualitative and quantitative composition of the gut microbiome [64]. Specifically, studies reported that exercise may have positive effects on gut microbiota increasing butyrate-producing bacteria (i.e., Roseburia hominis, Faecalibacterium prausnitzii, and Ruminococcaceae), for diversity and balance between beneficial and pathogenic bacterial communities, and colon health [65, 66]. Moderate intensity physical exercise (i.e., <70% VO2max) provide beneficial effects to the human body, thanks to physiological and metabolic adaptations, with changes in skeletal muscle including mitochondrial biogenesis, concentration of the substrate transporting proteins, activity of the enzymes involved in metabolic pathways, and glycan storage in the muscle [67] whereas intensive physical exercise (i.e., >70% VO2max) may disturb the homeostasis of the gut microbiota [13] by increasing gastrointestinal wall permeability and by diminishing the gut mucus thickness, potentially favoring pathogens to enter the bloodstream, thus increasing inflammation levels [29]. A parallelism can be drawn with regard to physical activity and mood, because moderate exercise has been shown to be useful in supporting affective state while intense exercise may lead to its deterioration [68]. An adequate level of physical activity increases the synaptic transmission of monoamines, releases endorphins, and improves positive emotions experienced after the exercise [68]. A recent systematic review has shown that combined resistance and aerobic training or aerobic training alone may
have positive effect on the microbiota, incrementing some bacteria phyla (i.e., Bacteroidetes, Firmicutes, and Proteobacteria) although further research with higher methodological rigor is needed to better understand such a relationship [9]. Studies on physical activity in clinical samples pointed out that it can normalize reduced levels of brain-derived neurotrophic factor (i.e., BDFN), with neuroprotective effects on the brain while other investigations have documented anxiolytic effects of aerobic exercise for induced-panic symptoms [69]. In addition, the aforementioned effects of physical activity on the gut microbiota suggest that the better the composition of the microbiota, the greater the capacity for nutrient degradation. Greater nutrient degradation results in both greater macronutrient availability and glycemic control [70]. All these effects have an impact on the neuronal activity. For example, it has been demonstrated that athletes present an enriched profile of SCFAs (especially, acetate, propionate, and butyrate), due to the specific activity of the microbacteria modulated by physical activity [66]. Subsequently, the produced SCFAs act as a nutritional substrate to support microglia function and this leads to an improvement in mental abilities [71].

4. Conclusion and Implications for Clinical Neuroscience Research and Therapeutics

The exact composition of the gut microbiota is different for each individual, and it is still unclear what may constitute a healthy profile. Determining a healthy microbiota should be a prerequisite for evaluating clinical deviations and proceeds towards tailored interventions. Such a kind of observation can be taken into consideration by clinicians to study in-depth the modification of the microbiota, also in the case of psychotropic medication orally taken [72, 73]. Alterations of the gut microbiota composition have been found in some psychiatric disorders but heterogeneity in terms of ethnicity, age, comorbidities, medication, unhealthy nutrition, antibiotics use, aging, and environmental factors, complicates a definite description [74, 75]. All these factors should be considered when planning a study on the microbiota and interpreting results. The probiotics could be useful when ingested in a definite quantity through the interaction with commensal gut bacteria and their benefits are mediated by several mechanisms referred to the hypothalamic-pituitary-adrenal (i.e., HPA) axis, the immune response and inflammation, and the production of neurohormones and neurotransmitters [76]. The rebalancing of a dysbiotic flora through the use of psychobiotics represents a therapeutic goal as a complementary intervention to standard care, especially for depressive symptoms [77, 78], even if additional RCTs in clinical populations are warranted to better evaluate their efficacy. Further, the stimulation of the vagus nerve is also recognized as an effective neurophysiological treatment in depression [79] because of the possibility to alter the cerebrospinal fluid concentration of neurotransmitter or their metabolites (e.g., GABA, and 5h1AA), and influence the functionality of certain brain regions that are dysregulated in mood disorders (i.e., orbitofrontal cortex, insula, thalamus and hypothalamus, and cingulate and hippocampus) [80]. Food hygiene and probiotics supplementations should be carefully taken into account as an integrative aspect of a multidimensional intervention on psychiatric disorders, due to the fact that many pathologies report unbalanced diet (e.g., consumption of highly saturated fats and sugar, low fiber intake, etc.) or difficulties in weight management, potentially impacting microbiota profile [81]. To this end, psychoeducational interventions focused on balanced diet adherence for a healthy lifestyle may improve quality of life of psychiatric patients, and nutritional psychiatry should be called into question with the final aim of improving clinical outcomes of standard treatments.

Evidence of positive effects of physical activity in mental disorders are limited to date. Nevertheless, outdoor activities are associated with greater feelings of revitalization, increased energy and positive engagement with tension, confusion, and anger decrease [82] and should be considered in structured psychotherapeutic protocols for depression, such as cognitive-behavioral ones implementing motor activation [83, 84]. Physical exercise further improves behavioral outcomes in psychiatric disorders by psychological mechanisms of body scheme reinforcement, changes in health attitudes, greater awareness in proprioception, and counteracts inactivity as a typical feature of patients with depression [85]. However, physical exercise as a psychosocial additional intervention for psychiatric disorders needs to be better investigated by rigorous RCTs [86] because of paucity and methodological limitations of the existing studies.

In the opinion of the authors, evidence on probiotics supplementation and physical activity in depressed mood treatment as adjunctive strategy in the context of a multidimensional intervention including pharmacology and psychotherapy is somewhat interesting. However, advances on MGB axis research have to be carefully integrated with clinical data derived from blood tests, neuropsychological and psychodiagnostic measures, and functional status examination, to better depict the relationship among the microbiota, the brain, and the musculoskeletal system.

Conflicts of Interest

The authors declare no conflict of interest.

Authors’ Contributions

D.M.C. was responsible for the conception of the work. D.M.C. J.F. and G.S. wrote the manuscript. F.F. S.D. and G.C. revised it critically.

References

[1] S. H. Podolsky, “Metchnikoff and the microbiome,” The Lancet, vol. 380, no. 9856, pp. 1810–1811, 2012.
[2] B. Bonaz, T. Bazin, and S. Pellissier, “The vagus nerve at the interface of the microbiota-gut-brain axis,” Frontiers in Neuroscience, vol. 12, p. 49, 2018.
[3] E. Thursby and N. Juge, “Introduction to the human gut microbiota,” Biochemical Journal, vol. 474, no. 11, pp. 1823–1836, 2017.
[4] L. McDonnell, A. Gilkes, M. Ashworth et al., “Association between antibiotics and gut microbiome dysbiosis in children:
systematic review and meta-analysis,” Gut Microbes, vol. 13, no. 1, p. 1870402, 2021.
[5] I. Moreno and C. Simon, "Relevance of assessing the uterine microbiota in infertility," Fertility and Sterility, vol. 110, no. 3, pp. 337–343, 2018.
[6] V. Cela, S. Daniele, M. E. R. Obino et al., "Endometrial Dysbiosis Is Related to Inflammatory Factors in Women with Repeated Implantation Failure: A Pilot Study," Journal of Clinical Medicine, vol. 11, no. 9, p. 2481, 2022.
[7] L. K. Ursell, J. L. Metcalf, L. W. Parfrey, and R. Knight, "Defining the human microbiome," Nutrients, vol. 7, Supplement 1, pp. S38–S44, 2012.
[8] G. Berg, D. Rybakova, D. Fischer et al., “Microbiome definition revisited: old concepts and new challenges,” Microbiome, vol. 8, no. 1, pp. 1–22, 2020.
[9] J. C. Clemente, L. K. Ursell, L. W. Parfrey, and R. Knight, "The impact of the gut microbiota on human health: an integrative view," Cell, vol. 148, no. 6, pp. 1258–1270, 2012.
[10] K. Rea, T. G. Dinan, and J. F. Cryan, "Gut microbiota: a perspective for psychiatrists," Neuropsychobiology, vol. 79, no. 1, pp. 50–62, 2020.
[11] G. Li, B. Jin, and Z. Fan, "Mechanisms involved in gut microbiota regulation of skeletal muscle," Oxidative Medicine and Cellular Longevity, vol. 2022, Article ID 2151191, 15 pages, 2022.
[12] K. L. Tooley, "Effects of the human gut microbiota on cognitive performance, brain structure and function: a narrative review," Nutrients, vol. 12, no. 10, p. 3009, 2020.
[13] M. U. Sohail, H. M. Yassin, A. Sohail, and A. A. Thani, "Impact of physical exercise on gut microbiome, inflammation, and the pathobiology of metabolic disorders," Review of Diabetic Studies, vol. 15, no. 1, pp. 35–48, 2019.
[14] D. Parada Venegas, M. K. De la Fuente, G. Landskron et al., "Short chain fatty acids (SCFAs)-mediated gut epithelial and immune regulation and its relevance for inflammatory bowel diseases," Frontiers in Immunology, vol. 10, p. 277, 2019.
[15] M. Rastelli, P. D. Cani, and C. Knauf, "The gut microbiome influences host endocrine functions," Endocrine Reviews, vol. 40, no. 5, pp. 1271–1284, 2019.
[16] S. Ghosh, R. Lertwattanarak, J. D. J. Garduño et al., "Elevated muscle TLR4 expression and metabolic endotoxemia in human aging," Journal of Gerontology Series A: Biomedical Sciences and Medical Sciences, vol. 70, no. 2, pp. 232–246, 2015.
[17] J. Y. Ryu, H. M. Choi, H. I. Yang, and K. S. Kim, "Dysregulated autophagy mediates Sarcopenic obesity and its complications via AMPK and PGC1α signaling pathways: potential involvement of gut Dysbiosis as a pathological link," International Journal of Molecular Sciences, vol. 21, no. 18, p. 6887, 2020.
[18] T. Sho and J. Xu, "Role and mechanism of ROS scavengers in alleviating NLRP3-mediated inflammation," Biotechnology and Applied Biochemistry, vol. 66, no. 1, pp. 4–13, 2019.
[19] R. D. Barclay, N. A. Burd, C. Tyler, N. A. Tillin, and R. W. Mackenzie, "The role of the IGF-1 signaling cascade in muscle protein synthesis and anabolic resistance in aging skeletal muscle," Frontiers in Nutrition, vol. 6, 2019.
[20] S. Lahiri, H. Kim, I. Garcia-Perez et al., "The gut microbiota influences skeletal muscle mass and function in mice," Science Translational Medicine, vol. 11, no. 502, 2019.
[21] M. Marttinen, R. Ala-Jaakkola, A. Laitila, and M. J. Lehtinen, "Gut microbiota, probiotics and physical performance in athletes and physically active individuals," Nutrients, vol. 12, no. 10, p. 2936, 2020.
[22] L. Santacroce, A. Man, I. A. Charitos, K. Haxhirexha, and S. Topi, "Current knowledge about the connection between health status and gut microbiota from birth to elderly. A narrative review," Frontiers in Bioscience-Landmark, vol. 26, no. 6, pp. 135–148, 2021.
[23] R. J. Manders, J. W. Van Dijk, and L. J. Van Loon, "Low-intensity exercise reduces the prevalence of hyperglycemia in type 2 diabetes," Medicine and Science in Sports and Exercise, vol. 42, no. 2, pp. 219–225, 2010.
[24] V. Monda, I. Villano, A. Messina et al., "Exercise modifies the gut microbiota with positive health effects," Oxidative Medicine and Cellular Longevity, vol. 2017, Article ID 3831972, 8 pages, 2017.
[25] L. M. Petersen, E. J. Bautista, H. Nguyen et al., "Community characteristics of the gut microbiomes of competitive cyclists," Microbiome, vol. 5, no. 1, pp. 1–13, 2017.
[26] J. Scheiman, J. M. Huber, T. A. Chavkin et al., "Meta-omics analysis of elite athletes identifies a performance-enhancing microbe that functions via lactate metabolism," Nature Medicine, vol. 25, no. 7, pp. 1104–1109, 2019.
[27] A. E. Wegierska, I. A. Charitos, S. Topi, M. A. Potenza, M. Montagnani, and L. Santacroce, "The connection between physical exercise and gut microbiota: implications for competitive sports athletes," Sports Medicine, pp. 1–15, 2022.
[28] L. J. Mailing, J. M. Allen, T. W. Buford, C. J. Fields, and J. A. Woods, "Exercise and the gut microbiome: a review of the evidence, potential mechanisms, and implications for human health," Exercise and Sport Sciences Reviews, vol. 47, no. 2, pp. 75–85, 2019.
[29] M. Claus, P. Gérard, A. Mosca, and M. Leclerc, "Interplay between exercise and gut microbiome in the context of human health and performance," Frontiers in Nutrition, vol. 8, 2021.
[30] M. J. Joyner and E. F. Coyle, "Endurance exercise performance: the physiology of champions," The Journal of Physiology, vol. 586, no. 1, pp. 35–44, 2008.
[31] M. I. Queipo-Ortuño, L. M. Sean, M. Murri et al., "Gut microbiota composition in male rat models under different nutritional status and physical activity and its association with serum leptin and ghrelin levels," PLoS One, vol. 8, no. 5, article e65465, 2013.
[32] S. F. Clarke, E. F. Murphy, O. Sullivan et al., "Exercise and associated dietary extremes impact on gut microbial diversity," Gut, vol. 63, no. 12, pp. 1913–1920, 2014.
[33] R. L. Hughes and H. D. Holscher, "Fueling gut microbes: a review of the interaction between diet, exercise, and the gut microbiota in athletes," Advances in Nutrition, vol. 12, no. 6, pp. 2190–2215, 2021.
[34] S. J. Fleck and W. Kraemer, Designing Resistance Training Programs, 4E, Human Kinetics, 2014.
[35] A. P. Castro, K. K. Silva, C. S. Medeiros, F. Alves, R. C. Araujo, and J. A. Almeida, "Effects of 12 weeks of resistance training on rat gut microbiota composition," Journal of Experimental Biology, vol. 224, no. 12, 2021.
[36] J. H. Moore, K. S. Smith, D. Chen et al., "Exploring the effects of six weeks of resistance training on the fecal microbiome of older adult males: secondary analysis of a Peanut protein supplemented randomized controlled trial," Sports, vol. 10, no. 5, p. 65, 2022.
[37] Y. J. Hsu, C. C. Chiu, Y. P. Li et al., "Effect of intestinal microbiota on exercise performance in mice," The Journal of Strength & Conditioning Research, vol. 29, no. 2, pp. 552–558, 2015.
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[38] K. Nay, M. Jollet, B. Goustard et al., “Gut Bacteria Are Critical for Optimal Muscle Function: A Potential Link with Glucose Homeostasis,” American Journal of Physiology-Endocrinology and Metabolism, vol. 317, no. 1, pp. E158–E171, 2019.

[39] T. Okamoto, K. Morino, S. Ugi et al., “Microbiome Potentiates Endurance Exercise through Intestinal Acetate Production,” American Journal of Physiology-Endocrinology and Metabolism, vol. 316, no. 5, pp. E956–E966, 2019.

[40] D. Martarelli, M. C. Verdenelli, S. Scuri et al., “Effect of a probiotic intake on oxidant and antioxidant parameters in plasma of athletes during intense exercise training,” Current Microbiology, vol. 62, no. 6, pp. 1689–1696, 2011.

[41] B. G. Spyropoulos, E. P. Misikos, C. Fotiadis, and C. N. Stoidis, “Antioxidant properties of probiotics and their protective effects in the pathogenesis of radiation-induced enteritis and colitis,” Digestive Diseases and Sciences, vol. 56, no. 2, pp. 285–294, 2011.

[42] Y. Qiao, J. Sun, Y. Ding, G. Le, and Y. Shi, “Alterations of the gut microbiota in high-fat diet mice is strongly linked to oxidative stress,” Applied Microbiology and Biotechnology, vol. 97, no. 4, pp. 1689–1697, 2013.

[43] K. Przewłocka, M. Folwarski, K. Kazmierczak-Siedlecka, K. Skonieczna-Zydecka, and J. J. Kaczor, “Gut-muscle axis exists and may affect skeletal muscle adaptation to training,” Nutrients, vol. 12, no. 5, p. 14551, 2020.

[44] L. Dumitrescu, I. Popescu-Olaru, L. Cozma et al., “Oxidative stress and the microbiota-gut-brain axis,” Oxidative Medicine and Cellular Longevity, vol. 2018, Article ID 2406594, 12 pages, 2018.

[45] A. R. Isaac, R. A. Lima-Filho, and M. V. Lourenco, “How does the skeletal muscle communicate with the brain in health and disease?,” Neuropharmacology, vol. 197, article 108744, 2021.

[46] S. Breit, A. Kuperberg, G. Rogler, and G. Hasler, “Vagus nerve as modulator of the brain–gut axis in psychiatric and inflammatory disorders,” Frontiers in Psychiatry, vol. 9, 2018.

[47] A. Sarkar, S. M. Lehto, S. Harty, T. G. Dinan, J. F. Cryan, and S. Breit, A. Kupferberg, G. Rogler, and G. Hasler, “Effect of probiotic supplementation on markers of skeletal muscle damage, perceived recovery and athletic performance after an intense single leg training bout,” Journal of the International Society of Sports Nutrition, vol. 12, Supple 1, pp. 1–2, 2015.

[48] G. Akkasheh, Z. Kashani-Poor, M. Tajabadi-Ebrahimi et al., “Clinical and metabolic response to probiotic administration in patients with major depressive disorder: a randomized, double-blind, placebo-controlled trial,” Nutrition, vol. 32, no. 3, pp. 315–320, 2016.

[49] A. Kazemi, A. A. Noorbala, K. Azam, M. H. Eskandari, and K. Difarian, “Effect of probiotic and prebiotic vs placebo on psychological outcomes in patients with major depressive disorder: a randomized clinical trial,” Clinical Nutrition, vol. 38, no. 2, pp. 522–528, 2019.

[50] T. Miyaoa, M. Kanayama, R. Wake et al., “Clostridium butyricum MIYAIRI 588 as adjunctive therapy for treatment-resistant major depressive disorder: a prospective open-label trial,” Clinical Neuropharmacology, vol. 41, no. 5, pp. 151–155, 2018.

[51] M. C. Cenit, I. C. Nuevo, P. Codoñer-Franch, T. G. Dinan, and Y. Sanz, “Gut microbiota and attention deficit hyperactivity disorder: new perspectives for a challenging condition,” European Child & Adolescent Psychiatry, vol. 26, no. 9, pp. 1081–1092, 2017.

[52] C. Gulbert, G. Kong, T. Renoir, and A. J. Hannan, “Exercise, diet and stress as modulators of gut microbiota: implications for neurodegenerative diseases,” Neurobiology of Disease, vol. 134, article 104621, 2020.

[53] C. M. Mitchell, B. M. Davy, M. W. Hulver, A. P. Neilson, B. J. Bennett, and K. P. Davy, “Does exercise alter gut microbial composition? A systematic review,” Medicine and Science in Sports and Exercise, vol. 51, no. 1, pp. 160–167, 2019.

[54] A. Dalton, C. Mermier, and M. Zuhl, “Exercise influence on the microbiome–gut–brain axis,” Gut Microbes, vol. 10, no. 5, pp. 555–568, 2019.

[55] M. A. Hearrris, K. M. Hammond, J. M. Fell, and J. P. Morton, “Regulation of muscle glycogen metabolism during exercise: implications for endurance performance and training adaptations,” Nutrients, vol. 10, no. 3, p. 298, 2018.
[68] M. A. M. Peluso and L. H. S. G. D. Andrade, “Physical activity and mental health: the association between exercise and mood,” *Clinics*, vol. 60, no. 1, pp. 61–70, 2005.

[69] A. Ströhle, C. Feller, M. Onken, F. Godemann, A. Heinz, and F. Dimeo, “The acute antipanic activity of aerobic exercise,” *American Journal of Psychiatry*, vol. 162, no. 12, pp. 2376–2378, 2005.

[70] N. Mach and D. Fuster-Botella, “Endurance exercise and gut microbiota: a review,” *Journal of Sport and Health Science*, vol. 6, no. 2, pp. 179–197, 2017.

[71] C. Long-Smith, K. J. O’Riordan, G. Clarke, C. Stanton, T. G. Dinan, and J. F. Cryan, “Microbiota-gut-brain axis: new therapeutic opportunities,” *Annual Review of Pharmacology and Toxicology*, vol. 60, no. 1, pp. 477–502, 2020.

[72] S. A. Flowers, K. M. Ward, and C. T. Clark, “The gut microbiome in bipolar disorder and pharmacotherapy management,” *Neuropsychobiology*, vol. 79, no. 1, pp. 43–49, 2020.

[73] A. R. Mackos, R. Maltz, and M. T. Bailey, “The role of the commensal microbiota in adaptive and maladaptive stressor-induced immunomodulation,” *Hormones and Behavior*, vol. 88, pp. 70–78, 2017.

[74] M. Aucoin, L. LaChance, K. Cooley, and S. Kidd, “Diet and psychosis: a scoping review,” *Neuropsychobiology*, vol. 79, no. 1, pp. 20–42, 2020.

[75] D. Del Toro-Barbosa, A. Hurtado-Romero, L. E. Garcia-Amezquita, and T. García-Cayuela, “Psychobiotics: mechanisms of action, evaluation methods and effectiveness in applications with food products,” *Nutrients*, vol. 12, no. 12, p. 3896, 2020.

[76] C. J. Wallace and R. Milev, “The effects of probiotics on depressive symptoms in humans: a systematic review,” *Annals of General Psychiatry*, vol. 16, no. 1, pp. 1–10, 2017.

[77] M. A. Ghannoum, M. Ford, R. A. Bonomo, A. Gamal, and T. S. McCormick, “A microbiome-driven approach to combating depression during the COVID-19 pandemic,” *Frontiers in Nutrition*, vol. 8, 2021.

[78] E. Ben-Menachem, “Vagus nerve stimulation, side effects, and long-term safety,” *Journal of Clinical Neurophysiology*, vol. 18, no. 5, pp. 415–418, 2001.

[79] A. J. Rush, L. B. Marangell, H. A. Sackeim et al., “Vagus nerve stimulation for treatment-resistant depression: a randomized, controlled acute phase trial,” *Biological Psychiatry*, vol. 58, no. 5, pp. 347–354, 2005.

[80] T. S. Rao, M. R. Asha, R. N. Ramesh, and K. J. Rao, “Understanding nutrition, depression and mental illnesses,” *Indian Journal of Psychiatry*, vol. 50, no. 2, pp. 77–82, 2008.

[81] J. Thompson Coon, K. Boddy, K. Stein, R. Whear, J. Barton, and M. H. Depledge, “Does participating in physical activity in outdoor natural environments have a greater effect on physical and mental well-being than physical activity indoors? A systematic review,” *Environmental Science & Technology*, vol. 45, no. 5, pp. 1761–1772, 2011.

[82] E. W. Martinsen, “Physical activity in the prevention and treatment of anxiety and depression,” *Nordic Journal of Psychiatry*, vol. 62, Supplement 47, pp. 25–29, 2008.