Frontiers in Bioscience Landmark

Review

Gut Microbiota in Primary Sarcopenia: Mechanisms and Potential Therapeutic Targets

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Academic Editor: Rosa Alduina

Abstract

As the global population ages, the risks associated with primary sarcopenia, including falls, fractures, functional decline, and frailty, are becoming increasingly apparent, all of which significantly impair the quality of life in older adults. Emerging evidence suggests that the gut microbiota plays a pivotal role in maintaining muscle physiology. Specific gut bacteria promote intramuscular protein synthesis through the production of certain amino acids (e.g., leucine, tryptophan), short-chain fatty acids (SCFAs), and hydrogen sulfide. Notably, Escherichia coli expressing the enzyme nicotinamidase (PncA) has been shown to enhance nicotinamide adenine dinucleotide (NAD+) synthesis, potentially improving mitochondrial function in muscle tissue. Furthermore, secondary bile acids and lactate influence the levels of fibroblast growth factor 15/19 and unacylated ghrelin in circulation by binding to receptors that are highly expressed in gut endocrine cells, thereby affecting muscle physiology. This review examines the characteristic composition of the gut microbiota in patients with sarcopenia, its role in primary sarcopenia, and potential therapeutic targets.

Keywords: sarcopenia; gut microbiota; SCFAs; bile acids; NAD+; ghrelin; LPS

1. Introduction

Sarcopenia affects 10% to 16% of the elderly population worldwide [1]. As the global population ages, age-related diseases, particularly sarcopenia, have garnered significant attention. Sarcopenia not only increases the risk of falls and fractures in older adults but also contributes to multi-organ dysfunction, imposing a substantial burden on patients, families, and society. In 1989, Irwin H. Rosenberg [2] first introduced the concept of sarcopenia, highlighting its characteristics of age-related muscle loss and reduced physical function. In 2016, sarcopenia was officially listed as a diagnosis in the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) [3]. In 2024, the Global Leadership Initiative on Sarcopenia (GLIS) defined sarcopenia as a systemic skeletal muscle disease with potential reversibility, characterized by the combined decline in muscle mass and strength, with prevalence increasing with age [4]. The primary parameters for diagnosing and assessing sarcopenia are muscle strength, muscle mass, and physical function, with diagnostic cut-off values varying across regions and ethnicities. In Asia, the Asian Working Group for Sarcopenia 2 (AWGS2) criteria, proposed in 2019, are widely recognized as the authoritative diagnostic standard for sarcopenia [5], with specific cut-off values detailed in Table 1 (Ref. [5,6]).

Sarcopenia can be classified as "primary" or "secondary" based on its etiology, with secondary sarcopenia associated with other diseases, whereas aging is considered the sole cause of primary sarcopenia [7]. The pathogenesis of sarcopenia is multifaceted. To initiate movement, the brain generates motor intent, and neural impulses are transmitted through motor neurons to the neuromuscular junction, triggering muscle contraction via the excitation-contraction coupling system [8], with skeletal muscle playing the primary role in movement. Skeletal muscle consists of muscle fibers, which contain mitochondria that are responsible for energy production. Muscle fibers are surrounded by a dense capillary network that provides oxygen and nutrients, while the extracellular matrix (ECM) tightly encases the fibers, housing satellite cells that repair muscle damage [9]. Muscle fiber contraction requires energy, and based on energy production pathways, fibers are classified as type I and type II. Type I fibers derive energy from lipid oxidation, and are resistant to fatigue, while type II fibers rely on glycolysis, and are more prone to fatigue, but generate higher force more rapidly [8]. As a plastic organ, skeletal muscle undergoes age-related changes, including protein homeostasis imbalance, fiber-type shifting from type I to type II, reduced vascular supply, chronic low-grade systemic inflammation, and ECM fibrosis, all of which contribute to the development of sarcopenia [10]. A 2023 systematic review and meta-analysis identified several risk factors for primary sarcopenia, including lack of physical activity, malnutrition, smoking, insufficient or excessive sleep, diabetes, osteoporosis, and obesity [1]. Currently, treatment for primary sarcopenia primarily focuses

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Table 1. Diagnostic parameters and cutoffs.

Classification	Detection method	Muscle mass	Muscle strength	Physical performance
EWGSOP2 [6]	DXA	ASM/height^2 (kg/m^2): Men <7.0; Women <5.5	Grip strength (kg): Men <27; Women <16; 5-times sit-to-stand (s): >15	Gait speed (m/s): $\leq$0.8
AWGS2 [5]	BIA	ASM/height^2 (kg/m^2): Men <7.0; Women <5.7	Grip strength (kg): Men <28; Women <18	Gait speed (m/s): <1.0; 5-times sit-to-stand (s): $\geq$12; SPPB $\leq$9 point score
	DXA	ASM/height^2 (kg/m^2): Men <7.0; Women <5.4		

ASM, appendicular skeletal muscle mass; EWGSOP, European Working Group on Sarcopenia in Older People; AWGS, Asian Working Group for Sarcopenia; DXA, dual-energy X-ray absorptiometry; BIA, bioelectrical impedance analysis; SPPB, short physical performance battery.

on exercise and nutritional support; however, significant unmet needs remain, prompting further exploration of potential therapeutic targets.

The gut microbiota, often referred to as the "central metabolic organ", weighs approximately 1.5–2.0 kg and contains approximately 100 trillion cells, ten times more than the human body's own cells [11]. A healthy gut microbiota produces a variety of bioactive metabolites that enter the bloodstream via the enterohepatic circulation, exerting beneficial effects on the host. Furthermore, a healthy gut microbiota ferments indigestible polysaccharides to produce compounds such as short-chain fatty acids (SCFAs), which help suppress local intestinal inflammation and enhance gut barrier function [12]. Maintaining a balanced gut microbiota is essential for overall health. Recent studies have highlighted a close association between dysbiosis and several high-risk factors for sarcopenia. For instance, smoking has been linked to a reduction in *Bifidobacteria* levels and SCFA production [13], and human gut microbiota diversity is negatively correlated with sedentary behavior [14]. The gut microbiota also influences energy metabolism by regulating appetite and affecting the development and function of adipose tissue, which is closely related to obesity [15]. Moreover, gut microbiota has been identified as a potential target for addressing sleep disorders [16,17], suggesting its potential as a therapeutic target for sarcopenia. Indeed, numerous studies have demonstrated that various gut metabolites are closely linked to the onset and progression of sarcopenia [18,19],

The treatment of primary sarcopenia still has significant gaps, and further exploration of potential therapeutic targets for this condition is needed. In recent years, the role of gut microbiota metabolites in the body has garnered increasing attention. While the relationship between gut microbiota and sarcopenia has been explored previously, we note that metabolites closely associated with gut microbiota—such as nicotinamide adenine dinucleotide (NAD+), nonacylated growth hormone-releasing peptide, hydrogen sulfide (H$_2$S), and Streptococcal quorum sensing peptide competence stimulating peptide 7 (CSP-7)—have not been widely discussed, despite their importance. This review will adopt a structured search strategy, aiming to describe and analyze current research to provide deeper insights into this emerging topic.

(1) Explore the characteristic intestinal flora profile of patients with primary sarcopenia.

(2) Explore the potential association between gut microbiota and the pathogenesis of sarcopenia and sarcopenic obesity.

(3) Explore practical strategies based on microbial therapies.

2. Characteristic Gut Microbiome Profile in Primary Sarcopenia

2.1 Search Strategy

The PubMed database (date last accessed 25 December 2024) was selected. The following keywords were used in the search strategy: (microbiota* OR microbiome* OR gut) AND (sarcopen*). Reference lists of related reviews were searched for additional studies.

2.2 Search Criteria

2.2.1 Inclusion Criteria

(1) Clinical original studies (Last 5 years; Patients were included according to recognized diagnostic criteria for sarcopenia).

(2) Preclinical studies (Last 1 years).

(3) Study on gut microbiota and its effects on sarcopenia.

(4) Study reporting muscle mass and function indicators.

2.2.2 Exclusion Criteria

(1) Review articles.

(2) Conference and abstract publications.

(3) Study not involving the gut microbiota or sarcopenia.

(4) Athletes and patients/animal models with other diseases rather than age-related sarcopenia.

(5) Lack of baseline characteristics data.

(6) Non-English article.

2.3 Selection of Studies

Screened titles and abstracts of articles obtained through the search strategy followed by full text for eligible criteria independently.

2.4 Data Extraction

The following data were extracted from pre-clinical studies: doi, published year, animal model, intervention, endpoints, muscle samples, sample type and detection, muscle measurement method, physical performance method, muscle mass comparison, physical performance comparison, gut microbiota, relationship: muscle/functions and gut microbiota, key findings. For clinical studies, the extracted data were: doi, published year, subject, study group, age (year), study type, follow-up duration, sample type and detection, muscle measurement method, physical performance method, diagnostic criteria, muscle mass comparison, physical performance comparison, gut microbiota, function of the fecal microbiota, relationship: muscle/functions and gut microbiota, key findings.

2.5 Results

A total of 413 studies were retrieved through electronic database searches. We initially excluded review articles, conference and abstract publications, and editorials by adjusting the search format. A total 214 studies were identified for title and abstract screening. Among these studies, 112 full texts were reviewed, and 24 studies (seven pre-clinical trials and seventeen clinical trials) satisfied all inclusion and exclusion criteria. It should be known that although we reviewed the last 5 years of pre-clinical studies according to the search strategy, we only selected reports from the last 1 year to list in the table. Supporting information, **Supplementary Table 1** shows the summary of clinical studies, and **Supplementary Table 2** shows the pre-clinical studies.

2.6 Clinical Studies

There were seventeen clinical studies of which fifteen were observational studies [20–34] and two were interventional studies [35,36]. All studies used recognized diagnostic criteria for sarcopenia, of which nine studies [21,22,24–28,34,36] used AWGS2 (2019) criteria, two studies [30,31] used AWGS (2014) criteria, two studies [33,35] used EWG-SOP2 (2018) criteria. Two studies [20,29] used EWG-SOP (2010) criteria, one study [32] used Foundation for the National Institutes of Health (FNIH) criteria, and one study [23] used International Working Group on Sarcopenia (IWGS) criteria. Please refer to **Supplementary Table 1**.

Key Findings

Roseburia and *Eubacterium* were significantly positively correlated with appendicular skeletal muscle mass index (ASMI) ($p < 0.05$) [21]. *Roseburia*, *Eubacterium*, and *Lachnospira* were negatively correlated with five-time chair stand test time [21]. *Lachnospira*, *Eubacterium*, and *Ruminococcus* were significantly positively correlated with grip strength [21]. Bacteria belonging to the genus *Roseburia*, including *R. inulinivorans*, are well-known SCFA producers [20,37]. Several studies have reported a significant decrease in *Roseburia* abundance in the feces of patients with sarcopenia [20,21,29]. *Roseburia* was negatively correlated with interleukin (IL)-6 [29]. The meta-analysis showed that IL-6 was associated with sarcopenia in people aged <75 [38]. *Desulfovibrio piger*, *Clostridium symbiosum*, *Hungatella effluvii*, *Bacteroides fluxus*, *Absiella innocuum*, and *Clostridium citroniae* were positively associated with sarcopenia severity [22]. *Anaerotruncus* and *Phascolarctobacterium* sp. correlated positively with sarcopenia at the genus level ($p = 0.005$) [24]. *Prevotella copri* abundance exhibited a negative linear relationship with sarcopenia ($p = 0.020$) [24]. *Bifidobacterium longum* showed a positive correlation with appendicular skeletal muscle mass, Handgrip strength, body mass index (BMI), and calf circumference [26]. *Enterobacteriaceae* ($p = 0.001$) and particularly *Escherichia-Shigella* ($p = 0.001$) correlated significantly negatively with muscle mass [27]. *Alloprevotella* ($p < 0.001$), *Succinivibrio* ($p < 0.05$), and *un_f_Prevotellaceae* ($p < 0.01$) were significantly positively correlated with ASMI [28]. *Un_f_Lachnospiraceae* ($p < 0.01$) and CAG-352 ($p < 0.05$) were significantly negatively correlated with ASMI [28]. *Escherichia Shigella* abundance was negatively correlated with skeletal muscle mass index and grip strength but positively correlated with IL-6 level [29]. LPC (*Prevotella copri*) treatment significantly mitigated muscle function and mass decline [31], *Actinobacteriota* was negatively correlated with grip strength and *Bifidobacterium* was negatively correlated with ASMI [34].

2.7 Pre-Clinical Studies

There were seven interventional animal studies [39–45]. A total of six studies were mice using Dexamethasone (DEX)-induced sarcopenia mouse model in two [44,45], BALB/c in one [41], C57BL/6J in two [42,43], and SAMP8 in one [40]. The seven pre-clinical studies examined the effects of dietary, probiotics, prebiotics, short-chain fatty acids, and intestinal immune status on models of sarcopenia and its metabolic complications, and highlighted the potential role of intestinal flora. Please refer to **Supplementary Table 1**.

Key Findings

Mo *et al.* [39] investigated whether a high-fat diet (HFD) causes sarcopenic obesity (SO) in natural aging animal models and specific microbial metabolites that are involved in linking HFD and SO. The results show that HFD caused decreases in muscle mass, strength, function, and fiber cross-sectional area and increase in muscle fatty in-

filtration in natural aging rats, which also contributed to gut dysbiosis, mainly characterized by increases in deleterious bacteria (such as *Parabacteroides*, *Akkermansia*, *Intestinimonas*, and *Butyricimonas*) and trimethylamine N-oxide (TMAO) [39]. Particularly, supplementation with *Akkermansia* or *Butyricimonas* effectively mitigated sarcopenic obesity by restoring gut dysbiosis to homeostasis and decreasing systemic inflammation [46,47]. Further study indicated that TMAO promotes the development of HFD-induced SO via the reactive oxygen species (ROS)-protein kinase B (Akt)/mechanistic target of rapamycin (mTOR) pathway [39]. Liu *et al*. [40] investigated whether the use of SCFAs as a supplement can be a therapeutic strategy for sarcopenia. The results show that increased muscle mass, myofiber cross-sectional area, grip strength, twitch, and tetanic force were found in SCFAs-treated mice compared with control SAMP8 mice, and *in vitro* studies indicated that SCFAs inhibited Forkhead box O3a (*FoxO3a*)/*Atrogin1* and activated mTOR pathways to improve myotube growth [40]. Ma *et al*. [41] investigated the crosstalk between the intestinal microbiota and the host's immunity and metabolism. The results show that the gut microbiota population structures altered with the subtherapeutic level of antibacterial agents facilitated growth phenotype in both piglets and infant mice, notably, increased colonization of *Prevotella copri* was observed in the intestinal microbiota, which shifted the immune balance from a CD4$^+$ T cell-dominated population toward a T helper 2 cell (Th2) phenotype, accompanied by a significant elevation of interleukin-13 (IL-13) levels in the portal vein, which was found to display a strong positive correlation with hepatic insulin-like growth factor-1 (IGF-1) levels. Subsequent investigations showed that gut-derived IL-13 stimulated the production of hepatic IGF-1 by activating the interleukin-13 receptor (IL-13R)/Janus Kinase 2 (Jak2)/signal transducer and activator of transcription 6 (Stat6) pathway *in vitro*. The IGF-1 levels were increased in the muscles, leading to an upregulation of and resulting in the increased genes associated with related to myofibrillar synthesis and differentiation, which ultimately improved the growth phenotype [41]. Zhang *et al*. [42] investigated the impact of *Bifidobacterium animalis* subsp. *lactis* Probio-M8 (Probio-M8) on old mice and sarcopenia patients. The results show that Probio-M8 significantly improved muscle function in aged mice and enhanced physical performance in sarcopenia patients. It reduced pathogenic gut species (such as *Romboutsia ilealis* (human) and *Intestinibacter bartlettii* (human)) and increased beneficial metabolites such as indole-3-lactic acid, acetoacetic acid, and creatine [42]. Kim *et al*. [43] investigated the beneficial effects of *L. paragasseri* SBT2055 on obesity along with obese sarcopenia and gut microbiome changes. The results show that SBT2055 reduces adiposity in obese mice and enhances muscle mass and function in the context of sarcopenic obesity [43]. The anti-obesity efficacy of SBT2055 was due to increased lipid excretion into

feces by reducing the mRNA levels of fatty acid binding protein 1 (Fabp1), fatty acid binding protein 2 (Fabp2), fatty acid transport protein 4 (Fatp4), cluster of differentiation 36 (Cd36), and apolipoprotein 48 (ApoB48) in the small intestine [43]. Two studies examine the effect of probiotics on skeletal muscle atrophy in dexamethasone-induced C2C12 cells and a mouse animal model [44,45]. The results show that supplementation with *Lacticaseibacillus rhamnosus* IDCC3201 resulted in significant enhancements in body composition, particularly in lean mass, muscle strength, and myofibril size. IDCC3201 increased the production of branched-chain amino acids (BCAAs) and improved the *Allobaculum* genus within the gut microbiota of muscle atrophy-induced groups [44]. Another study showed that KL-Biome (Postbiotic Formulation of *Lactiplantibacillus plantarum* KM2) significantly downregulated the expression of genes (*Atrogin-1* and muscle-specific RING finger protein 1 (*MuRF-1*)) associated with skeletal muscle degradation but increased the anabolic phosphorylation of FoxO3a, Akt, and mTOR in C2C12 cells. Furthermore, it significantly increased the relative abundances of the genera *Subdoligranulum*, *Alistipes*, and *Faecalibacterium prausnitzii*, which are substantially involved in short-chain fatty acid production [45].

To summarize, five of the studies involved the Akt/mTOR signaling pathway [39,40,43–45], and one study highlighted the modification of gut immunity states as a central strategy for increasing anabolism of the host, which has significant implications for addressing sarcopenia [41].

2.8 Microbial-Derived Gut Contents

In 2022, a study explored the metabolism and community composition of gut contents and mucus in mice. It was found that compared to germ-free mice, specific pathogen-free (SPF) mice had an average concentration of 24 metabolites in the colon that was at least four times higher. This study also provided evidence of the microbial origin of 11 metabolites in the small intestine [48]. Many of these microbial-derived metabolites, such as nicotinamide, spermidine [49], deoxycholate [18], short-chain fatty acids (SCFAs) [50], histidine [51], and Indole-3-propionic acid (IPA) [52], have previously been linked to sarcopenia. Therefore, we will discuss the role of the gut microbiome and its metabolites in the development of sarcopenia, focusing on three aspects: protein homeostasis, systemic chronic low-grade inflammation, and mitochondrial dysfunction, while exploring potential therapeutic targets within these pathways.

3. Pathogenesis of Sarcopenia

3.1 Protein Homeostasis Imbalance

Protein homeostasis refers to the delicate balance between protein synthesis and degradation, which is closely linked to muscle fiber size [53]. A decline in protein

homeostasis is a hallmark of aging [54]. The mechanistic target of rapamycin (mTOR) in mammals is a key regulator of muscle protein synthesis and metabolism. As shown in Fig. 1, in skeletal muscle, the phosphoinositide 3-kinase (PI3K)/Akt/mammalian target of rapamycin complex 1 (mTORC1) pathway mediates protein synthesis and can be activated by mechanical stimuli, insulin-like growth factors, insulin, amino acids, and other factors [55,56]. This pathway promotes muscle protein synthesis and hypertrophy through the following mechanisms [53]: (1) Activation of mTORC1-mediated phosphorylation of p70S6 kinase, which promotes protein synthesis [57]. (2) Activation of mTORC1-mediated phosphorylation of eukaryotic translation initiation factor 4E-binding protein (4EBP), leading to its dissociation from eukaryotic translation initiation factor 4E (eIF4E), initiating translation and increasing protein synthesis [58]. (3) PI3K/Akt activation also prevents protein degradation in skeletal muscle by phosphorylating and thereby inactivating O-type fork head box (FOXO) transcription, which downregulates the expression of MuRF-1 and Atrogin-1, inhibiting protein degradation [53]. These processes are depicted in Fig. 1.

Tumor necrosis factor-alpha (TNF-α) and interleukin-1 (IL-1) and -6 (IL-6) are relevant inflammatory cytokines promoting protein degradation in muscle [59]. Protein degradation is primarily mediated by the ubiquitin-proteasome system (UPS), which is activated via the p38 mitogen-activated protein kinase (MAPK) and nuclear factor kappa B (NF-κB) pathways. As illustrated in Fig. 1, (1) Both the MAPK p38 and NF-κB pathways can activate the expression of muscle-specific E3 ligases MuRF-1 and Atrogin-1 [53]. These ubiquitin E3 ligases target polyubiquitinated proteins for degradation by the 26S proteasome [60]. (2) The NF-κB pathway not only activates MuRF-1 and Atrogin-1 but also binds to kappaB elements on the myostatin gene, promoting myostatin expression [53]. Myostatin is a negative regulator of muscle growth [61]. With aging, protein homeostasis imbalance increases, contributing to the development of sarcopenia. The gut microbiota and its metabolites may help prevent the onset and progression of sarcopenia by regulating protein homeostasis, as discussed further below.

3.2 Systemic Chronic Low-Grade Inflammation

Systemic chronic low-grade inflammation is a key feature of sarcopenia [62], characterized by elevated levels of pro-inflammatory markers such as IL-1, IL-6, IL-8, IL-13, IL-18, C-reactive protein (CRP), Interferon (IFN)α, IFNβ, transforming growth factor (TGF)β, and TNF [63]. Meta-analysis revealed that higher levels of CRP, TNF, and IL-6 were associated with lower muscle strength and muscle mass over time [64]. Study indicate that aging upregulates the expression of NF-κB activators while downregulating NF-κB inhibitors [65], suggesting that aging induces a gradual pro-inflammatory state in the body. Pro-

inflammatory factors promote protein degradation through the NF-κB pathway [53]. Moreover, the upregulation of NF-κB in muscle satellite cells (MuSCs) can inhibit the transition of MuSCs from low to high glutathione (GSH) levels, depleting GSH and accelerating MuSC aging, which contributes to the progression of sarcopenia [66].

3.3 Mitochondrial Dysfunction

With aging, mitochondrial function progressively declines [67]. A quantitative proteomics analysis of skeletal muscle from 58 healthy individuals aged 20 to 87 revealed a marked reduction in proteins related to energy metabolism, including those involved in the tricarboxylic acid (TCA) cycle, mitochondrial respiration, and glycolysis, as aging progresses [65]. This decline in mitochondrial function during aging disrupts protein homeostasis and leads to muscle atrophy.

4. Gut Microbiome-Mechanism-Sarcopenia

4.1 Escherichia coli-Nicotinamidase PncA-NAD+-Mitochondria

Nicotinamide adenine dinucleotide (NAD+) is a critical coenzyme in cells, playing a vital role in the tricarboxylic acid (TCA) cycle and oxidative phosphorylation, both of which are essential for maintaining mitochondrial function. Low NAD+ levels have been identified as a significant marker in patients with sarcopenia [68,69]. In humans, NAD+ synthesis primarily occurs through two pathways: the salvage pathway and the *de novo* synthesis pathway: (1) Salvage Pathway: This pathway regenerates NAD+ from its breakdown product, nicotinamide (NAM). (2) *De Novo* Synthesis Pathway: Nicotinic acid (NA) synthesizes NAD+ through the Preiss-Handler pathway, while tryptophan is converted to nicotinamide mononucleotide (NMN) via the kynurenine pathway, which eventually integrates into the Preiss-Handler pathway for NAD+ synthesis [70].

Among these, the NAD+ salvage pathway via NAM is the primary route in humans, forming a delicate cycle between NAD+ consumption and regeneration. Nicotinamide phosphoribosyltransferase (NAMPT), the rate-limiting enzyme, converts NAM to NMN. As individuals age, the expression of NAMPT decreases, resulting in reduced NAD+ synthesis. The gut microbiome is closely associated with NAD+ homeostasis [71]. As illustrated in Fig. 2A, gut bacteria expressing nicotinamidase (PncA), such as Escherichia coli, can bypass the limitation of NAMPT, converting NAM into NA, which then generates NAD+ through the *de novo* synthesis pathway, thereby stabilizing NAD+ levels [71]. In one study [71], NAD+ precursors were administered to both microbiota-rich normal mice and antibiotic-treated mice via gavage. It was found that in normal mice, isotopically labeled NAM was rapidly converted to NA, whereas this conversion was significantly diminished or absent in antibiotic-treated mice. Further in-
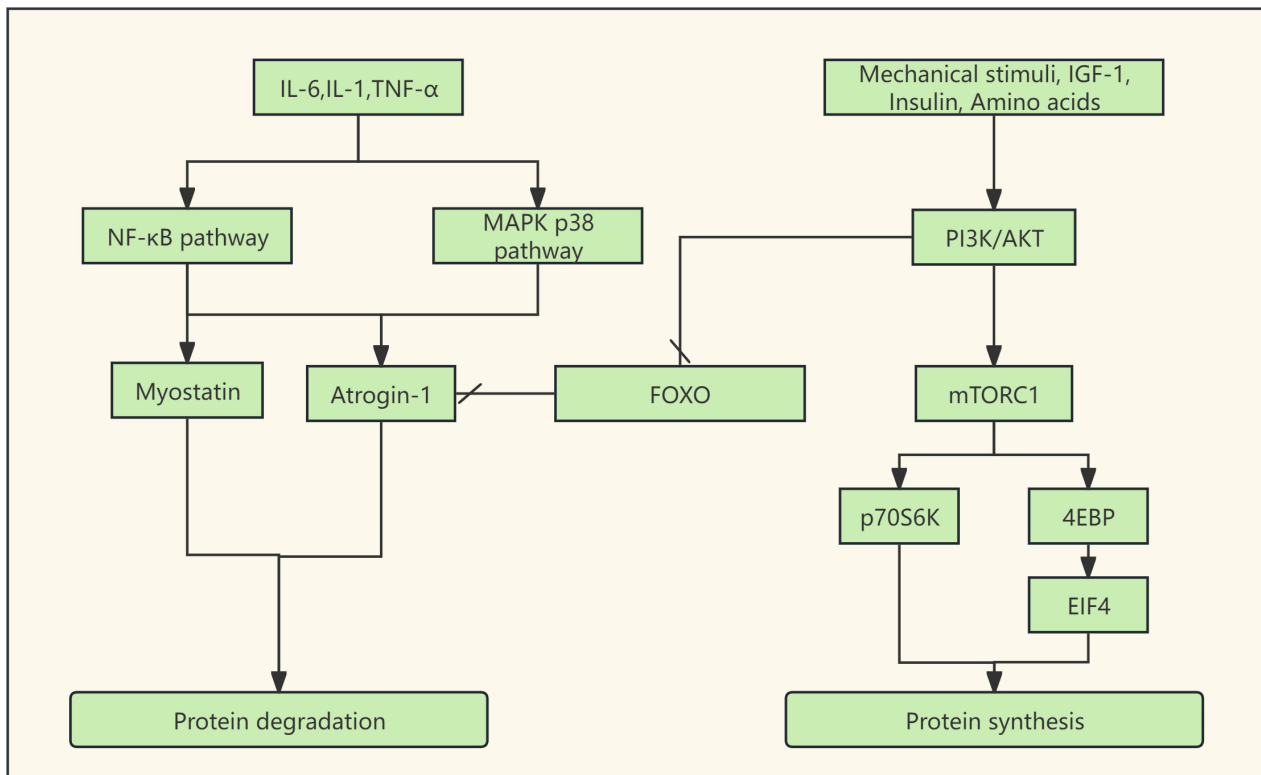
Fig. 1. The Akt/mTOR-centered protein synthesis pathway and the main protein degradation pathways. (1) Factors such as mechanical stimuli, insulin-like growth factors, insulin, and amino acids can activate the PI3K/Akt pathway. This pathway can promote protein synthesis by activating mTORC1 and inhibit protein degradation by phosphorylating FOXO. (2) Inflammatory cytokines such as IL-6, IL-1, and TNF-α promote protein degradation through the activation of the MAPK p38 and NF-κB pathways. IL-6, interleukin 6; IL-1, interleukin 1; TNF-α, tumor necrosis factor alpha; IGF-1, insulin-like growth factor 1; mTORC1, mammalian target of rapamycin complex 1; p70S6K, p70 ribosomal S6 kinase; EIF4, eukaryotic initiation factor 4; PI3K, phosphoinositide 3-kinase; Akt, protein kinase B; 4EBP, eukaryotic translation initiation factor 4E-binding protein; NF-κB, nuclear factor kappa B; MAPK, mitogen-activated protein kinase; FOXO, fork head box. The figure was created by us using the WPS Office 12.1 (Kingsoft Office Software Corporation Limited, Zhuhai, Guangdong, China).

vestigation revealed that *E. coli* expressing nicotinamidase PncA could protect CRC119 cells from NAMPT inhibitors, reversing the decline in NAD+ levels. Notably, deletion of the *PncA* gene in *E. coli* completely eliminated this protective effect. Additionally, liquid chromatography-mass spectrometry (LC-MS) confirmed that *E. coli* stably converts NAM to NA in culture [71]. Other research similarly found that NAM is rapidly deaminated to NA by the microbiota, a process closely associated with the abundance of gut microorganisms [72].

Furthermore, the gut microbiome can produce NAD+ precursors such as trigonelline and NA [48,73,74]. One study found that supplementing with fenugreek alkaloids improved NAD+ levels in Caenorhabditis elegans, mice, and primary myotubes (derived from both healthy individuals and those with sarcopenia) (Fig. 2A). It also enhanced mitochondrial respiration and biosynthesis, while reducing age-related muscle loss [74]. Another study investigated the clinical application of NAD+ precursors with 20 pairs of identical twins. Over five months, they gradually increased

nicotinamide riboside (NR, an NAD+ precursor) supplementation from 250 mg/day to 1000 mg/day to examine its impact on mitochondrial biogenesis and metabolic health. Results indicated that NR supplementation enhanced mitochondrial presence in type I muscle fibers by approximately 14%, expanded mitochondrial coverage within muscle fibers, and significantly increased mitochondrial DNA (mtDNA) by around 30%. These effects were linked to the upregulation of genes such as *SIRT1*, *ERR*α, *TFAM*, and *MFN2*. NR supplementation was also found to promote muscle satellite cell differentiation. *Faecalibacterium prausnitzii*, a gut microbiota strain, may promote NAD+ synthesis by competing for NAD+ precursors, thereby enhancing its anti-inflammatory effects and abundance within the gut [75].

While the gut microbiome has demonstrated potential in maintaining NAD+ homeostasis and mitigating sarcopenia in animal models, particularly through bacterial strains expressing nicotinamidase PncA, these findings should be interpreted with caution. The direct applicability of these
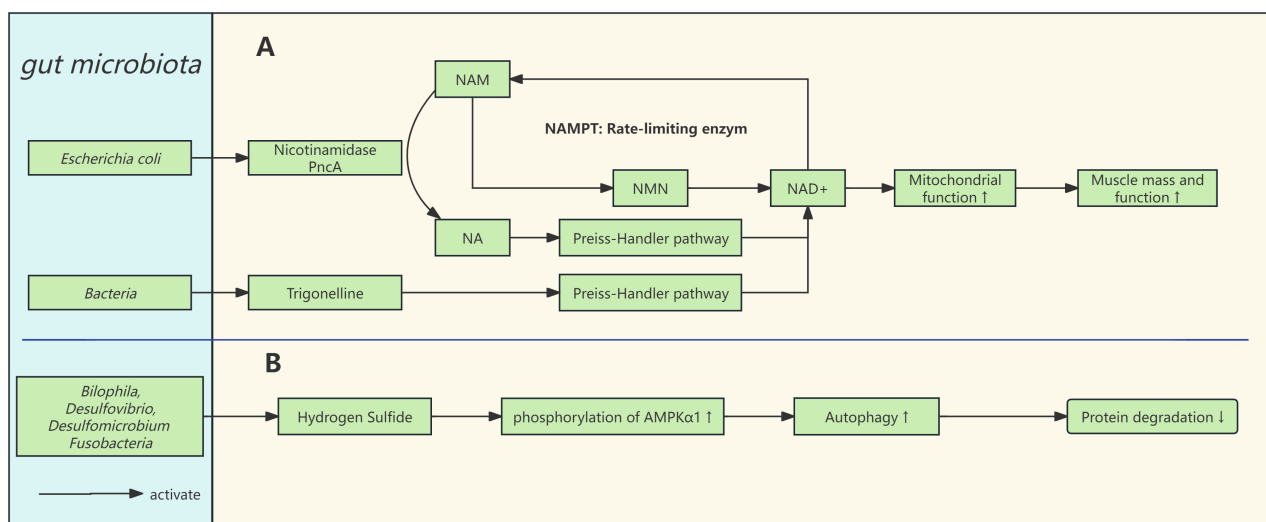
Fig. 2. Gut microbiota and the pathways associated with mitochondria and autophagy. (A) The NAD+ salvage pathway is the primary source of NAD+ in the body and is limited by the enzyme NAMPT. Gut microbiota can convert NAM to NA through nicotinamidase (PncA), bypassing the NAMPT restriction to promote NAD+ homeostasis in the body. (B) Hydrogen sulfide and lipopolysaccharides are involved in skeletal muscle metabolism. Abbreviations: NA, nicotinic acid (Niacin); NAM, nicotinamide; NMN, nicotinamide mononucleotide; NAD+, nicotinamide adenine dinucleotide; NAMPT, nicotinamide phosphoribosyltransferase; AMPKα1, adenosine monophosphate-activated protein kinase alpha 1; $\uparrow$, an increase or activation of a process or molecular activity; $\downarrow$, a decrease or inhibition of a process or molecular activity. The colors in the figure do not have any specific meaning. The figure was created by us using the WPS Office 12.1 (Kingsoft Office Software Corporation Limited, Zhuhai, Guangdong, China).

results to human health remains to be validated through clinical trials.

4.2 Gut-Bile Acid-FGF15/19-FGFR4-KLB-mTORC1 Axis

Research suggests that the gut microbiota can influence the Farnesoid X Receptor (FXR) by modulating the bile acid pool, which subsequently affects muscle protein homeostasis through the fibroblast growth factor (FGF)15/19/fibroblast growth factor receptor (FGFR)4/klotho beta (KLB)/mTORC1 signaling pathway, playing a role in the onset and progression of sarcopenia [18,76]. The bile acid pool comprises primary and secondary bile acids, which regulate bile acid circulation and various host metabolic processes via FXR activation [18]. FGF15/19 (the mouse and human homologs of FGF15 and FGF19, respectively) are induced by FXR [77] and influence skeletal muscle protein synthesis [76]. Different bile acids exert varying agonist effects on FXR, in the following order: chenodeoxycholic acid (CDCA) > deoxycholic acid (DCA) > lithocholic acid (LCA) > cholic acid (CA), while tauro-beta-muricholic acid (TβMCA), tauro-alpha-muricholic acid (TαMCA), beta-muricholic acid (βMCA), and ursodeoxycholic acid (UDCA) function as FXR antagonists [78]. Primary conjugated bile acids can be deconjugated by microbes possessing bile salt hydrolase (BSH) activity, and these secondary bile acids are subsequently metabolized by the distal gut microbiota.

Qiu *et al*. [76] found that antibiotic-treated mice exhibited a characteristic bile acid profile dominated by the accumulation of the FXR antagonist TβMCA. In these mice, the levels of gut microbes with high BSH activity (such as *Lactobacillus* and *Bifidobacterium*) were significantly reduced, and they showed a decrease in skeletal muscle mass. However, treatment with FGF15/19 was able to reverse the muscle mass loss induced by antibiotics [77]. As shown in Fig. 3A, the proposed mechanism is as follows: Gut microbes with BSH activity promote the conversion of primary conjugated bile acid βTMCA to secondary bile acids, thereby mitigating the antagonistic effects of βTMCA on FXR. This alleviates the inhibition of the FXR-FGF15/19 pathway. Upon entering the bloodstream, FGF15/19 can bind to FGFR4 in skeletal muscle and, with the assistance of the co-receptor KLB, upregulate the expression of the mTORC1-p70 ribosomal S6 kinase (p70S6K) and extracellular signal-regulated kinase (ERK)-p90 ribosomal S6 kinase (p90RSK) signaling pathways, thereby promoting muscle protein synthesis [18,76]. Moreover, FXR activation also enhances gut barrier function and reduces gut inflammation [79].

Clinical study has demonstrated that the FGF19 signaling pathway is downregulated in elderly men ($\geq$60 years), and plasma FGF19 levels are positively correlated with relative skeletal muscle mass in the limbs [80]. However, due to differences in bile acid profiles between humans and mice, further research is required to explore the effects of BSH-active probiotics on circulating FGF19 in humans. This may represent a potential therapeutic target for sarcopenia.
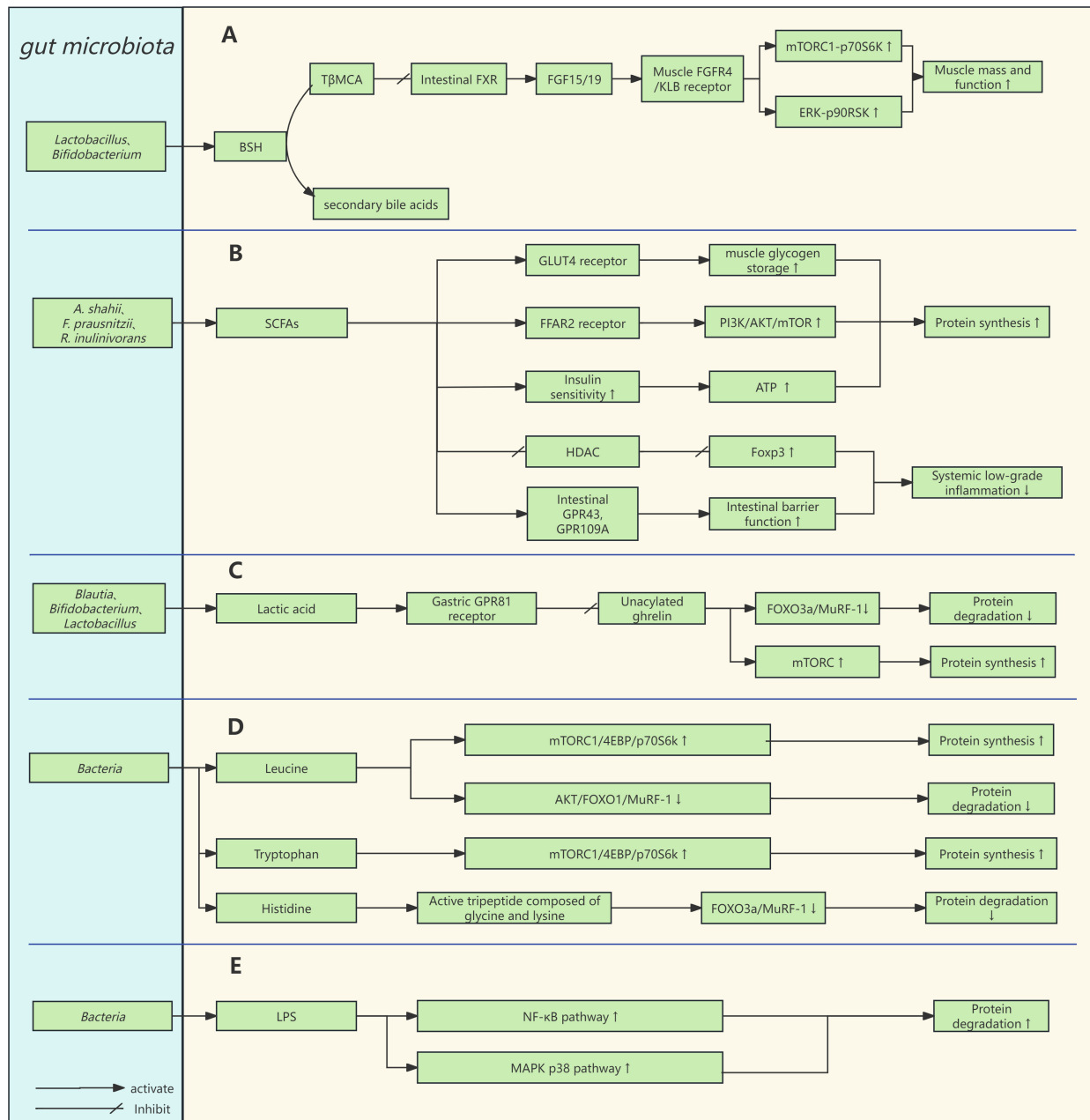
Fig. 3. Gut microbiota and signaling pathways for muscle protein synthesis and degradation. (A) Gut microbiota can indirectly regulate circulating FGF15/19 levels by influencing bile acid metabolism, thereby participating in skeletal muscle metabolism. (B,D,E) SCFAs, amino acids, and lipopolysaccharides are involved in skeletal muscle metabolism. (C) Intestinal lactate affects the level of circulating unacylated ghrelin by binding to receptors on intestinal endocrine cells, thus influencing muscle protein metabolism. Abbreviations: TβMCA, tauro-β-muricholic acid; FGF15/19, fibroblast growth factor 15/19; FGFR4/KLB, fibroblast growth factor receptor 4/Klotho β protein; GLUT4 receptor, glucose transporter type 4 receptor; FFAR2 receptor, free fatty acid receptor 2; GPR43, GPR109A receptors, G protein-coupled receptor 43/G protein-coupled receptor 109A; Ghrelin, growth hormone-releasing peptide; mTORC1, mammalian target of rapamycin complex 1; p70S6K, p70 ribosomal S6 kinase; ERK, extracellular signal-regulated kinase; p90RSK, p90 ribosomal S6 kinase; PI3K, phosphoinositide 3-kinase; Akt, protein kinase B; ATP, adenosine triphosphate; FOXO, forkhead Box O; MuRF-1, muscle-specific RING finger protein 1; 4EBP, eukaryotic translation initiation factor 4E-binding protein; IPA, indole-3-propionic acid; miR-26a-2-3p, microRNA-26a-2-3p; IL-1β, interleukin-1 beta; NF-κB, nuclear factor kappa B; MAPKs, mitogen-activated protein kinases; LPS, lipopolysaccharides; Foxp3, forkhead box protein P3; FXR, Farnesoid X Receptor; HDAC, Histone Deacetylase; ↑ , an increase or activation of a process or molecular activity; ↓ , a decrease or inhibition of a process or molecular activity. The colors in the figure do not have any specific meaning. The figure was created by us using the WPS Office 12.1 (Kingsoft Office Software Corporation Limited, Zhuhai, Guangdong, China).

4.3 Short-Chain Fatty Acids (SCFAs)

Indigestible substrates in the gut, such as dietary fiber, are fermented by gut bacteria (e.g., *A. shahii*, *F. prausnitzii*, *R. inulinivorans*) to produce short-chain fatty acids (SCFAs), including acetate, propionate, butyrate, and pentanoate. Approximately 95% of SCFAs are rapidly absorbed in the colon, where they act through the FFAR3 (G protein-coupled receptor (GPR)41) and FFAR2 (GPR43) receptors, which are closely associated with the development of sarcopenia [50,81,82].

As illustrated in Fig. 3B, Tang *et al.* [19] found that butyrate upregulates the PI3K/Akt/mTOR1 signaling pathway via the FFAR2 receptor, providing protection against muscle atrophy. The study established *FFAR2*-overexpressing C2C12 myoblasts and an *FFAR2* gene silencing group as a control. It was found that *FFAR2* over-expression significantly upregulated the expression of p-PI3K, p-Akt, and p-mTOR, whereas no such effects were observed in the *FFAR2* gene silencing group. Moreover, the researchers observed that butyrate alleviated atrophy in C2C12 myoblasts induced by high glucose and lipopolysaccharides (LPS), but no such protective effects were noted in the *FFAR2* gene silencing group [19].

Additionally, Luo *et al.* [83] discovered that pentanoate significantly upregulated the expression of *FFAR2*, myogenic differentiation 1 (*MyoD*) and *myogenin*. Pentanoate also promoted the transition of oxidative muscle fibers (Type I) to glycolytic muscle fibers (Type II) by activating the Akt/mTOR1 pathway, thereby benefiting sarcopenia [83]. Propionate has been linked to enhanced exercise performance. Scheiman *et al.* [84] observed that lactate produced during exercise enters the gut, where it is metabolized by *Veillonella* in the colon to propionate. Propionate then enters the bloodstream and serves as an energy source for other metabolic organs, improving exercise performance in mice [84].

In clinical study, SCFA intake has been negatively correlated with muscle strength loss over a 7.8-year follow-up period among 823 elderly individuals aged 60–87 [85]. Lv *et al.* [47] found that in healthy postmenopausal women, *F. prausnitzii* was positively correlated with butyrate synthesis and skeletal muscle mass index. Mendelian randomization analysis suggested a causal relationship between SCFAs and appendicular lean mass [47]. Moreover, supplementing sarcopenic mice with puerarin increased the abundance of SCFA-producing *Peptococcaceae* and *Clostridiales* in the gut, and a linear relationship was observed between total SCFAs and skeletal muscle strength [86].

4.3.1 Enhancing Energy Supply

As illustrated in Fig. 3B, study has shown that SCFAs improve glycogen storage capacity by increasing the expression of glucose transporter type 4 (GLUT4) in skeletal muscle, thereby enhancing glucose uptake and glycogen resynthesis. SCFAs also increase the capacity of skeletal muscle to obtain energy by promoting lipid uptake and oxidation, enhancing glucose uptake, and increasing glycogen synthesis rates [81].

4.3.2 Regulating Systemic Chronic Inflammation

SCFAs regulate systemic inflammation through the following pathways: (1) Activation of GPR43 and GPR109A receptors in intestinal epithelial cells enhances gut barrier function and prevents the translocation of LPS into the bloodstream (Fig. 3B). LPS in circulation can bind to Toll-like receptor 4 (TLR4) on immune cells, upregulating the NF-κB pathway and promoting inflammatory cytokine production. (2) As illustrated in Fig. 3B, inhibition of histone deacetylases, which promotes *Foxp3* expression and enhances Treg cell function, maintaining immune balance and suppressing excessive inflammation [87], Treg cells, characterized by the expression of the transcription factor Foxp3 [88], have their differentiation and function suppressed by histone deacetylase [89].

4.3.3 Increasing Insulin Sensitivity

SCFAs are closely linked to insulin sensitivity. A meta-analysis has shown that SCFA intervention groups had significantly lower fasting insulin levels compared to placebo groups. Moreover, fasting insulin and homeostasis model assessment of insulin resistance (HOMA-IR) values significantly improved from baseline in SCFA intervention groups [90]. Insulin regulates muscle function by modulating glucose metabolism. When insulin acts on muscle cells, it recruits GLUT4 transporters to the cell surface, facilitating glucose transport into the muscle. Phosphate, a key component of adenosine triphosphate (ATP), enters the cell via sodium-phosphate cotransporters and participates in ATP synthesis. Insulin plays a crucial role in phosphate transport [91]. Reduced insulin sensitivity in muscle fibers decreases intramuscular phosphate, activating adenosine monophosphate deaminase 1 (AMPD1) and accelerating phosphate depletion. This depletion further reduces AMPD1 inhibition, leading to adenosine monophosphate (AMP) conversion to inosine monophosphate (IMP), thus accelerating phosphate skeleton depletion and creating a vicious cycle [92]. SCFAs may help prevent sarcopenia by enhancing insulin sensitivity and promoting ATP synthesis in muscles.

4.4 Gut-Hydrogen Sulfide (H$_2$S)-AMPKα1-Autophagy Pathway

Human skeletal muscle expresses significant quantities of enzymes responsible for hydrogen sulfide (H$_2$S) production, including cystathionine γ-lyase (CSE), cystathionine β-synthase (CBS), and 3-mercaptopyruvate sulfurtransferase (3-MST). H$_2$S acts as a regulator of various physiological processes and plays a crucial role in skeletal muscle [93]. Study has demonstrated that the expression of CSE is significantly reduced in the skeletal muscle of ag-

ing mice, while supplementation with H_2S donors can induce the expression of myogenic genes and promote muscle repair [94]. As illustrated in Fig. 2B, Yang *et al*. [95] discovered that H_2S enhances the phosphorylation of adenosine monophosphate-activated protein kinase alpha 1 (AMPKα1), a key autophagy initiation protein, thereby promoting autophagy and alleviating skeletal muscle atrophy. Autophagy is essential for recycling cellular components, maintaining organelle homeostasis, and preventing the accumulation of dysfunctional proteins, mitochondria, and endoplasmic reticulum membranes. Maintaining stable autophagy is beneficial for preventing muscle atrophy [53].

The gut hosts a large population of sulfate-reducing bacteria (SRB), including *Bilophila*, *Desulfovibrio*, *Desulfomicrobium*, and *Fusobacteria*, which metabolize organic sulfur compounds from food (e.g., cysteine or taurine from red meat) to produce endogenous H_2S [96]. A study analyzing the metagenomes of 195 centenarians revealed that the gut microbiota of these long-lived individuals exhibited enhanced sulfide transformation capabilities, such as the conversion of methionine to homocysteine and the reduction of sulfate and taurine to sulfides [97]. This suggests that the gut microbiota may serve as a potential therapeutic target. However, H_2S in the gut can be a double-edged sword, carrying potential risks. Research has shown that at certain concentrations, H_2S can promote energy metabolism, proliferation, and migration of colorectal cancer cells [98]. The effects of H_2S are complex, and further studies are necessary to elucidate its mechanisms and provide more precise guidance for interventions targeting sarcopenia.

4.5 Gut-Lactate-Stomach-Unacylated Ghrelin-mTOR Pathway

Ghrelin is a peptide hormone primarily produced by enteroendocrine cells in the stomach [99]. It exists in two forms: acylated ghrelin (AG) and unacylated ghrelin (UnAG, also known as des-acyl ghrelin) [100]. AG binds to the GHSR1a receptor in the pituitary gland, stimulating growth hormone secretion, promoting appetite, and influencing metabolism, which is why it is commonly referred to as the "hunger hormone". In contrast, UnAG is the predominant form of ghrelin in circulation (90%–95%) [101]. While UnAG does not act on the pituitary gland as AG does, recent studies have highlighted its beneficial effects in combating sarcopenia. Kim *et al*. [101] divided four-month-old and eighteen-month-old mice into control and UnAG treatment groups, and after 10 months, analyzed their skeletal muscle strength, mass, mitochondrial respiration capacity, protein synthesis, and downstream pathways. The results confirmed that UnAG directly alleviated sarcopenia in mice, independent of food intake or body weight. Specifically, UnAG improves mitochondrial respiration and protects against NMJ disruption in aged mice, upregulating mTOR expression and downregulating MuRF-1 expression, thereby influencing protein synthesis and degradation

[101]. Other studies have also observed UnAG's beneficial effects on muscle, including the improvement of mitochondrial dysfunction, redox balance, and targeting mitochondrial apoptosis within neurons [102–104]. Ranjit *et al*. [105] found UnAG's downstream effects in skeletal muscle, discovering increased phosphorylation of FoxO3a at Ser253, which leads to downregulation of the FoxO3a-MuRF-1 pathway and inhibition of protein degradation. However, these findings do not fully explain UnAG's enhancement of muscle strength, and Ranjit *et al*. [105] speculated that calcium release and sensitivity might play a key role, as these are essential for excitation-contraction coupling in skeletal muscle.

Changes in the gut microbiota can influence the levels of ghrelin in the bloodstream [106]. Bo *et al*. [107] found a positive correlation between Ruminococcus and serum UnAG levels, suggesting that ghrelin may serve as a critical hormone transmitting essential signals along the gut-muscle axis. Martín-Núñez *et al*. [108] discovered that after Helicobacter pylori eradication therapy, circulating total ghrelin levels (including both AG and UnAG) were significantly reduced. They speculated that this reduction was due to the high expression of the lactate-specific receptor GPR81 on ghrelin-producing cells in the stomach. Lactate binds to this receptor and dose-dependently inhibits ghrelin secretion [109]. Long-term antibiotic treatment can disrupt the balance between lactate producers (e.g., *Blautia*) and consumers (e.g., *Megasphaera*, *Lachnospiraceae*, and *Prevotella*) in the gut, leading to changes in circulating ghrelin levels [108].

Clinical studies also support the influence of the gut microbiota on ghrelin. Sempach *et al*. [110] studied the effects of probiotics on circulating ghrelin levels in 43 patients with depression (19 received probiotics, and the rest were in the placebo group). After four weeks of intervention, blood tests showed a significant increase in ghrelin levels in the probiotic group compared to baseline [110]. Similarly, Wu *et al*. [111] found that supplementation with *Lacticaseibacillus paracasei* PS23 increased circulating ghrelin levels compared to the control group.

Therefore, as illustrated in Fig. 3C, gut microbiome metabolites may influence serum UnAG levels by binding to receptors on ghrelin-producing cells, thereby contributing to the prevention of sarcopenia through mechanisms such as upregulating mTOR expression and downregulating MuRF-1 expression. For instance, tryptophan can stimulate the secretion of ghrelin via the GPR142 receptor, while long-chain fatty acids can inhibit ghrelin secretion through the GPR120 receptor [109]. While these receptors show promise as therapeutic targets for sarcopenia in animal models, it is crucial to validate these findings through further clinical studies.

4.6 Amino Acids Derived from Gut Microbiota

Research has shown that the gut microbiota can synthesize amino acids *de novo*, including branched-chain amino acids (BCAAs) [112], tryptophan [113], and histidine [48]. These amino acids play a positive role in skeletal muscle health and contribute to the prevention of sarcopenia. Studies have identified *Prevotella copri* and *Bacteroides vulgatus* as strong producers of BCAAs [114]. Leucine, a key branched-chain amino acid, can relieve the inhibitory effect of Sestrin2 on Gap Activity Towards Rags 2 (GATOR2) by competitively binding to Sestrin2. GATOR2, a complex of unknown function, acts as a positive regulator of mTORC1 [115]. Consequently, leucine promotes protein synthesis through the mTORC1/4EBP/p70S6K signaling pathway. Furthermore, leucine activates the Akt pathway to phosphorylate FOXO1, preventing its translocation to the nucleus, which lowers nuclear FOXO1 levels, downregulates *MuRF-1* expression, and inhibits muscle atrophy [58], the mechanism of action of leucine can be referred to in Fig. 3D. Clinical study has demonstrated that increasing leucine intake can enhance myofibrillar protein synthesis in elderly women [116]. Additionally, supplementation with tryptophan has been shown to increase skeletal muscle mass in mice on a low-protein diet by raising IGF-1 levels in muscle tissue and upregulating the mTOR1/p70S6K pathway, thus promoting protein synthesis [117] (Fig. 3D). Therefore, amino acids derived from the gut microbiota can influence protein synthesis and degradation through the mTORC1 axis.

Histidine, an essential amino acid, has recently been shown to have a microbial origin [48]. It is a crucial component of the bioactive tripeptide Glycyl-L-Histidyl-L-Lysine (GHK), particularly in its copper-bound form, GHK-Cu. Studies have demonstrated that GHK-Cu can alleviate C2C12 myotube skeletal muscle dysfunction induced by cigarette smoke extract (CSE) and protect mice from CSE-induced muscle dysfunction. The underlying mechanisms include: (1) GHK-Cu activates SIRT1 deacetylase activity, which downregulates the FOXO3a/MuRF-1/Atrogin-1 pathway (Fig. 3D), thereby reducing protein degradation; (2) SIRT1 modulates Nrf2 through deacetylation, enhancing the production of Nrf2-mediated antioxidant enzymes to reduce ROS generation; (3) SIRT1 also increases the expression of PGC-1α, thereby improving mitochondrial function [47]. These findings suggest that amino acids derived from the gut microbiota play a significant role in muscle health by supporting protein synthesis, reducing protein degradation, and improving mitochondrial function, thus offering potential therapeutic targets for combating sarcopenia [51].

4.7 Gut-LPS-NF-κB/MAPKs-Atrogin-1/MuRF-1 Pathway

Research has indicated that alterations in gut barrier function may play a pivotal role in regulating both intestinal and extraintestinal inflammation [19,118,119]. When the gut barrier is compromised, harmful microbial metabolites such as lipopolysaccharides (LPS) can translocate into the bloodstream. As illustrated in Fig. 3E, these metabolites activate the NF-κB and MAPKs signaling pathways, leading to increased expression of *Atrogin-1* and *MuRF-1*, genes encoding E3 ubiquitin ligases involved in muscle degradation and inflammation. This process accelerates muscle atrophy and exacerbates the progression of sarcopenia [120]. Another study has also demonstrated that LPS can upregulate the expression of *Atrogin-1* and *MuRF-1* by enhancing NF-κB activity and its downstream inflammatory mediators, such as TNF-α, IL-1β, or NLRP3, ultimately leading to skeletal muscle atrophy [121]. Additionally, another study found that L-arginine can protect C2C12 myotube cells from LPS-induced toxicity by modulating the SIRT1-Akt-Nrf2 and SIRT1-FOXO3a-mitochondrial apoptosis pathways [122].

4.8 Other Gut Microbial Products and Their Effects on Sarcopenia

4.8.1 Lactate

Bifidobacterium and *Lactobacillus*, representative heterolactic bacteria, produce lactate through the fermentation of indigestible carbohydrates. Once produced in the gut, lactate can enter the systemic circulation and serve as an energy source for skeletal muscle. It can also be metabolized by bacteria such as *Anaerostipes caccae* and *Eubacterium hallii* to generate acetyl-CoA and butyrate. Butyrate provides energy to colonic cells and enhances gut barrier function [81]. The significant role of butyrate in preventing sarcopenia has been discussed earlier.

4.8.2 Indole-3-Propionic Acid (IPA)

Clostridium sporogenes, a beneficial gut bacterium, metabolizes tryptophan to produce the anti-inflammatory metabolite indole-3-propionic acid (IPA). IPA promotes the proliferation of C2C12 muscle cells through activation of the myogenic regulatory factor (MRF) signaling pathway and alleviates myotube inflammation via the IPA/miR-26a-2-3p/IL-1β pathway. These actions contribute to muscle development and increase skeletal muscle mass in mice [52].

4.8.3 Trimethylamine N-oxide (TMAO)

Recent research has linked trimethylamine N-oxide (TMAO) to increased intestinal permeability, systemic inflammation, and mitochondrial dysfunction, all of which are associated with the progression of sarcopenia [48,123, 124]. TMAO intervention studies indicated that TMAO promotes the development of HFD-induced SO via the ROS-Akt/mTOR pathway [39].

4.8.4 Streptococcal Quorum Sensing Peptide CSP-7

Recent research has demonstrated that CSP-7 selectively stimulates the production of IL-6 in muscle cells, has

the capability to enter the human systemic circulation, and induces a muscle-wasting phenotype in a preclinical mouse model [125]. Sundin *et al*. [126] identified substantial numbers of *Streptococcus mitis* on the jejunal mucosa. The effects of CSP-7 quorum sensing peptide, produced by streptococci strains, on skeletal muscle creates new diagnostic and therapeutic opportunities.

5. Gut Microbiota and Sarcopenic Obesity

Different from simple obesity, sarcopenic obesity refers to a pathological condition characterized by decreased skeletal muscle mass and function accompanied by excessive fat accumulation [127]. A meta-analysis of 50 studies showed a prevalence of sarcopenic obesity of 11% among individuals aged ≥60 globally [128]. Another study involving 4197 elderly Japanese individuals (mean age 74.6 years, 54.2% female) categorized patients based on AWGS 2019 sarcopenia criteria and Japanese obesity standards and followed them up for 5 years. It was found that compared to the non-sarcopenic/non-obese group, the risk of disability (defined by Japan's long-term care insurance system as the inability to independently perform seven daily life domains such as eating, dressing, and bathing) increased by 2.48 times in the sarcopenic obesity group, and by 2.09 times in the sarcopenia-only group [129].

Both muscle and adipose tissue have endocrine functions and maintain the homeostasis of muscle and adipose tissue by secreting myokines and adipokines. Excessive free fatty acids can stimulate adipose tissue or infiltrate macrophages within it to produce pro-inflammatory cytokines such as IL-6 and TNF-α, further leading to systemic inflammation [130]. Therefore, dysregulation of obesity-induced myokines and adipokines is considered one of the main causes of sarcopenic obesity, characterized by increased myostatin, resistin, leptin, and IL-6, and decreased IGF-1, FGF-21, adiponectin, and IL-15 [129]. With aging and reduced physical activity, excessive energy intake can lead to hyperlipidemia. Excess lipids in circulation redistribute to other tissues, leading to intramuscular and intermuscular fat deposition, inducing mitochondrial dysfunction, enhancing ROS production, leading to lipotoxicity, insulin resistance (IR), and inflammation, and further inhibiting protein synthesis. On the other hand, local intramuscular lipid deposition and muscle IR can lead to reduced local lipid uptake and increased local free fatty acid concentration, thus forming a vicious cycle that promotes the occurrence and development of sarcopenic obesity [131,132].

In 2022, a study explored the potential of propolis to improve sarcopenic obesity by altering gut microbiota. Using db/db mice to simulate sarcopenic obesity and db/m mice as controls, the study fed them a normal diet or propolis at different concentrations for 8 weeks and collected blood, feces, epididymal fat, and muscle tissue for analysis. The researchers observed significant improvements in muscle weight, grip strength, and epididymal fat weight

in the db/db + 2% propolis group compared to the db/db group. *Ruminococcaceae* and *Acetivibrio* significantly increased in the db/m group and db/db + 2% propolis group. This study affirmed the positive impact of altered gut microbiota on sarcopenic obesity [133]. Another study found that transplantation of fecal matter from the Milk group can improve sarcopenia obesity in db/db mice [46]. Moreover. *Lactobacillus paragasseri* SBT2055 (LG2055) treatment has also been reported to reduce free fatty acids (FFA) in mice models of sarcopenia [43]

6. Practical Strategies Based on Microbial Therapies

6.1 Probiotic Formulations

Several preclinical studies have reported positive effects of probiotic formulations in models of sarcopenia: *Bifidobacterium bifidum* and *Lactobacillus paracasei* can alleviate aging-dependent sarcopenia and cognitive impairment by regulating gut microbiota-mediated Akt, NF-κB, and/or FOXO3a signaling pathways [134]. *Lactobacillus rhamnosus* JY02 supplementation promoted the production of muscle-enhancement markers (myosin heavy chain (MHC) Iβ, MHC IIα, and MyoD) and reduced both the production of muscle degradation markers and the symptoms of muscle atrophy (loss of lean mass and muscle strength) [135]. As previously described, both *Lacticaseibacillus rhamnosus* IDCC3201 and Postbiotic Formulation of *Lactiplantibacillus plantarum* KM2 showed positive effects of the sarcopenia model [44,45]. In clinical study: Reports indicate that consecutive supplementation of *Lactobacillus plantarum* TWK10 for more than six weeks could effectively improve the muscle strength and endurance of the elderly, reducing sarcopenia and physical fragility [136].

6.2 Dietary Interventions

Several studies have reported the potential role of dietary fiber in preventing sarcopenia. The study by Montiel-Rojas *et al*. [137] showed a beneficial impact of dietary fiber intake on skeletal muscle mass in older adults. Fielding and Lustgarten [138] investigated the impact of a high-soluble-fiber diet (HSFD) on the gut-muscle axis. The results show that female (but not male) HSFD-fed mice had significant increases in SCFAs, the quadriceps/body weight (BW) ratio, and treadmill work performance (distance run × BW), which suggests that an HSFD can positively impact the gut–muscle axis. The HSFD significantly altered gut bacterial community structure (β-diversity), and more specifically, within- and between-group differences for phyla and genus abundance were identified [138]. One study showed that in six patients after 12 weeks of 1-kestose administration, the skeletal muscle mass index was greater, and the body fat percentage was lower [139]. A randomized controlled trial evaluated the effectiveness of a dietary supplement (DS) (Hydroxy-Methyl-Butyrate, Carnosine, Magnesium, Butyrate, and Lactoferrin) on muscle mass, muscle

function and walking speed, inflammation, and visceral adipose tissue (VAT) and gut axis. The results showed that supplementation of DS (Hydroxy-Methyl-Butyrate, Carnosine, Magnesium, Butyrate, and Lactoferrin) improved muscle mass and function, and a significant reduction in VAT was observed in the intervention group. The gut-muscle axis has emerged as a new intervention target for sarcopenia [35].

6.3 Fecal Microbiota Transplantation (FMT)

Studies have found that germ-free mice exhibit reduced skeletal muscle mass, while fecal transplantation (using feces from wild-type mice) can increase the muscle mass of germ-free mice [140]. In contrast, another study conducted fecal microbiota transplantation (FMT) from human donors into antibiotic-treated recipient mice to investigate the causal relationship between sarcopenia and the gut microbiome. The results revealed that mice receiving microbiota from sarcopenic individuals exhibited lower muscle mass and strength compared to those receiving microbiota from non-sarcopenic donors [123].

6.4 Physical Activity

Yerrakalva *et al*. [141] found that individuals with higher baseline physical activity (light physical activity (LPA) and moderate-to-vigorous activity (MVPA)) and lower sedentary time levels (total time and prolonged sedentary bout time) had higher subsequent muscle mass indices (relative appendicular lean muscle mass (ALM) and BMI-scaled ALM, but not height-scaled ALM) an average of 5.5 years later. Baldanzi *et al*. [142] investigated the associations of accelerometer-based sedentary (SED), moderate-intensity (MPA), and vigorous-intensity (VPA) physical activity with the gut microbiota. The results show that MPA and VPA were associated with a higher abundance of the butyrate-producers *Faecalibacterium prausnitzii* and *Roseburia* spp. [142]. Moreover, MPA was associated with a higher capacity for acetate synthesis, and SED with lower carbohydrate degradation capacity [142]. The positive effects of short-chain fatty acids on sarcopenia have been described previously. Therefore, physical activity can prevent sarcopenia by influencing the composition of the intestinal flora, which in turn affects the metabolic functions of the body.

6.5 Multimodal Approach

The combined multimodal approach of dietary intervention and physical activity also shows significant therapeutic potential. Alway *et al*. [143] investigated whether the combination of resveratrol and exercise is more effective in reducing or reversing sarcopenia in humans compared to exercise alone. The study collected muscle samples from the participants to precisely assess muscle changes. The results showed that resveratrol treatment combined with exercise significantly enhances hypertrophy of type I and IIA fiber sizes compared to exercise alone, and

leads to an increase in total muscle nuclei (satellite cells and myonuclei) [143]. Wang *et al*. [144] demonstrate that resveratrol supplementation alleviates high-fat diet (HFD)-induced gut microbiota dysbiosis, enhancing the abundance of anti-obesity bacterial strains such as *Akkermansia*, *Bacteroides*, and *Blautia*. Liao *et al*. [145] investigated the effectiveness of oligopeptide nutritional supplementation combined with exercise intervention in older individuals with sarcopenia in the community. The study enrolled 219 sarcopenic patients aged 65 and above, who were randomly assigned to four groups: a control group, a nutrition group, an exercise group, and a combined group. After 16 weeks of intervention, it was found that the weight and grip strength of the older people receiving exercise intervention increased, while the weight, grip strength, and gait speed of the subjects receiving nutritional intervention increased. However, neither exercise nor nutrition intervention alone could maintain the fat-free mass of older people. Only the subjects in the combined group maintained the muscle mass and fat-free mass of each segment after the intervention [145]. A systematic review found that combined exercise and nutrition intervention significantly enhanced lower extremity muscle strength in older adults with sarcopenia in Asia, compared to exercise alone [146]. Nutritional supplementation, including polyunsaturated fatty acids (PUFA), vitamin D, and protein, provided additional benefits to physical exercise in increasing appendicular skeletal mass and lower limb muscle mass over 12 weeks [147]. Multimodal interventions seem to be the best strategy for preventing primary sarcopenia.

7. Conclusions

While lifestyle factors, disease status, and nutritional conditions significantly influence muscle mass, the distinct gut microbiome profiles observed in patients with primary sarcopenia suggest a compelling possibility: the gut microbiota may serve as a potential target for improving primary sarcopenia. For example, *Prevotella copri* has been observed to decrease in sarcopenic populations across multiple studies [24,31,148], suggesting that supplementation with *Prevotella copri* could be a promising therapeutic approach for sarcopenia. Additionally, the gut microbiota possesses several "processing" capabilities that the host organism lacks. For instance, *Escherichia coli* expressing the nicotinamidase enzyme PncA can help maintain NAD+ homeostasis, which is crucial for supporting mitochondrial function [71]. Similarly, *Lactobacillus* and *Bifidobacterium*, which express bile salt hydrolase (BSH) enzymes, can alter the intestinal bile acid environment, influencing circulating FGF15/19 and subsequently affecting protein synthesis [76]. The gut microbiota's ability to express specific enzymes warrants further investigation as a potential avenue for therapeutic intervention. Furthermore, recent studies have highlighted the beneficial effects of hydrogen sulfide (H_2S) and unacylated ghrelin on skeletal

muscle [53,101]. The gut harbors sulfate-reducing bacteria that produce endogenous H_2S, as well as ligands for receptors on ghrelin-producing cells. These findings suggest that these microbial products could also serve as therapeutic targets for sarcopenia. And the CSP-7 quorum-sensing peptide may become a biomarker for the early diagnosis of sarcopenia [125]. However, we must acknowledge the limitations of such preclinical studies, as their applicability to human populations remains uncertain and requires further validation through clinical research. Together, we provide novel perspectives on the gut-muscle axis for the prevention of sarcopenia.

Author Contributions

LC, XX, JC, WC, and HT contributed to the conception and design of the work, including the development of literature search strategies, criteria, and the analytical framework for evidence synthesis. YC, LC, and LY devised the overall structure of the review. LC drafted the initial manuscript and designed comparative tables to integrate findings from selected studies. XX and JC performed systematic data extraction from included literature, validated the consistency of tabulated results, and resolved discrepancies through consensus discussions. WC and HT revised the manuscript for intellectual coherence, enhanced the analytical rigor of tables, and ensured alignment with the predefined research objectives. All authors contributed to editorial changes in the manuscript. All authors have given approval to the final version of the manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

We would like to express our gratitude to all those who helped us during the writing of this manuscript.

Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/FBL36204.

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