Research progress on the mechanism of exercise fatigue and the role of probiotics in counteracting it

Zi-Xia Chen1, Jing Yang2, Jia-Jia Song3, Hua-Yi Suo4

1 College of Food Science, Southwest University, Chongqing, 400715, China; 2 Chongqing Engineering Research Center for Processing & Storage of Distinct Agricultural Products, Chongqing Technology and Business University, Chongqing 400067, China.

*These authors contributed equally to this work and are co-first authors for this paper.
*Corresponding to: Jia-Jia Song, Hua-Yi Suo. College of Food Science, Southwest University, No. 2 Tiansheng Road, Chongqing 400715, China.
E-Mail: jiajias@swu.edu.cn (J. Song); birget@swu.edu.cn (H. Suo)

Abstract

Exercise fatigue is a physiological phenomenon where the body cannot maintain a specific level after being stimulated by excessive exercise. Its five main theories include “energy depletion”, “accumulation of metabolites”, “homeostasis disorder of the internal environment”, “free radicals”, and “central nervous system protection inhibition”. The imbalance of intestinal flora caused by vigorous exercise can further lead to fatigue. Therefore, maintaining healthy intestinal flora is crucial for athlete health and performance. Recent studies have demonstrated that probiotics can regulate intestinal flora and alleviate exercise fatigue; however, there are no systematic reviews on the anti-fatigue effects of probiotics. Based on the mechanisms of exercise-induced fatigue, this article summarizes the effects and mechanisms by which probiotics combat exercise fatigue, aiming to provide research ideas for the development of probiotics that prevent exercise fatigue.

Keywords: probiotics; gut microbiota; exercise fatigue; mechanism

Author contributions
Zixia Chen: Visualization, Writing-original draft; Jing Yang: Writing-original draft, Writing-review & editing; Jia-Jia Song: Conceptualization, Writing-review & editing, Supervision, Funding acquisition. Huayi Suo: Conceptualization, Supervision.

Competing interests
The authors declare no conflicts of interest.

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Abbreviations
ATP, adenosine triphosphate; CP, creatine phosphate; ADP, adenosine diphosphate; CK, creatine kinase; NEFA, non-esterified fatty acid; LA, lactic acid; BUN, Blood urea nitrogen; SR, sarcoplasmic reticulum; RyR1, ryanodine receptor 1; FR, Free radicals; ROS, reactive oxyradical; NOX, reduced nicotinamide adenine dinucleotide phosphate oxidase; PLA2, phospholipase A2; XO, xanthine oxidase; GSH-Px, glutathione peroxidase; CAT, catalase; SOD, superoxide dismutase; MDA, malondialdehyde; TNF-α, tumor necrosis factor-α; IL-6, interleukin-6; S-HT, 5-hydroxytryptamine; DA, dopamine; Trp, Tryptophan; f-Trp, free-tryptophan; BCAAs, branched-chain amino acids; 6-OHDA, 6-hydroxydopamine; AMP, adenosine monophosphate; SCFAs, short-chain fatty acids; AMPK, adenosine monophosphate (AMP) -activated protein kinase; PGC-1α, peroxisome proliferator-activated receptor y co-activator-1α; GSH, glutathione; Mn-SOD, Mn-superoxide dismutase; γ-GCS, γ-glutamylcysteine synthetase; GSS, glutathione synthetase; Nrf2, nuclear factor erythroid-derived 2-like 2; ARE, antioxidant response element.

Citation
Introduction

Exercise fatigue is a physiological phenomenon caused by the body's inability to sustain a specific level or maintain its predetermined exercise intensity. While moderate exercise can enhance endurance and is recoverable through certain methods, extreme high-intensity or long-term exercise can induce a variety of adverse physical and mental health issues, such as disturbances in intestinal flora, increased intestinal mucosal permeability, upper respiratory tract infections, oxidative stress, and ultimately impaired competitive sports performance [1, 2]. In recent years, various anti-fatigue nutritional drinks have been introduced, however, significant concerns have been raised regarding the safety of some key ingredients such as caffeine, guarana, and ginseng [3]. Thus, it is urgent to find a safe nutritional supplement to alleviate gastrointestinal dysfunction, energy depletion, and oxidative stress caused by exercise fatigue.

Intestinal flora is a general term for the trillions of microorganisms that reside in the digestive tract of mammals, maintaining both body health and the physiological balance of the host [4]. Normally, these microorganisms are in dynamic balance. However, when the body is fatigued, this balance is disrupted. Studies have shown that probiotic supplements can regulate intestinal flora, improve intestinal function, combat oxidative stress, enhance energy metabolism, and more [5, 6]. Moreover, probiotics have been shown to alleviate exercise-induced gastrointestinal discomfort, enhance exercise performance, and delay the onset of exercise-induced fatigue [7]. Therefore, understanding the anti-fatigue effects and mechanisms of probiotics is highly significant.

This paper explores the generation and mechanisms of exercise fatigue, the effects and mechanisms of probiotic supplements in combating exercise fatigue and evaluates the influence of probiotics on the exhaustion of energy and substances, accumulation of metabolites, free radicals, and central nervous system fatigue. This study aims to provide references for the future screening and application of probiotics designed to combat exercise fatigue.

Generation and Mechanism of Exercise Fatigue

Exercise fatigue is a complex physiological phenomenon caused by multiple environmental factors. Currently, scholars have proposed several theories for the generation and mechanism of exercise-induced fatigue, including energy depletion, accumulation of metabolites, homeostasis disorder of the internal environment, free radicals, and central nervous system protection inhibition (Figure 1).

Exercise Fatigue Mediated by Energy Depletion

Energy depletion refers to the excessive consumption of major energy sources such as adenosine triphosphate (ATP), creatine phosphate (CP), glycogen, and adipose tissue, resulting in a breakdown and insufficient synthesis of energy substances. Studies have found that energy depletion is a key factor leading to the decline of exercise ability and increased fatigue. During exercise, the hydrolysis of high-energy phosphate bonds in ATP rapidly releases energy to support muscle contraction [8]. Prolonged high-intensity activity may cause the rate of ATP consumption to exceed the rate of its resynthesis, leading to reduced ATP levels and resulting in exercise fatigue [9]. CP is converted to adenosine diphosphate (ADP) by the action of creatine kinase (CK) and serves as an energy reserve for ATP. Carbohydrates are crucial for maintaining glycolysis and oxidative phosphorylation, providing energy through both aerobic and anaerobic pathways to produce ATP [10]. High-intensity exercise leads to substantial consumption of muscle glycogen and liver glycogen, exacerbating fatigue. When glycogen stores are depleted, adipose tissue breaks down, serving as an alternative energy source. The serum marker for lipid metabolism is non-esterified fatty acid (NEFA). Excessive consumption of adipose can elevate NEFA levels and impair exercise performance by increasing plasma NEFA uptake and fatty acid oxidation [11].

Mitochondria are the primary organelles for ATP synthesis and energy transduction in skeletal muscle cells and play a pivotal role in energy metabolism [12]. Regular exercise can improve strength and endurance; however, long-term high-intensity exercise increases mitochondrial permeability, leading to swelling, cristae dissolution, and the release of apoptosis-inducing factors into the cytoplasm. This results in an energy metabolism disorder, weakened muscle contraction intensity, and reduced exercise endurance [13].

Figure 1 Mechanism of exercise fatigue. ATP, adenosine triphosphate; CP, creatine phosphate; LA, lactic acid; BUN, blood urea nitrogen; CK, creatine kinase; NOX, reduced nicotinamide adenine dinucleotide phosphate oxidase; PLAD2, phospholipase A2; XOD, xanthine oxidase; 5-HT, 5-hydroxytryptamine; DA, dopamine; AMP, adenosine monophosphate; BCAAs, branched-chain amino acids.
Exercise Fatigue Mediated by Accumulation of Metabolites
Intense exercise leads to significant consumption of energy and substances, accompanied by the production of a large number of metabolites. If these metabolites are not promptly removed, muscle contraction ability decreases, leading to exercise fatigue. Strenuous exercise causes body hypoxia, and pyruvate is converted to lactic acid (LA) in the glycolytic pathway, entering the bloodstream. The dissociation of H+ from LA lowers the pH in muscles and blood, causing acidosis, disrupting the acid-base balance, inhibiting muscle contraction, interfering with nerve signals, and inducing fatigue [14, 15]. Blood urea nitrogen (BUN) is a metabolite of proteins and amino acids. During intense exercise, protein and amino acid metabolism compensates for energy needs, leading to an increase in BUN content, particularly when the body lacks energy from glycogen and lipid metabolism [16]. CK can phosphorylate creatine to form CP, which contains high-energy phosphate bonds used as a rapid energy source for cells, integral to body energy metabolism. Severe exercise can lead to muscle cell injury, increased cell membrane permeability, and the release of CK into the blood, indicative of muscle injury and breakdown [17]. Efficient elimination of metabolites is crucial for athletes’ adaptation to exercise load and recovery post-exercise.

Exercise Fatigue Mediated by Homeostasis Disorder of the Internal Environment
When the body engages in high-intensity exercise, both intracellular homeostasis and resting membrane potential become disordered, leading to an imbalance in internal homeostasis. As exercise intensity increases, the continued excretion of K+ and the influx of Na+ result in cell membrane depolarization and loss of excitability. Na+-K+-ATPase, an important regulator of excitability, helps eliminate extracellular K+ [18]. Studies have shown that the activity of Na+-K+-ATPase decreases after prolonged strenuous exercise, which leads to reduced muscle contraction ability and fatigue [19].

Ca2+ is an indispensable ion in physiological activities and plays a critical role in the excitation-contraction coupling of skeletal muscle. It is released from the sarcoplasmic reticulum (SR) via the ryanodine receptor 1 (RyR1) channel. Research indicates that SR function, including Ca2+ release and uptake, is impaired after muscle fatigue contractions, and abnormal Ca2+ metabolism leads to excitation-contraction decoupling [20]. This decoupling occurs in excessive muscle contractions and muscular dystrophy and is considered a cause of long-term fatigue [21].

Exercise Fatigue Mediated by Free Radicals
Free radicals (FR) are highly unstable molecules with one or more unpaired electrons, produced naturally within the body. Normally, the production and removal of FRs are balanced. However, when energy metabolism increases, so does FR production. Overproduction of FRs can lead to lipid and nucleic acid oxidation, increased oxidative stress, disrupted normal metabolic functions, destabilized homeostasis, and other negative effects, resulting in various diseases and fatigue [22]. Excessive reactive oxyradicals (ROS) produced by strenuous exercise can lead to muscle injury. The mitochondrial respiratory chain is a significant source of ROS. During aerobic respiration in mitochondria, 2-5% of molecular oxygen is consumed, and superoxide is produced through electron reduction, which initiates a series of reactions transforming into ROS [23]. The increase in ROS can also directly cause mitochondrial disorder and reduce exercise capability. Furthermore, studies have shown that several intracellular enzymes, including reduced nicotinamide adenine dinucleotide phosphate oxidase (NOX), phospholipase A2 (PLA2), and xanthine oxidase (XOD), are involved in ROS production. During muscle contraction, the NOX family can transfer electrons from reduced coenzyme II to molecular oxygen, producing more superoxide anions than mitochondria. NOX is present in various cellular locations within muscle fibers, contributing to exercise-induced production in skeletal muscle [24]. PLA2 promotes the release of arachidonic acid, leading to the formation of ROS and lipid peroxidation [25]. Studies have indicated that XOD activation in rat skeletal muscle is a significant source of ROS production [26].

In skeletal muscle, antioxidant enzymes such as glutathione peroxidase (GSH-Px), catalase (CAT), and superoxide dismutase (SOD) protect muscle fibers from damage and reduce fatigue by eliminating ROS [27]. However, excessive ROS can counteract the protection offered by these antioxidant enzymes. The imbalance between ROS production and the antioxidant defense system leads to oxidative stress. High-intensity exercise can also lead to lipid peroxidation and increase the levels of malondialdehyde (MDA). Additionally, oxidative stress during fatigue may trigger an inflammatory response, leading to the secretion of inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), which further promote fatigue.

Exercise Fatigue Mediated by Central Nervous Protection Inhibition
The central nervous system controls the body’s responses and initiates muscle contractions. During intense exercise, a large number of nerve impulses enter the cerebral cortex, keeping it in a long-term state of excitement. When the motor cortex’s output energy is insufficient, the brain produces protective inhibition, which weakens or even stops the excitement, prevents excessive consumption, thus reducing motor ability and causing fatigue [28].

Many neurotransmitters, such as 5-hydroxytryptamine (5-HT) and dopamine (DA), play an important role in the signal transduction of neurons [29, 30]. Animal studies show that central nervous system fatigue caused by long-term exercise is related to an excess of 5-HT and a decrease in DA in the brain. Tryptophan (Trp) is the precursor of 5-HT. Most Trp in plasma is bound to albumin, with only a small amount of Trp existing in blood in a free state. The increase of 5-HT in the brain is due to the transport of free tryptophan (F-Trp) across the blood-brain barrier [31]. Branched-chain amino acids (BCAAs) and F-Trp use the same transporter to cross the blood-brain barrier, meaning that during long-term exercise, the ratio of BCAAs to F-Trp increases, leading to decreased synthesis of 5-HT in the brain. It has been found that the increase of plasma f-Trp caused by forced running in rats is also related to an increase in NEFA [32]. Long-term exercise increases fat metabolism, producing NEFA, which displaces Trp molecules from albumin, and thus increases the content of F-Trp in blood, in turn increasing the content of 5-HT in the brain. Unlike 5-HT, DA content decreases during fatigue caused by continuous exercise, while the content of 5-HT reaches its peak during fatigue [33]. Additionally, 5-HT and DA may have inhibitory effects on each other. After 6-hydroxydopamine (6-OHDA) destroys dopaminergic neurons, endurance performance is also impaired [34].

In addition to neurotransmitters, an increase in ammonia content in the brain can also cause central nervous system fatigue. It has been found that deamination of adenosine monophosphate (AMP) and BCAAs caused by muscle contraction increases blood ammonia levels [35]. When the content is too high, blood ammonia can enter the cerebral cortex through the blood-brain barrier and disrupt the function of important signaling pathways within the neuron, affecting the regulation of exercise [36].

Effect of Probiotics on Exercise Fatigue
Probiotics are indispensable living microorganisms in the human body. When present in sufficient quantities, they can bring health benefits to the host. Many studies have demonstrated that probiotics play a beneficial role in the human body, such as maintaining the balance of intestinal flora, improving nutrient utilization and energy metabolism, enhancing antioxidation and immune regulation, and playing a critical role in the digestive, respiratory, and immune systems [37]. Additionally, probiotics are used to produce fermented foods like yogurt, pickles, natto, and fermented soybeans. Products derived from probiotics, ROS production, probiotics, postbiotics, and synbiotics, have also attracted considerable attention. Currently, increasing evidence suggests that exercise fatigue can promote an imbalance in intestinal flora, lead to intestinal stress in

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athletes, and cause adverse reactions such as nausea and stomachache. Previous studies have shown that probiotics can mitigate the adverse effects caused by exercise fatigue (Table 1). In animal experiments, mice or rats are commonly used to continuously administer a specific dose of probiotics. It has been found that probiotics can improve animal endurance performance, increase glycogen content, and reduce fatigue-related indices to varying degrees, primarily by increasing endurance running and weight-bearing swimming times, enhancing grip strength of forelimbs, increasing muscle and liver glycogen content, and decreasing levels of lactate (LA), blood urea nitrogen (BUN), and creatine kinase (CK). Additionally, the intake of probiotics can increase the number of type I muscle fibers (slow-twitch muscle), enhance the level of antioxidant enzymes, and alleviate exercise fatigue. Similar conclusions have also been obtained in population trials. Reports indicate that long-term consumption of single or mixed probiotics can prolong the time to exercise-induced fatigue, regulate intestinal flora, reduce the levels of LA and blood ammonia, and alleviate muscle soreness caused by exercise. Therefore, probiotics can effectively improve exercise fatigue.

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Probiotic supplement</th>
<th>Outcomes</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>32 Male ICR Mice (5 weeks old)</td>
<td>1.03 × 10⁹ CFU/kg Bifidobacterium longum subsp. Longum OLP-01 was gavaged daily for 6 weeks.</td>
<td>Increase forelimb grip, weight-bearing swimming time and glycogen content, decrease fatigue-related indices (ammonia, lactic acid, blood urea nitrogen and creatine kinase).</td>
<td>[38]</td>
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<tr>
<td>40 Male SD Rats (7 weeks old)</td>
<td>Feeding yeast polypeptide feed and 1 mL 4 × 10⁷ CFU Lactobacillus plantarum casri Zhang for 10 weeks.</td>
<td>Compared with the normal group, the running endurance is improved by 6.78 min.</td>
<td>[39]</td>
</tr>
<tr>
<td>40 Male ICR Mice (6 weeks old)</td>
<td>6.15 × 10⁹ CFU/d, 1.23 × 10⁷ CFU/d and 3.09 × 10⁶ CFU/d Lactiplantibacillus plantarum Yana were gavaged for 4 weeks respectively.</td>
<td>Increase forelimb grip, swimming time, glycogen storage and intestinal beneficial bacteria abundance, decrease fatigue-related biochemical indices, and have dose dependence.</td>
<td>[40]</td>
</tr>
<tr>
<td>24 Male ICR Mice (6 weeks old)</td>
<td>Lactiplantibacillus plantarum TKW10 were gavaged for 6 weeks respectively.</td>
<td>Increase grip strength, endurance swimming time and type I muscle fiber quantity, decrease fatigue-related index, serum albumin and creatinine levels.</td>
<td>[17]</td>
</tr>
<tr>
<td>75 ICR Mice</td>
<td>Lactiplantibacillus plantarum CQPC02 were gavaged for 4 weeks respectively.</td>
<td>Increase glycogen content, elevate the levels of long oxide dismutase and catalase, decrease the contents of lactic acid, blood urea nitrogen, creatine kinase and malondialdehyde, prolong the swimming time under weight.</td>
<td>[41]</td>
</tr>
<tr>
<td>60 Kunming Male Mice (6 weeks old)</td>
<td>Lactiplantibacillus plantarum CQPC08 (1.0 × 10⁹ CFU/mL) and a combination of Lactiplantibacillus plantarum CQPC08 (1.0 × 10⁶ CFU/mL) with galactooligosaccharide (200 mg/kg GOS) were administered via gavage for 5 weeks following exercise training.</td>
<td>CQPC08 alleviates exercise-induced fatigue by reducing metabolite accumulation and increasing antioxidant capacity in mice. Additionally, the combination of GOS and CQPC08 further enhances CQPC08’s effectiveness in mitigating exercise-induced fatigue.</td>
<td>[42]</td>
</tr>
<tr>
<td>10 Male Runners</td>
<td>4.5 × 10⁷ CFU/d capsules of 9 mixed probiotics (Lactobacillus acidophilus, Lactococcus lactis, Lacticaseibacillus casei, Lactiplantibacillus plantarum, Limosilatococcus fermentum, Bifidobacterium animalis subsp. lactis, Bifidobacterium brevis, Bifidobacterium bifidum and Streptococcus salivarius subsp. thermophilus) for 4 weeks.</td>
<td>Increase the time of running to fatigue in the heat</td>
<td>[43]</td>
</tr>
<tr>
<td>19 Male Elite Rugby Union Athletes</td>
<td>Ultrabiotic 60° (6 × 10⁷ CFU mixed probiotics) and SBFloraactiv® (containing 250 mg of Saccharomyces boulardii) were supplemented twice a day for 17 weeks.</td>
<td>Relieve the muscle soreness of elite rugby league players self-reported.</td>
<td>[44]</td>
</tr>
<tr>
<td>20 Male Triathletes</td>
<td>Lactiplantibacillus plantarum PS128 capsules containing 1.5 × 10⁷ CFU were supplemented twice a day for 4 weeks.</td>
<td>Adjust the intestinal flora of athletes, increase short-chain fatty acids and endurance exercise time.</td>
<td>[45]</td>
</tr>
<tr>
<td>54 Healthy Humans (27 Males And 27 Females)</td>
<td>3 × 10⁶ CFU or 9 × 10⁶ CFU Lactiplantibacillus plantarum TKW10 capsules were supplemented daily for 6 weeks.</td>
<td>Dose-dependently prolong the fatigue time of exhaustive exercise at 85%/VO2max intensity and reduce the content of lactic acid and blood ammonia after exhaustive exercise.</td>
<td>[46]</td>
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<tr>
<td>24 Male Athletes</td>
<td>1 × 10⁹ CFU of mixed probiotic freeze-dried powder (Lactococcus lactis subsp. lactis and Lacticaseibacillus paracasei IMC 502) was supplemented daily for 4 weeks.</td>
<td>Increase plasma antioxidant levels and neutralize reactive oxygen species</td>
<td>[47]</td>
</tr>
<tr>
<td>21 Middle- and Long-Distance Runners (14 Males And 7 Females)</td>
<td>Bifidobacterium longum subsp. Longum OLP-01 was ingested at a dose of 1.5 × 10⁹ CFU/d for 5 weeks.</td>
<td>Improve endurance sports performance, increase the abundance of beneficial bacteria and reduce the proportion of harmful bacteria.</td>
<td>[48]</td>
</tr>
<tr>
<td>15 Resistance-Trained Males</td>
<td>For three weeks, take one capsule each day of Bifidobacterium breve BR03 and Streptococcus salivarius subsp. thermophilus FP4 (5 × 10⁷ CFU).</td>
<td>Relieve the performance reductions and muscle tension caused by muscle injury after exercise.</td>
<td>[49]</td>
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</table>
Probiotics have been increasingly recognized for their potential to combat exercise-induced fatigue, with various strains demonstrating unique mechanisms of action. In particular, *Lactiplantibacillus plantarum* and *Bifidobacterium* species have shown promising results. *Lactiplantibacillus plantarum* primarily exerts its anti-fatigue effects through its antioxidant properties, which help mitigate oxidative stress caused by strenuous exercise, thereby protecting cells from damage. It also modulates immune function by increasing the production of anti-inflammatory cytokines, reducing inflammation, and promoting LA metabolism to decrease muscle fatigue. Studies have indicated that supplementation with *Lactiplantibacillus plantarum* enhances endurance and reduces fatigue, likely due to improved gut microbiota composition and nutrient absorption. On the other hand, *Bifidobacterium* species contribute to anti-fatigue effects by maintaining gut microbial balance, increasing muscle mass, and decreasing fatigue indexes. Research has shown that *Bifidobacterium* supplementation can improve athletic performance, shorten recovery times, and reduce perceived fatigue. Other probiotics, such as *Lactobacillus acidophilus* and *Lactic acid bacillus rhamnosus*, have been demonstrated to combat exercise-induced fatigue through mechanisms such as reducing inflammation. Studies have consistently shown that these probiotics improve endurance, shorten recovery periods, and reduce exercise fatigue in mice, healthy individuals, and athletes. In conclusion, different probiotic strains contribute to the reduction of exercise-induced fatigue and enhancement of athletic performance through various mechanisms, including antioxidant activity, anti-inflammatory effects, and gut microbiota modulation.

**Mechanism of Probiotics Against Exercise Fatigue**

Research on probiotics and sports performance has shown that probiotics can help the body avoid the adverse effects caused by exercise fatigue. This benefit is related to factors such as enhancing the body's energy utilization, improving the clearance rate of metabolites, increasing the level of oxidative resistance, and promoting the production of neurotransmitters (Figure 2).

**Probiotics Regulate Intestinal Flora Metabolites to Increase Energy Supply**

Intestinal flora is closely related to host metabolism, energy utilization, and storage. Petersen et al. [55] compared the intestinal flora of professional and amateur cyclists through metagenomic whole genome shotgun and metatranscriptomic sequencing. They found that the abundance of *Prevotella* and *Methanobrevibacter smithii* in the intestines of professional cyclists increased, which affected pathways in amino acids, carbohydrates, and energy metabolism. Studies have shown that *Prevotella* can improve glucose metabolism and promote an increase in glycogen storage [56]. Additionally, probiotics can promote beneficial bacteria and inhibit harmful bacteria by regulating the diversity and richness of the intestinal flora, thus affecting the body's energy metabolism. Lee et al. [40] isolated a strain of *Lactiplantibacillus plantarum* Tana from gold medal weightlifters. After four weeks of supplementation, the abundance and proportion of *Prevotella* in the intestines of mice increased by adjusting the intestinal flora, which improved glycogen storage and muscle mass, thus enhancing the sports performance of the mice. Chen et al. [17] found that mice ingesting *Lactiplantibacillus plantarum* TWK10 could increase the number of type I muscle fibers, improve glucose utilization, and increase endurance exercise time.

Probiotics also increase the energy supply during exercise by promoting the production of beneficial metabolites such as short-chain fatty acids (SCFAs) [57]. SCFAs are fermentation products of carbohydrates that cannot be digested and absorbed by the small intestine by intestinal flora, affecting the host's energy utilization [58]. It was found that antibiotic treatment reduced SCFAs and exercise endurance in the feces and plasma of mice [59]. After subcutaneous injection of acetate, exercise ability recovered, suggesting that acetic acid is an important energy substrate during exercise. Propionate has been proven to increase heart rate and maximum oxygen consumption. Animal experiments show that a propionate enema can increase exercise time and reduce exercise fatigue in mice [60]. Butyrate is the main energy source for colon cells and can be transported to mitochondria. By activating the adenine adenine 5'-monophosphate (AMP)-activated protein kinase (AMPK)/peroxisome proliferator-activated receptor-γ co-activator-1α (PGC-1α) pathway, it regulates mitochondrial biosynthesis and affects endurance exercise [61]. Huang et al. [45] found that after a triathlete ingested *Lactiplantibacillus plantarum* PS128 continuously for 4 weeks, the content of SCFAs (acetate, propionate, and butyrate) in feces increased significantly, and the endurance exercise ability increased by about 130% compared with the placebo group. The above research shows that probiotics and their metabolites can participate in the regulation of energy metabolism and improve energy supply during exercise.
Probiotics Accelerate the Elimination of Metabolites Produced by Exercise

Studies have shown that probiotics can accelerate the elimination of metabolites (LA, BUN, CK, etc.) produced by acute exercise and maintain the balance of the body. Scheiman et al. [60] found that the relative abundance of Veillonella increased significantly after a marathon. Veillonella was transplanted into mice, and the exercise time of mice increased. It was found that Veillonella can metabolize LA produced by exercise as the only carbon source and convert it into propionate to improve exercise fatigue. *Bifidobacterium longum* subsp. *longum* OLP-01 isolated from Olympic gold medal weightlifters and *Lactiplantibacillus plantarum* CQPC02 isolated from Sichuan pickles have been proven to significantly reduce the levels of LA, BUN, and CK in mice after exhaustive exercise and increase the endurance swimming time [38, 41]. Therefore, supplementing probiotics can accelerate metabolism, remove fatigue-related indicators such as LA, BUN, and CK produced by exercise, and alleviate muscle fatigue.

Probiotics Regulating Antioxidant System

Probiotics play an antioxidant role by chelating metal ions, regulating antioxidant enzyme activity, producing antioxidant metabolites, and regulating pathways related to oxidative stress [62]. Probiotics are strain-specific, and different strains have varying capacities and mechanisms for antioxidant activity. For example, *Streptococcus salivarius* subsp. *thermophilus* 821 can chelate Fe$^{2+}$ and Ca$^{2+}$ [63]; *Bifidobacterium longum* subsp. *longum* LTBL16 can encode the gene for SIR2, which is related to antioxidant activity [64]; *Limosilactobacillus fermentum* E3 and E18 contain glutathione (GSH) and can express Mn-superoxide dismutase (MnSOD) [65]; *Streptococcus agalactiae* can synthesize GSH by catalyzing γ-glutamylcysteine synthetase (Γ-GCS) and glutathione synthetase (GSS) [66].

Hsu et al. [67] found that compared with germ-free mice, SPF mice have a longer endurance swimming time and higher serum levels of GSH-Px and CAT, indicating that intestinal flora can affect exercise fatigue by improving antioxidant enzymes. Martarelli et al. [47] found that a mixture of *Lactococcus lactis* rhamnosus IMC 501 and *Lactisacebacilus paracasei* IMC 502, supplemented in a 1:1 ratio for 4 weeks, could improve the athletes' plasma antioxidant levels and alleviate oxidative stress caused by exercise. *Limosilactobacillus fermentum* HFY03 can reduce the level of MDA and increase the levels of CAT and SOD after exhaustive exercise, demonstrating anti-fatigue and antioxidant effects [68].

In addition, probiotics can also regulate signal pathways related to oxidative stress. For example, *Lactiplandibacillus plantarum* DF189 can activate the nuclear factor erythroid-derived 2-like 2 (Nrf2)/antioxidant response element (ARE) pathway and inhibit oxidative stress in Parkinson's mice [69]. Studies have shown that soybean products fermented by mixed probiotics can activate the Nrf2/ARE pathway, inhibit oxidative damage caused by acute exercise, and relieve fatigue in mice [70]. Therefore, probiotics can be considered a nutritional supplement that improves the level of antioxidant enzymes, regulates pathways related to oxidative stress, and reduces the oxidative damage caused by exercise fatigue.

Probiotics Regulate the Intestinal-Brain Axis to Improve Central Nervous Fatigue

Probiotic supplements have been proven to promote the content of BCAAs, thus reducing the intake of f-Trp in the brain and inhibiting the synthesis of 5-HT. Jäger et al. [71] used a randomized, double-blind, cross-over trial to evaluate the effects of plant protein and probiotic supplements (*Lactisacebacilus paracasei* LP-DG and *Lactisacebacilus paracasei* LPC-501) on the amino acid levels in the blood of healthy men. It was found that probiotic supplements significantly increased the concentrations of methionine, histidine, valine, leucine, isoleucine, tyrosine, total BCAAs, and total essential amino acids, suggesting that probiotic supplements can overcome the composition defects of plant protein, and the added amino acids are very important for athletes and sports recovery. BCAAs can competitively inhibit the transport of f-Trp to the brain, increase the ratio of BCAAs to 5-HT, and reduce the release of 5-HT from the lateral hypothalamus [72].

In addition, probiotics can reduce the blood ammonia content after exhaustive exercise and prevent excessive blood ammonia from entering the brain and causing central nervous system fatigue [38, 45]. Probiotics can also directly regulate the level of 5-HT and relieve depression [73]. In summary, probiotics can reduce blood ammonia concentration, thus inhibiting ammonia production in the brain. By regulating the intestinal-brain axis, they can increase the content of BCAAs and inhibit the accumulation of 5-HT in the brain.
Discussion and Prospect

It is of great significance to study the relationship between probiotics and exercise fatigue. Currently, most research focuses on the effects of probiotics on energy regulation, metabolites, and oxidative stress in the peripheral body after exercise, but there is limited research on the effect and mechanism of homeostasis regulation of the internal environment and central nervous system fatigue relief after exercise. Therefore, future studies should combine physical and central nervous system fatigue to comprehensively explore the potential and molecular mechanisms of probiotics in combating exercise fatigue.

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