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Therapeutic strategies to modulate gut microbial health: Approaches for sarcopenia management

Shreya Das[1], B Preethi[1], Sapana Kushwaha[2] and Richa Shrivastava[1]

[1]Department of Pharmacy, Birla Institute of Technology and Science (BITS), Pilani Campus, Pilani, Rajasthan and [2]Department of Pharmacology and Toxicology, National Institute of Pharmaceutical Education and Research, Raebareli, Lucknow, India

Summary. Sarcopenia is a progressive and generalized loss of skeletal muscle and functions associated with ageing with currently no definitive treatment. Alterations in gut microbial composition have emerged as a significant contributor to the pathophysiology of multiple diseases. Recently, its association with muscle health has pointed to its potential role in mediating sarcopenia. The current review focuses on the association of gut microbiota and mediators of muscle health, connecting the dots between the influence of gut microbiota and their metabolites on biomarkers of sarcopenia. It further delineates the mechanism by which the gut microbiota affects muscle health with progressing age, aiding the formulation of a multi-modal treatment plan involving nutritional supplements and pharmacological interventions along with lifestyle changes compiled in the review. Nutritional supplements containing proteins, vitamin D, omega-3 fatty acids, creatine, curcumin, kefir, and ursolic acid positively impact the gut microbiome. Dietary fibres foster a conducive environment for the growth of beneficial microbes such as *Bifidobacterium*, *Faecalibacterium, Ruminococcus*, and *Lactobacillus*. Probiotics and prebiotics act by protecting against reactive oxygen species (ROS) and inflammatory cytokines. They also increase the production of gut microbiota metabolites like short-chain fatty acids (SCFAs), which aid in improving muscle health. Foods rich in polyphenols are anti-inflammatory and have an antioxidant effect, contributing to a healthier gut. Pharmacological interventions like faecal microbiota transplantation (FMT), non-steroidal anti-inflammatory drugs (NSAIDs), ghrelin mimetics, angiotensin-converting

Corresponding Author: Dr. Richa Shrivastava, Department of Pharmacy, Birla Institute of Technology and Science (BITS), Pilani campus, Pilani, Rajasthan, 333031, India. e-mail: richa.shrivastava@pilani.bits-pilani.ac.in and Dr. Sapana Kushwaha, Department of Pharmacology and Toxicology, National Institute of Pharmaceutical Education and Research, Raebareli, Lucknow (UP) 226002, India. e-mail: sapana.k@niperraebareli.edu.in

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Abbreviations. ICD, International Classification of Diseases; EWGSOP, European Working Group on Sarcopenia in Older People; SCFAs, short-chain fatty acids; TMA, trimethylamine; GABA, γ-aminobutyric acid; CNS, central nervous system; FFAR, free fatty acid receptor; GLP-1, glucagon-like peptide-1; PYY, peptide YY; GPR, G-protein coupled receptors; GPBAR, G-protein-coupled bile acid receptor; DIO2, iodothyronine deiodinase 2; GLUT4, Glucose transporter type 4; PI3K, phosphoinositide 3-kinase; TMAO, trimethylamine N-oxide; DMD, Duchenne Muscular Dystrophy; BCAAs, branched-chain amino acids; mTOR, mammalian target of rapamycin; TNFα, tumour necrosis factor α; IL, interleukin; MuRF1, muscle ring finger protein 1; ATP, Adenosine triphosphate; TGF-β, Transforming growth factor β; LPS, lipopolysaccharide; DAMPs, damage-associated molecular patterns; IGF-1, Insulin-like growth factor 1; ROS, reactive oxygen species; ER, endoplasmic reticulum; ActRIIB, activin type II B receptor; MAFbx, muscle atrophy F-box protein; UPS, Ubiquitin-proteasome system; FOXO1, Forkhead Box protein O 1; MAPK, Mitogen-activated protein kinase; TAK-1, Transforming growth factor-β-activated kinase 1; FNDC5, fibronectin type III domain-containing protein 5; PGC1α, Peroxisome proliferator-activated receptor (PPAR)-γ coactivator-1α; ERK, extracellular signal-regulated kinase; BDNF, Brain-derived neurotrophic factor; FOS, fructooligosaccharides; GOS galactooligosaccharides; TrkBR, tropomyosin-related kinase-B receptor; p75NTR, p75 neurotrophin receptor; FST, Follistatin; BMP, bone morphogenetic protein; GDF-15, Growth/Differentiation Factor-15; MIC-1, macrophage inhibitory cytokine 1; AMPK, AMP-activated protein kinase; ACVR1B/ALK4, activin A receptor type 1B; FGF21, fibroblast growth factor 21; FMT, faecal microbiota transplantation; SIRT1, Sirtuin 1; Metrnl, meteorin-like protein; JAK, Janus kinase; STAT, signal transducer and activator of transcription; FAPs, fibro-adipogenic progenitors; EAAs, essential amino acids; HMB, β-hydroxy β-methyl butyrate; IFN-γ, Interferon gamma; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; ALA, α-linoleic acid; PUFA, polyunsaturated fatty acid; NF-κB, nuclear factor kappa B; CLAs, conjugated linoleic acids; ISSN, International Society of Sports Nutrition; MRF, myogenic regulatory transcription factor; NSAIDS, Non-steroidal anti-inflammatory drugs; GH, growth hormone; ACE, Angiotensin-converting enzyme; MABs, Monoclonal antibodies; SPRINTT, Sarcopenia and Physical fRailty IN older people: multi-componenT Treatment; COPD, chronic obstructive pulmonary disease; CytOx; cytochrome oxidase; APH, animal protein hydrolysate, APH; AB-PAS, Alcian Blue-Periodic acid; H&E, hematoxylin and eosin.

enzyme inhibitors (ACEIs), and butyrate precursors lead to the production of anti-inflammatory fatty acids and regulate appetite, gut motility, and microbial impact on gut health. Further research is warranted to deepen our understanding of the interaction between gut microbiota and muscle health for developing therapeutic strategies for ameliorating sarcopenic muscle loss.

Key words: Gut microbiota, Sarcopenia, Gut-muscle axis, Biomarkers, Dietary interventions

Introduction

Ageing exposes people to various chronic diseases and disorders, the most common of which are cardiovascular diseases, cancer, neurological disorders, and diabetes mellitus. In addition to contributing to early mortality, they also decrease the patient's quality of life by generating numerous adverse complications associated with the disease (Cesari et al., 2016). A significant health concern in the older population is the gradual loss of skeletal muscle mass and the associated decline in its strength and function, called sarcopenia, which contributes to higher morbidity, disability, and mortality (Landi et al., 2018). This disease was given an "International Classification of Diseases (ICD)-10 code M62.84" in 2016 (Anker et al., 2016). According to the European Working Group on Sarcopenia in Older People (EWGSOP), 2018 the updated definition of sarcopenia is "Sarcopenia is a progressive and generalised skeletal muscle disorder that is associated with increased likelihood of adverse outcomes including falls, fractures, physical disability, and mortality". The modification emphasised that deterioration in muscle strength is a major determining factor of sarcopenia (Swan et al., 2021). Sarcopenia affects 9.9 to 40.4% of community-dwelling older persons, 2 to 34% of geriatric outpatients, and up to 56% of hospitalised older patients (Xu et al., 2022). Due to the rapidly growing prevalence of sarcopenia in the older population, new insights into the mechanisms driving muscle loss are constantly being investigated.

The human gut microbiota constitutes 10-100 trillion microorganisms that populate the mammalian gastrointestinal tract (Picca et al., 2018; Liu et al., 2021). This diverse microbiota produces various nutrients and metabolites that directly impact skeletal muscle physiology (Qi et al., 2021). The microbiome influences muscle mass and function by regulating systemic inflammation and immunity, hormonal and insulin sensitivity, and metabolism, thus directing towards a "gut-muscle axis" and its possible connection with sarcopenia (Zhao et al., 2021). Recent investigations have shown that modulating muscle physiology via the gut-microbiota axis can ameliorate the progression of sarcopenia (Picca et al., 2018). Muscle mass and strength were significantly enhanced, along with a decrease in oxidative stress in aged mice treated with *Lactobacillus* and *Bifidobacterium* supplements (Ni et al., 2019b). In addition, some clinical evidence suggests that therapies involving the gut microbiota-muscle axis can help older people by decreasing sarcopenia-related morbidity and mortality (Buigues et al., 2016). Therefore, understanding the underlying mechanisms that link the gut microbial population to muscle wasting and dysfunction can help to identify novel targets as treatment strategies to prevent or delay age-related sarcopenia.

Gut-Muscle Axis: Interplay between gut microbiota and muscles

The human gut is host to a complex ecology of microorganisms, a dynamic collection of bacteria, archaea, eukaryotes, fungi, and viruses, referred to as the gut microbiota (Thursby and Juge, 2017; Mangiola et al., 2018). The four major bacterial phyla, "*Firmicutes*, *Bacteroidetes*, *Proteobacteria*, and *Actinobacteria*", represent 98% of this diverse microbial population involved in a mutually beneficial relationship (symbiosis) with the host (Ragonnaud and Biragyn, 2021). Their functions include facilitating digestion and absorption of food, strengthening gut integrity via building an intestinal barrier by metabolising dietary fibres into bioactive short-chain fatty acids (SCFAs) (Jones, 2016), providing essential nourishment by generating vitamins and nutrients, and modulation of the host's local (intestinal) and systemic immunity (Mangiola et al., 2018; Ragonnaud and Biragyn, 2021). The gut microbiota, however, changes with the normal ageing process, and the resulting alteration significantly influences human health and disease (Zhao et al., 2021). A significant implication of this imbalance is the impact on muscle mass and muscle function, leading to sarcopenia in older adults (Zhang et al., 2022). Several *in vitro* and preclinical experiments have been conducted to prove the association between gut microbiota and muscle (Liao et al., 2020), thus establishing this axis as an interventional target to eliminate or manage age-related sarcopenia.

Bacteroidetes and *Firmicutes* comprise the microbiota of the large intestine and are essential for maintaining normal intestinal homeostasis. *Lactobacilli*, *Diptheriods*, and *Candida* are the most common microbes in the small intestine. A healthy individual's primary composition of microorganisms is covered by a relatively low number of species, *i.e.*, *Bacteroides*, *Prevotella*, *Eubacterium*, and *Alistipes*. Many species cover the rest with low relative abundance (including *Clostridium*, *Anaerotruncus*, *Butyrivibrio*, *Faecalibacterium*, and *Akkermansia*), having significant metabolic activity (Huttenhower et al., 2012). This microbiota aids in essential functions for the host, the most prominent among these being amino acid synthesis and nutrient absorption (Portune et al., 2016; Gizard et al., 2020).

The gut microbiota metabolises organic substrates

obtained either from food or those that remain undigested, like complex carbohydrates from dietary fibres, branched-chain amino acids (BCAAs), dietary phenolics, polyunsaturated essential fatty acids (PUFAs), etc., to various metabolites, like SCFAs (acetate, propionate, butyrate), and trimethylamine (TMA) (Gizard et al., 2020; Tomášová et al., 2021). Gut microbiota also synthesises neurotransmitters (like histamine, γ-aminobutyric acid (GABA), serotonin, and catecholamines) and gases (like hydrogen sulphide and nitrogen oxide) as well as regulates their synthesis (Strandwitz, 2018). These neurotransmitters and other by-products enhance glucose homeostasis, energy consumption, and protein synthesis in skeletal muscle, thereby improving physical performance by controlling intestinal permeability, inter-organ (endocrine, enteric, and central nervous system (CNS)) cross-talks, and direct targeting of skeletal muscle (Chen et al., 2021; Li et al., 2022). The microbiota's synthesis of these compounds impacts bacterial interactions and host intestinal immunity. Different signalling mechanisms could be implicated, such as neuroendocrine circuits involving gastrointestinal neurons and vagus nerves and modification of systemic metabolites and inflammatory hallmarks (Wang et al., 2020). SCFAs, the prominent regulators of the crosstalk between the gut microbiota and skeletal muscle, are derived from the metabolism of nutrients by bacteria and enhance mitochondrial biogenesis in skeletal muscle (Ticinesi et al., 2017). The primary SCFA metabolites of gut microbiota include butyrate, acetate, and propionate. They regulate blood glucose and insulin levels with a positive impact on skeletal muscle functioning (He et al., 2020). A study showed that feeding a combination of SCFAs to germ-free mice partially rescued skeletal muscle function, which was impaired by gut microbiota deficiency. There was a remarkable improvement in muscle strength as measured by increased skeletal muscle mass, reduced expression of muscle atrophy markers, increased expression of neuromuscular assembly genes, and an improved oxidative metabolic capacity of muscles (Lahiri et al., 2019). In another study, continuous subcutaneous infusion of acetate in antibiotic-treated mice restored their exercise capacity, stressing the importance of SCFAs produced by the intestinal microbiome (Okamoto et al., 2019). Therefore, skeletal muscle, intestine, and adipose tissues are essential targets that influence muscle metabolism (Canfora et al., 2015). These SCFAs modulate the release of gut hormones, influencing insulin production and appetite (Tolhurst et al., 2012). In enteroendocrine L-cells (located in the ileum and colon), SCFAs bind to Free Fatty Acid Receptor (FFAR)1 and FFAR3, which are G-protein coupled receptors (GPRs) responsible for enhancing the release of glucagon-like peptide-1 (GLP-1) and anorexigenic peptide YY (PYY). GLP-1 is an anti-diabetic hormone that has an incretin action and acts as an insulin sensitiser, *i.e.*, it enhances after-meal insulin production (Heppner and Perez-Tilve, 2015). This ability to enhance GLP-1 release is also shared by tryptophan, indole derivatives, secondary bile acids, deoxycholic acid, and lithocholic acid (Gérard and Vidal, 2019; Rastelli et al., 2019). Butyrate, propionate, and its precursor, succinate, are also known to activate gluconeogenesis in intestinal lining cells via complementary mechanisms that improve insulin sensitivity and metabolism through activation of gastrointestinal nerves (De Vadder et al., 2014, 2016). Gut bacteria *Faecalibacterium*, *Butyricimonas*, and *Succinivibrio* produce SCFAs, which enter the bloodstream and are taken up by the myocytes (Fig. 1). There they serve as ligands binding to FFAR2 and FFAR3, regulating glucose uptake and its metabolism (Ticinesi et al., 2017).

Butyrate has proven to be the most crucial mediator among SCFAs from the perspective of skeletal muscle (Yan and Ajuwon, 2017; van der Hee and Wells, 2021; Han et al., 2022; Tang et al., 2022; Guan et al., 2023). Its anti-inflammatory functions have already been elaborated in inflammatory bowel diseases (Chen and Vitetta, 2020). Butyrate improves gut barrier function as it is taken up by colonial epithelial cells to be used as an energy source (Yan and Ajuwon, 2017). It also decreases intestinal permeability by enhancing the synthesis of tight junction proteins viz. claudins, occludin and zona occludens, and mucins, which prevents endotoxemia (Canfora et al., 2015). SCFAs, propionate, and butyrate in small quantities and acetate in higher amounts enter the circulation and directly impact the function of peripheral cells and tissues (van der Hee and Wells, 2021). Butyrate has also been reported to prevent low-grade inflammation generated by the interaction between adipocytes and macrophages, reduce lipid breakdown, and inhibit inflammatory signalling (Ohira et al., 2013). It impacts skeletal muscle by increasing the count of anti-inflammatory regulatory T cells and decreasing proinflammatory cytokine and chemokine levels (Yoo et al., 2020). In addition, SCFAs mediate the relationship between gut microbiota and skeletal muscle by potentiating fatty acid oxidation via its receptors on skeletal muscle tissue, GPR41 (FFAR3) and GPR43 (FFAR2), proving their worth as potential regulators of skeletal muscle metabolism and function (Frampton et al., 2020).

In addition to the role of secondary bile acids, tertiary bile acids (*e.g.*, ursodeoxycholic acid) increase energy expenditure by activating G-protein-coupled bile acid receptor (GPBAR)-1 (TGR5), which is expressed in skeletal muscle, thus, inducing the thyroid hormone deiodinase 2 (DIO2). DIO2 activates thyroxine (T4) by converting it to the Triiodothyronine (T3) thyroid hormone, which plays a significant role in metabolism, energy homeostasis, myogenesis, and regeneration of skeletal muscle (Di Ciaula et al., 2017; Bloise et al., 2018). Phenolic metabolites of the microbiome, such as isovanillic acid 3-o-sulphate, have also exhibited a dose-dependent boosting effect on glucose uptake in muscles *via* glucose transporter type 4 (GLUT4) and phospho-

inositide 3-kinase (PI3K)-dependent processes, demonstrating their role in muscle cell glucose uptake and metabolism (Houghton et al., 2019). Conjugated linoleic acid (CLA) is another metabolite produced from the conversion of linoleic acid to stearic acid by rumen bacteria. They can also be obtained in minimal amounts from meat and milk products from ruminants. Their potentiating effects on lean body mass have been attributed to physiological changes in the skeletal muscle, like muscle fibre type transformation and

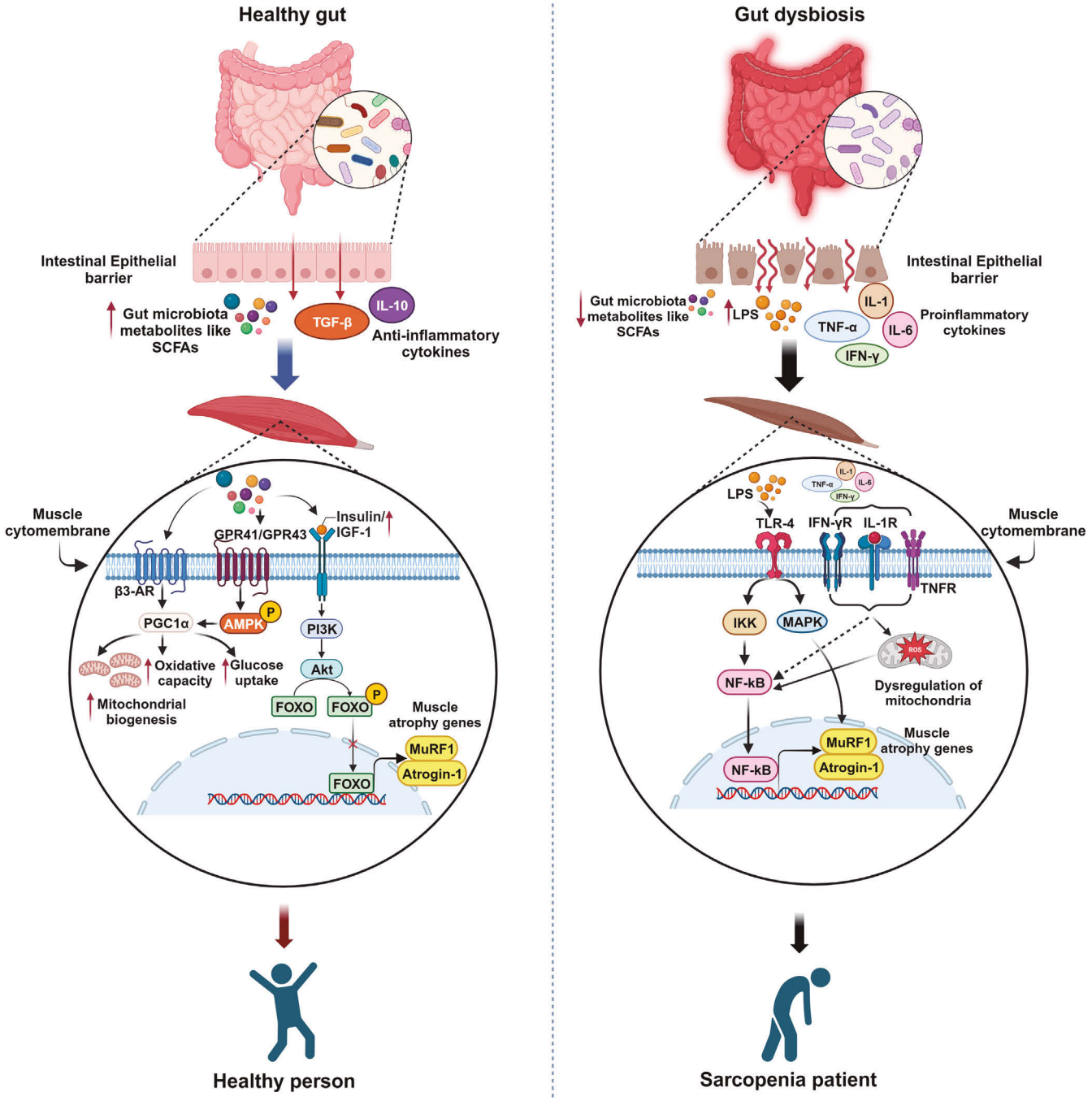

Fig. 1. Correlation between gut dysbiosis and muscle health. Gut microbiota metabolites like SCFAs contribute to increased mitochondrial biogenesis, oxidative capacity, and glucose uptake in muscle cells, which boosts muscle health in a healthy person. Intestinal epithelial barrier integrity is compromised in a dysbiotic gut, which facilitates the leakage of LPS and pro-inflammatory cytokines into the bloodstream. This results in the increased expression of muscle atrophy genes leading to sarcopenia. Created in BioRender.com.

modulation of intracellular signalling pathways linked to muscle metabolism (Kim et al., 2016).

Gut microbiota metabolises choline, a trimethylamine-containing compound, which produces TMA (Romano et al., 2015). Apart from choline, its other precursors are L-carnitine, γ-butyrobetaine, betaine, and choline-containing compounds from the diet (Zeisel and Warrier, 2017). The concentration of TMA was found to be lower in patients suffering from Duchenne Muscular Dystrophy (DMD), emphasising its importance to muscle function (Hsieh et al., 2009). BCAAs are among the other gut microbiota-derived compounds that have the potential to impact on host metabolism. Previously, increased circulating levels of BCAAs have been associated with insulin resistance and diabetes. Persistent high levels of BCAAs were responsible for the induction of mTOR signalling in skeletal muscle, which led to reduced uptake of glucose and insulin resistance (Lynch and Adams, 2014; Yin et al., 2020). However, BCAAs have also been shown to activate insulin synthesis via mTOR (Wang et al., 2018) and stimulate incretin secretion (Gojda et al., 2017), suggesting its insulinotropic effects. They also have been shown to prevent skeletal muscle proteolysis and enhance muscle protein synthesis and myogenesis. Studies have shown that nutraceuticals containing leucine and its derivatives can revert sarcopenia in patients with chronic liver disease and Type 2 diabetes mellitus (Gojda and Cahova, 2021; Hey et al., 2021). Gut microbiota utilises histidine to produce another metabolite imidazole propionate, which has been associated with insulin resistance. It affects the insulin signalling pathway via mTORC1 (Koh et al., 2018), and its levels were found to be enhanced in type 2 diabetes mellitus. Some correlation between its levels and markers of low-grade inflammation also suggested its impact on host inflammation (Agus et al., 2021). All this evidence is directed toward a gut-muscle axis that regulates normal muscle physiology and warrants deeper molecular investigations into the impact of each of these metabolites at the individual level.

Mechanisms of dysbiotic gut and sarcopenia in old age

Dysbiosis, which exhibits lesser variability in microbial populations, compromises the intactness of the gut barrier, allowing the entry of toxic microbial products into circulation (Fig. 1) (Gizard et al., 2020). Once in circulation, these products can induce low-grade systemic inflammation by triggering innate immunity and result in metabolic alterations leading to muscle disorders. Gut dysbiosis plays a key role in various metabolic disorders affecting skeletal muscle degradation, like type II diabetes mellitus and obesity (Bleau et al., 2015), cancer (Panebianco et al., 2023), cardiovascular (Zhou et al., 2020), liver (Ponziani et al., 2021), and kidney (Margiotta et al., 2021) disorders. Sarcopenia is a geriatric disorder that exhibits an altered gut microbial population (Marzetti et al., 2017). It has been reviewed that microbial products like indoxyl sulphate and endotoxins like lipopolysaccharide promote inflammatory signalling by stimulating the expression of tumour necrosis factor α (TNFα) and interleukin 6 (IL-6) in immune tissues and skeletal muscle cells (Grosicki et al., 2018). An increase in *Lactobacillus* species and a lower abundance of *Fusicantenibacter*, *Lachnoclostridium*, *Eubacterium*, *Roseburia*, and *Lachnospira* genera was observed in patients with sarcopenia as compared with healthy subjects (Kang et al., 2021). A similar trend was observed when a reduced abundance of *Faecalibacterium prausnitzii*, *Alistipes shahii*, and *Roseburia inulinivorans* species was found in sarcopenic patients, suggesting the association of altered microbial diversity with sarcopenia (Ticinesi et al., 2019b). Past preclinical evaluations concluded an association between muscle degradation and altered microbial diversity in the intestine (Picca et al., 2018). Oral administration of *Lactobacillus* species in acute leukaemia mouse model ameliorated skeletal muscle loss by reducing inflammation (Bindels et al., 2012). *Lactobacillus* species were shown to have an inverse association with markers of muscle atrophy like MuRF1 and Atrogin1 as well as inflammatory cytokines (Picca et al., 2018). The mechanisms involved in the crosstalk leading to muscle wasting are hereby discussed in detail.

Alteration in muscle protein synthesis

Gut dysbiosis or alteration in microbiota composition increases the demand for proteins required for muscle synthesis. This phenomenon is an anabolic resistance characteristic of aged muscle cells (Vaiserman et al., 2017). The consequences are a reduction in muscle protein synthesis leading to subsequent degradation of muscle, marking the initiation of sarcopenia (Mitchell et al., 2017; Picca et al., 2018). There is a marked decrease in gene expression of proteins involved in myogenesis, decreased absorption and digestion of proteins, altered flow of nutrition to skeletal muscle cells, enhanced protein catabolism in myocytes, and accelerated loss of skeletal muscle stem cells (Casati et al., 2019). Gut dysbiosis-induced reduction in the production of SCFAs also impacts the modulation of systemic anabolic or catabolic balance via altered ATP production and glucose uptake in skeletal muscle cells (Casati et al., 2019; Ticinesi et al., 2019a). This further hinders the process of muscle protein anabolism and marks the onset of muscle wasting and, ultimately, sarcopenia. The pro-anabolic effects of vitamins like folate, vitamin B12, and riboflavin are also reduced with a decrease in the microbial population involved in synthesising these vitamins (LeBlanc et al., 2013).

Protein metabolism

Skeletal muscle mass is mainly regulated by protein metabolism in muscles, which is maintained by a dynamic balance of protein synthesis mediated by

anabolic stimuli and protein degradation mediated by catabolic stimuli. One of the impacts of alterations in gut microbiota is on the bioavailability of dietary amino acids like tryptophan, leucine, isoleucine, valine, and lysine (Puiman et al., 2013), and dietary proteins (Siddharth et al., 2017). The availability of dietary amino acids and their kinetics inside the body significantly influence the process of myogenesis (Martone et al., 2017). Enzymes like proteases and peptidases derived from the host or microbiome convert proteins from the diet into peptides and amino acids along the length of the alimentary canal (Ma and Ma, 2019). These peptides are essential for enriching microbial diversity in the gastrointestinal tract and maintaining their energy and protein homeostasis (Lach et al., 2018; Covaşă et al., 2019). Moreover, amino acids regulate the synthesis of SCFAs (propionate, butyrate, and acetate) by bacteria (Louis and Flint, 2017), which improve muscle health in significant ways (Morrison and Preston, 2016). They positively modulate muscle biology by reducing gut permeability (van Krimpen et al., 2021). The population of beneficial microbes maintains high levels of SCFAs, which regulate the translocation of harmful substances, like pro-inflammatory cytokines, across the lumen into the circulation (Parada Venegas et al., 2019).

Moreover, beneficial microbes reduce the levels of systemic inflammation and have a positive impact on insulin sensitivity in muscles (de Marco Castro et al., 2021). However, gut dysbiosis reverses the situation as the unhealthy microbiota fails to prevent the harmful translocation of substances from the lumen into the bloodstream, resulting in poor-grade chronic systemic and local inflammation contributing to insulin and anabolic resistance in muscle. A reduction in the levels of SCFAs triggers the secretion of mucins by epithelial cells of the intestine, which facilitates the entry of pathogens into the intestinal mucosa (Biagi et al., 2010; Parada Venegas et al., 2019). Among the SCFAs, alteration in the level of butyrate is of primary concern as it maintains intestinal homeostasis via the development of regulatory T cells from $CD4^+$ T cells. These regulatory T-cells induce epithelial transforming growth factor β (TGF-β) secretion and secretion of IL-10 and retinoic acid by dendritic cells and macrophages (Shapiro et al., 2014). A decrease in butyrate levels increases intestinal inflammation (Gasaly et al., 2021) and results in the entry of bacteria and inflammatory by-products into the circulation (Amabebe and Anumba, 2020).

Intramuscular fat infiltration

Among the cascade of metabolic disturbances caused by the reduced microbiota population, intramuscular lipid accumulation also alters skeletal muscle fibre composition (Klančič and Reimer, 2020). The accumulation of these intramyocellular lipids (like ceramides and diacylglycerols) and fat lead to insulin resistance in muscle cells and mitochondrial dysfunction, resulting in metabolic breakdowns in skeletal muscle, increase in oxidative stress, and chronic inflammation (Capel et al., 2019; Ebadi et al., 2019). It results in an inability to activate protein synthesis and anabolic resistance, which ultimately marks the onset of skeletal muscle atrophy (Rivas et al., 2016).

Inflammation

The imbalance in the composition of the intestinal microbiota also disturbs the balance between pro- and anti-inflammatory pathways in the host (Cristofori et al., 2021), a phenomenon known as "inflammaging" as it is a characteristic of advanced age (Casati et al., 2019). The pro-inflammatory cells include T-helper cells (Th cells), and Th17 cells, while anti-inflammatory cells include Foxp3+ receptor T cells or regulatory T cells. A healthy microbiota population potentiates the host immune system and helps in immune cell maturation. Inflammation can be both a reason or a result of gut dysbiosis. The intestinal epithelial barrier isolates bacteria from host immune cells, serving as a defence mechanism. Disruption of this epithelial membrane enhances the delivery of gut microbiota metabolites to the host, resulting from decreased stability of the mucosal barrier. It also increases susceptibility to infection by disrupting the host's immune system, inducing chronic inflammation and oxidative stress (Cristofori et al., 2021). A decrease in SCFA production, an aftermath of gut dysbiosis, also leads to the potentiation of inflammation by enhanced secretion of pro-inflammatory cytokines and chemokines (Casati et al., 2019). Bacterial endotoxin lipopolysaccharide (LPS), a component of the cell wall of gram-negative bacteria, is abundant in the gastrointestinal tract and mediates systemic inflammation and septic shock (Ghosh et al., 2020). LPS and other bacterial endotoxins have a pro-inflammatory role regulated by the gut microbiome through healthy gut barrier dynamics (Ticinesi et al., 2017). Therefore, increased permeability of LPS in the gut creates a mechanistic link between gut dysbiosis and an increase in inflammation, leading to insulin resistance in skeletal muscles. Evidence supports that LPS leakage from the gut into the bloodstream reduces glucose tolerance and enhances the levels of inflammation markers (Picca et al., 2018). It also stresses the central role that chronic inflammation plays in the crosstalk between microbial dysbiosis and initiation of muscle degradation in old age. Preclinical evaluations have proven the impact of geriatric alterations in gut microbiota on intestinal permeability (Grosicki et al., 2018; Picca et al., 2018). Gut dysbiosis enhances the production of mucins from epithelial cells of the intestine, facilitating the entrance of pathogens into intestinal mucosa (Lobionda et al., 2019). SCFAs, butyrate in particular, mediate their anti-inflammatory role by reinforcing the tight epithelial junctions of the intestinal barrier, which checks the translocation of

endotoxins through it (Liu et al., 2018). All these altered immune responses mediated by gut dysbiosis potentiate sarcopenia by inducing catabolism in the skeletal muscle cells.

Mitochondrial dysfunction and related mechanisms

An imbalance in gut microbiota composition also alters their antioxidant activity, leading to impaired mitochondrial function in host myocytes. This mitochondrial damage releases mitochondrial damage-associated molecular patterns (DAMPs), which initiate potent inflammatory responses by activating the innate immune system (Gong et al., 2020). Inflammatory mediators like TNF-α, IL-6, IL-1β, etc., induce a circle of damage in myocytes by altered quality control signalling, leading to progression in mitochondrial impairment and increased oxidative stress. The products of mitochondrial damage induce mitochondrial DNA-related inflammation, which ultimately releases pro-inflammatory cytokines, chemokines, ROS, and nitric oxide, inducing a cycle of persistent chronic inflammation. Overall, it leads to a degrading impact on muscle homeostasis (Picca et al., 2018). Oxidative stress impairs the composition and function of the intestinal microbial population and intestinal barrier permeability, interfering with the chances of xenobiotic molecules reaching the bloodstream (Reese et al., 2018). Mitochondrial dysfunction is one of the hallmarks of ageing myocytes. Alterations in mitochondrial quality control and decreased expression of autophagy markers lead to failed clearance of damaged mitochondria and other dysfunctional organelles. This induces the degradation of muscle fibres and leads to muscle atrophy (Romanello and Sandri, 2016; Cantó-Santos et al., 2020). Studies in animal models have shown that SCFAs like butyrate increase mitochondrial biogenesis markers and decrease oxidative stress markers in skeletal muscles, further proving the role of gut microbiota in strengthening muscle mass (Walsh et al., 2015). Insulin-like growth factor 1 (IGF-1) links gut microbiota and the mitochondrial level in skeletal muscle (Qi et al., 2021). In a study by Lahiri et al., muscle atrophy was suggested to be linked to reduced expression of IGF-1 and skeletal muscle growth and mitochondrial function markers (Lahiri et al., 2019).

Insulin resistance

The reduced production of gut metabolites and increased levels of LPS and BCAAs in circulation are a result of altered microbiota composition. Both of these consequences of gut dysbiosis impact muscle health by contributing to insulin resistance (Saad et al., 2016). LPS contributes to insulin resistance by binding to toll-like receptor 4, inducing adiposity and inflammation. SCFAs reduce insulin resistance by promoting insulin sensitivity, modulating glucose uptake and metabolism, and increasing energy expenditure to enhance glucose tolerance. The role of secondary bile acids against insulin resistance was also established earlier by their ability to activate GLP-1 secretion (Casati et al., 2019). Insulin mediates its muscle-protective role by inducing a cascade of phosphorylation events, which stimulate mitochondrial protein synthesis and inhibit protein breakdown in muscle cells. Insulin and IGF-1 act as potent anabolic mediators, facilitating muscle growth by the insulin/IGF1-Akt-mTOR pathway (Sartori et al., 2021). This forms the mechanistic link between insulin resistance and sarcopenia. Resistance to the anabolic function of insulin in ageing myocytes precedes the clinical manifestations of sarcopenia (Cleasby et al., 2016). Insulin resistance contributes to sarcopenia by impaired lipid oxidation in mitochondria, increased lipid accumulation, inflammation, endoplasmic reticulum (ER) stress by enhanced ROS production, and, consequently, increased mitochondrial dysfunction (Hong and Choi, 2020). There is evidence of decreased secretion of growth hormone and IGF-1 in sarcopenia, causing impaired muscle growth (Sakuma and Yamaguchi, 2012a). SCFAs contribute to IGF-1 release, strengthening their impact on the maintenance of muscle health (Yan et al., 2016b).

The correlation between sarcopenia biomarkers and gut microbiota

A plethora of factors are involved in mediating gut dysbiosis-related pro-sarcopenia mechanisms. Due to its multifactorial pathogenesis, a panel of biomarkers has been identified that mediate the multitude of pathways in sarcopenia (Fig. 2). The possible association of these markers with simultaneous modulation of gut microbiota hints at a probable correlation between gut dysbiosis and the occurrence of sarcopenia, which warrants further investigation. Identifying the biomarkers involved makes it easy to characterise the cause of the disease at a molecular level and predict its progression. It also helps to decide the treatment strategy needed.

Myostatin

There is evidence of a correlation between myostatin and gut microbiota composition, which can be linked to muscle degradation. Recently, a study showed that myostatin mutation impacts host metabolism through regulation of the gut bacteria, *Ruminococcaceae UCG-013*, *Clostridium sensu stricto 1*, and *Ruminococcaceae UCG-010* (Wen et al., 2022). Another study performed an integrated microbiome and metabolome analysis, showing that myostatin gene editing altered the composition of microbes and their metabolites in the jejunum and cecum, suggesting the influence of myostatin on gut microbiota (Pei et al., 2021). It is well established that myostatin acts as an autocrine, paracrine, and endocrine negative regulator of muscle mass by influencing molecular mediators of muscle atrophy (Ryan et al., 2017). It belongs to the TGF-β

family, predominantly expressed in myocytes. It is synthesised from its precursors, pre-pro-myostatin and pro-myostatin, and activates the ubiquitin-proteasome system in mature muscle cells (Bataille et al., 2021). Myostatin acts through its receptor, activin type II B receptor (ActRIIB), at the surface of myocytes, activating Smad2 and Smad3, which are primary signal transducers to the TGF-β superfamily. These transcription factors then translocate to the nucleus, where they mediate the expression of E3 ubiquitin ligases, atrogin-1 or muscle atrophy F-box protein (MAFbx) and muscle ring finger protein 1 (MuRF1), which facilitate muscle protein degradation via the ubiquitin-proteasome system (UPS) machinery (Conte et al., 2020a). Insulin and IGF-1 stimulation activates Akt, leading to the inhibition of dephosphorylation of Forkhead Box protein O 1 (FOXO1), which results in its inactivation and, ultimately, inhibition of muscle protein atrophy by the UPS pathway (Hay, 2011). Smad2 and Smad3 also inhibit the activation of Akt, aiding in muscle wasting (Verzola et al., 2019), which was proved when a decrease in the expression of phosphorylated Akt was observed following incubation of myotubes with myostatin (Elkina et al., 2011). Myostatin also mediates the activation of MAPKs using the Ras/Raf/MEK1 or TAK-1/MAPKK pathway (Drysch et al., 2021). This results in inhibition of genes responsible for myogenesis. Thus, signal transduction of myostatin leads to a cascade of events modulating several molecular signalling pathways, which ultimately downregulate the expression of myogenic factors. In addition to this, the possible association of myostatin with gut microbiota modulation

Fig. 2. Sarcopenia biomarkers of gut microbiota and muscle health. Figure depicting biomarkers associated with gut microbiota composition and their effect on the gut microbiome and muscle health.

may also be a factor in mediating the negative regulation of muscle health, which can be proved through further research.

Insulin-like growth factor-1 (IGF-1)

Gut microbiota has an essential role in maintaining muscle health via IGF-1, since most studies pointed out that microbiota-derived metabolites like SCFAs are potent inducers of IGF-1 in the host as an anabolic hormone for skeletal muscle synthesis and reduction of inflammation (Daily and Park, 2022). Microbiota-induced IGF-1 has previously been evidenced to ameliorate muscle wasting in mice, strongly suggesting that IGF-1/insulin signalling directly bridges the gap between sarcopenia and the gut microbiota composition (Yan and Charles, 2018). IGF-1, also called "somatomedin C", is a polypeptide hormone in the blood that stimulates muscle growth by mediating skeletal myogenesis and has been proven to increase muscle mass entity, strength, and proliferation of muscle satellite cells. IGF-1 mediates its function by binding to its receptor, IGF-1R, which activates the PI3K/Akt signalling pathway and has tyrosine kinase-like activity. The activation of this pathway results in increased protein synthesis in muscle fibres, myoblast proliferation, and differentiation, leading to overall muscle mass maintenance (Ahmad et al., 2020). Increased synthesis of IGF-1 has been observed in muscle satellite cells of injured muscles, aiding their healing by stimulating proliferation and myogenic differentiation (Chen et al., 2020a). Poor handgrip strength and deterioration in physical performance have also been associated with decreased levels of IGF-1 in the aged population (van Nieuwpoort et al., 2018). Because of its role in myogenesis and muscle growth, IGF-1 is utilised in the management of DMD, muscle atrophy, and other muscle-wasting conditions (Ahmad et al., 2020).

Irisin

There is limited data unravelling the association between irisin and intestinal microbiota; however, studies have shown that SCFA producers can contribute to an increase in irisin levels as SCFAs are potent inducers of GLP-1 secretion (Valder and Brinkmann, 2022). Irisin and GLP-1 show similar effects and act through related signalling mechanisms involving the gut, muscle and endocrine pancreas (Marrano et al., 2021). Irisin is produced from fibronectin type III domain-containing protein 5 (FNDC5) and is a sensitive molecular marker of reduced muscle strength and atrophy (Planella-Farrugia et al., 2019). Irisin levels have been evidenced to correlate positively with muscle mass. Skeletal muscle cells uptake most glucose under the action of insulin and are considered one of the primary sites of insulin resistance. Previously conducted experiments have proven that irisin influences glucose homeostasis in skeletal muscle in an autocrine fashion (Kurdiova et al., 2014). Peroxisome proliferator-activated receptor (PPAR)-γ coactivator-1α (PGC1α) is an upstream regulator of irisin. The deficiency of myostatin leads to activation and induction of irisin secretion in muscle cells (Huh et al., 2014). Irisin treatment has been shown to potentiate muscle growth through the ERK pathway and by decreasing negative regulators of muscle mass, like myostatin, while increasing IGF-1, a stimulator of myogenesis (Huh et al., 2014).

Brain-derived neurotrophic factor (BDNF)

SCFAs, particularly butyrates, have been evidenced to positively regulate the expression of trophic factors such as neurotrophins, including pro-BDNF and BDNF (Ziemka-Nalecz et al., 2017; Ojeda et al., 2021). Many studies have shown that germ-free and antibiotic-treated mice exhibit decreased expression of BDNF in the hippocampus compared to the mice with standard gut microbiota composition. Treatment with prebiotics fructooligosaccharides (FOS) and galactooligo-saccharides (GOS), which increase the amount of intestinal *Bifidobacterium* spp. and *Lactobacillus* spp., upregulates hippocampal gene and protein expression of BDNF (Yu and Hsiao, 2021). The maintenance of healthy muscle mass and function is mediated by the equilibrium between the positive and negative factors of muscle development. BDNF, belonging to the neurotrophin family, is one of the positive regulators (Kalinkovich and Livshits, 2015). Its role in skeletal muscle involves stimulating myogenesis by differentiating myoblasts into myocytes, developing muscle fibres, maintaining motoneuron survival and the postsynaptic region in muscle fibres, and aiding in the presynaptic release of neurotransmitters (Raschke and Eckel, 2013; Sakuma et al., 2015). The link between BDNF levels and susceptibility to sarcopenia was proved when a reduction in the high-affinity tropomyosin-related kinase-B receptor (TrkBR) was observed following a loss of endogenous BDNF in diaphragm muscle of old mice (Greising et al., 2015). The BDNF/TrkBR signalling pathway mediates anti-inflammatory effects and immune regulation in myofibers through the p75 neurotrophin receptor (p75NTR) (Kalinkovich and Livshits, 2015). As a result of its role in muscle repair, regeneration, and differentiation, as well as its link to immunology, inflammation, and muscular pathology, BDNF might be regarded as an important marker of sarcopenia.

Follistatin (FST)

Studies have shown that altered diet, and subsequently altered gut microbiota composition, lower the levels of follistatin (FST), which also negatively impacts skeletal muscle mass (Li et al., 2019). Increased dietary protein intake has been shown to stimulate follistatin secretion (Bojsen-Møller et al., 2021). These dietary proteins are broken down into amino acids,

which impact the gut microbiota composition and microbial metabolites, thus affecting muscle health in the host (Zhao et al., 2019a). FST is a positive mediator of muscle mass, which strongly inhibits myostatin-mediated muscle atrophy. It is expressed in several tissues, like the brain, muscles, bone marrow, ovary, liver, and blood vessels, and antagonises the action of proteins from the TGF-β superfamily, myostatin, activin A, and bone morphogenetic protein (BMP) (Skrzypczak et al., 2021). FST proteins are thought to potentiate the myogenic ability of muscle progenitor cells by binding to myostatin and rendering it undetectable (Kalinkovich and Livshits, 2015). FST overexpression is also related to increased Akt phosphorylation and its activation, mTOR signalling, and translation of muscle proteins by inhibiting Smad3 activity (Winbanks et al., 2012). Signalling networks between the Wnt/β-catenin system, FST, and TGF-β signalling pathways have been discovered (Han et al., 2014). Given the crucial role of the Wnt/β-catenin pathway in myofibroblast proliferation and myofiber growth regulation, this crosstalk further strengthens the function of FST in muscle mass maintenance (Xu et al., 2017). FST-based therapies, like recombinant adeno-associated viral vectors expressing FST (Sepulveda et al., 2015), FST-like 3-Fc-fusion protein (Ozawa et al., 2021), and other gene-based treatments are being extensively evaluated because of their therapeutic potential to curb the harmful effects of muscle atrophy.

Growth/Differentiation Factor-15 (GDF-15)

The correlation of GDF-15 with gut dysbiosis-induced sarcopenia can be traced to a study in which a greater abundance of the *Enterobacteriaceae* family was found in the faecal microbiota of patients with high serum GDF-15 concentrations (Bilson et al., 2021). Another observational study showed that a prominent feature of gut microbiota dysbiosis was an increase in the amount of *Enterobacteriaceae* found in elderly patients with sarcopenia (Liu et al., 2021). GDF-15 negatively affects muscle health and is involved in the enhancement of muscle growth suppressors. It is also known as serum macrophage inhibitory cytokine 1 (MIC-1) and is a significant member of the TGF-β superfamily (Wischhusen et al., 2020). Circulating levels of GDF-15 increase with age and have an inverse relationship with muscle mass and muscle endurance, making it a potential biomarker of sarcopenia (Kim et al., 2020). In Taurin transporter knockout mice, GDF-15 is shown to induce muscle fibre apoptosis and increase inflammation. Also, increased levels of GDF-15 have been associated with cachexia and muscle atrophic conditions in human subjects (Ito et al., 2018; Conte et al., 2020b). Both serum and mRNA concentrations of GDF-15 were elevated in subjects who had developed atrophy in the quadriceps muscle following heart surgery (Bloch et al., 2013). All this evidence of a consistent correlation of GDF-15 with reduced muscle mass suggests its involvement in potentiating sarcopenia. However, the signalling pathways by which it mediates the muscle wasting function are not clear. Thus, it warrants further investigation into its role as a biomarker of sarcopenia.

Decorin

Gut microbiota is known to positively regulate the function of this myokine by increasing the production of SCFAs, BCAAs, secondary bile acids, and endo-cannabinoids, and inhibiting inflammatory cytokines (Suriano et al., 2020; Daily and Park, 2022). Decorin is a small leucine-rich myokine secreted by cells in adipose tissue in response to physical exercise. It is involved in skeletal muscle differentiation and repair (Bahl et al., 2018). Decorin mediates its muscle-protective function by inhibiting the responsiveness of myogenic satellite cells to TGF-β1 during differentiation, which induces their proliferation (Kelc et al., 2015). Studies on myogenic cells have shown that decorin overexpression boosts muscle cell proliferation and differentiation by suppressing myostatin activity, which negatively affects muscle growth (Kishioka et al., 2008; Bahl et al., 2018). The contribution of decorin to muscle hypertrophy by increased expression of promyogenic genes and inhibition of muscle atrophy genes has also been well established (Kanzleiter et al., 2014). Also, it has a role in regulating connective tissue formation in skeletal muscles by stimulating collagen synthesis in connective tissue (Bahl et al., 2018). Decorin has been identified as a potential therapeutic target in sarcopenia as well as sarcopenic obesity (Bilski et al., 2022).

Apelin

A potential relationship between gut bacteria and the apelinergic system was observed in a study where LPS from gram-negative bacteria stimulated apelin expression (Geurts et al., 2011). This study was conducted to associate gut flora and apelin. Apelin is an adipokine and myokine, which is an endogenous ligand of the G-protein coupled receptor APJ (Wysocka et al., 2018). Ageing decreases Apelin release, which can be partially recovered from exercise. Apelin restoration leads to enhanced muscle strength by anti-inflammatory function, targeting satellite cells and muscle stem cells and stimulating mitochondriogenesis, which increases the regenerative abilities of muscle cells. Apelin supplementation promoted protein synthesis in sarcopenic muscle fibres via AMPK, Akt, and P70S6K activation (Vinel et al., 2018; Bilski et al., 2022). Thus, apelin and its receptor can serve as markers and therapeutic targets to ameliorate age-related sarcopenia.

Activin A and B

Blocking of activin receptor ligands has previously resulted in a decrease in bacterial diversity, which was

proved by the reduced bacterial richness in the respective stool samples of C26 cachectic mice (Pekkala et al., 2019). Activins A and B belong to the TGF-β family and are categorised as inhibitors of muscle growth. Activins are synthesised as precursor molecules and are cleaved by ActRIIA/II receptors, resulting in the activation of Activin receptor type-1B (ACVR1B) or ALK4. Activated ALK4 phosphorylates Smad2/3, which binds with Smad4 (Kalinkovich and Livshits, 2015). This ActRII/ALK/Smad2/3 signalling pathway starts a protein degradation program via autophagy and UPS, which accelerates muscle atrophy (Lodberg, 2021). It has been shown that activin A inhibition leads to the induction of muscle hypertrophy in mice and primates (Latres et al., 2017). It has been well established that activins, along with myostatin and GDF-11, activate Smad2/3 signalling to induce muscle atrophy, eventually contributing to muscle-wasting disorders (Rodgers and Ward, 2022). Thus, myostatin/activin pathway antagonism also holds significant promise as a therapeutic target in the management of sarcopenia.

Fibroblast Growth Factor 21 (FGF21)

Previous reports provide evidence that dietary proteins induce elevated levels of FGF21 in plasma and that normal gut microbiota composition is required for this increased FGF21 response to a protein-rich diet (Martin et al., 2021). Administration of *Lactobacillus rhamnosus* GG also increases hepatic FGF21 expression (Zhao et al., 2019b). Consistent with these findings, a research study by Kundu et al. reported that young germ-free mice receiving faecal microbiota transplantation (FMT) showed an increase in FGF21 levels due to high concentrations of microbiota-derived butyrate (Kundu et al., 2019). FGF21, a member of the FGF superfamily, regulates metabolic activities rather than cell division and differentiation (Tezze et al., 2019). Apart from the liver, adipocytes and myocytes are also prominent sources of FGF21; it has anti-obesity action and reverses insulin resistance. It also increases thermogenesis in fat tissue and skeletal muscle through increased expression of the peroxisome proliferator-activated (PGC)-1-alpha gamma receptor (Cuevas-Ramos et al., 2019). It was observed that deficiency of FGF21 increased the expression of muscle atrophy factors (MuRF1 and Atrogin-1), and also increased TNF-α-mediated inflammation in skeletal muscles (Kim et al., 2019). The literature emphasises the role of FGF21 in aerobic muscle fibre formation via the FGF21-SIRT1-AMPK-PGC1α axis (Liu et al., 2017). A study conducted on pigs showed that it can suppress adipogenesis in intramuscular fat cells (Wang et al., 2016). Thus, FGF21 levels can be significant in studies related to sarcopenia and sarcopenic obesity.

Bone Morphogenetic Proteins (BMPs)

Previous studies have shown that BMP treatment increased the proportion of *Verrucomicrobia*, *Blautia*, and *Allobaculum* genera, known producers of SCFAs, especially butyrates, which exert a protective effect on muscle atrophy (Bai et al., 2018). BMPs play an essential role in both bone and muscle homeostasis. They are molecules of the TGF-β family that mediate various pathways linked to cell homeostasis and proliferation, differentiation, morphogenesis, and regeneration (Scimeca et al., 2017). They potentiate muscle mass by negatively regulating the activity of Smad proteins 6 and 7, which inhibit Smad1/5/8 activation. The stimulation of Smad1/5/8 activates mTOR, which enhances protein synthesis. This BMP-Smad1/5/8 axis counters the myostatin/activin-Smad2/3 axis, inhibiting muscle wasting (Winbanks et al., 2013). Thus, increased signalling via activation of the BMP-Smad1/5/8 axis offers treatment by promoting myofiber hypertrophy and preventing pathology-associated muscle wasting.

Meteorin-like Protein (Metrnl)

Metrnl is an adipo-myokine having pleiotropic functions in adipose tissue. It induces the browning of white adipose tissue and reduces insulin resistance (Bilski et al., 2022). It is expressed in high levels in intestinal epithelial cells (Li et al., 2016) and skeletal muscle post-exercise. It promotes the regeneration of injured muscle via Stat3/IGF-1 signalling (Schmid et al., 2021). Baht et al. proved that Metrnl induces macrophage-dependent IGF-1 production, which directly affects muscle satellite cell proliferation (Baht et al., 2020). This caused an anti-inflammatory response and aided in the muscle regeneration process.

Interleukins (IL-6/7/15/17)

IL-15, IL-17A, IL-7, and IL-6 can also serve as biomarkers of sarcopenia. Positive associations have been observed between the severity of sarcopenia and IL-17A levels in the older population (Ying et al., 2022b). IL-17A contributes to skeletal muscle atrophy by activating JAK2/STAT3 signalling, which results in myosin heavy chain loss and myotube atrophy (Ying et al., 2022a). Gut microbiota-derived SCFAs have been shown to repress IL-17 production (Dupraz et al., 2021). IL-6 released during exercise regulates muscles' glucose and lipid metabolism (Bilski et al., 2022). It was previously proved that increased levels of IL-6 induce geriatric poor-grade inflammation, resulting in sarcopenia (Bano et al., 2017; Dalle et al., 2017). It was also found that denervation-activated STAT-3-IL-6 signalling in fibro-adipogenic progenitors (FAPs) reduced skeletal muscle mass (Madaro et al., 2018). Since denervation associated with ageing can be causative of sarcopenia, this mechanism could be of significance in the process (Bilski et al., 2022). Also, IL-6 activates glycogen and lipid breakdown in muscle via AMPK signalling. Exercise increases IL-6 levels, which

leads to upregulation of GLUT4 and insulin sensitivity in skeletal muscles (Ikeda et al., 2016). Studies have reported that bacterial metabolites, like SCFAs, promote the secretion of IL-7 in the intestinal epithelium (Paturi et al., 2020). IL-7 is produced by stromal cells in the thymus and bone marrow (West, 2019); it is also considered a myokine due to its expression and secretion from myocytes (Haugen et al., 2010). IL-7 is critical for muscle tissue development and helps in the differentiation of satellite cells into mature skeletal muscle cells (Severinsen and Pedersen, 2020; Bilski et al., 2022). Gut-microbiota depletion has been shown to lower the expression of IL-15 (Jiang et al., 2013). IL-15, which lies within the IL-2 superfamily, has been linked to adipose tissue-skeletal muscle crosstalk (Nielsen et al., 2007; Quinn et al., 2009; Bilski et al., 2022). IL-15 was also found to facilitate muscle fibre regeneration and inhibit intramuscular fat infiltration through modulation of FAPs (Kang et al., 2018). Studies have proven that decreased levels of IL-15 are associated with sarcopenia (Bilski et al., 2022). Evidence of its declined levels with age further strengthens these findings. Thus, the levels of these interleukin myokines can be significant markers of muscle health.

Association between the gut microbiome and muscle histology

Interventions targeting the gut-muscle axis have improved age-related degradation of muscle health (Picca et al., 2018). Moreover, histological changes in skeletal muscle provide crucial insights into muscle disorder pathology, aiding diagnosis and treatment strategies (Lau et al., 2018). Mean myofiber diameter, myofiber cross-sectional area, and myofiber size distribution are pivotal histological parameters enabling precise evaluation of age-related muscle loss (Lau et al., 2018; Laghi et al., 2022). Faecal microbiota transplantation (FMT) from young donor rats (12 weeks) improved the cross-sectional area of myofibers in gastrocnemius and soleus muscles, which was significantly decreased in old rats (88 weeks) (Mo et al., 2023). This improvement was attributed to the preservation of gut barrier integrity, characterized by enhanced levels of beneficial bacteria such as *Lactobacillus*, *Akkermansia*, and *Lactococcus*, along with increased production of metabolites like methoxyacetic acid, 3R-hydroxy-butanoic acid, and γ-glutamyltyrosine. Histological analysis using Masson's and Sirius red staining further revealed a reduction in interstitial fibrosis in both gastrocnemius and soleus muscles following FMT treatment in aged rats (Mo et al., 2023). Another study reported that ghrelin antagonization decreased protein deposition in pig muscles by reducing the abundance of acetate-producing bacteria and depleting the levels of serum amino acids like arginine, methionine, tyrosine, and isoleucine (Yan et al., 2022).

These findings correspond with muscle morphological changes that exhibit a significant decrease in the cross-sectional area of the longissimus dorsi and gastrocnemius muscle fibers. Furthermore, supplementation with animal protein hydrolysate (APH) induced positive alterations in gut microbiota and increased SCFA levels like isovaleric, acetic, and propionic acid, improving the sarcopenia phenotype by enhancing muscle protein synthesis (Lee et al., 2023). Also, hematoxylin and eosin (H&E) and Sirius Red staining results demonstrated a significant increase in muscle fiber size and reduced collagen accumulation, respectively. These findings were further confirmed by the reduction in the expression of the muscle atrophy marker, myostatin, in the muscle tissues of aged mice following supplementation with APH.

A recent study on C57BL/6 mice subjected to four weeks of antibiotic treatment revealed suppressed gut microbiota activity, suggesting its significant influence on skeletal muscles (Qiu et al., 2021). This was evident through results from H&E and immunofluorescence staining, which showed smaller myofiber size in the gastrocnemius muscles of treated mice compared to controls. Quantitative morphometric analysis further confirmed these effects, highlighting a higher proportion of myofibers with decreased mean fiber area in the antibiotic-treated group. Collins et al. conducted histological assessments of vastus lateralis muscles by Oil Red O and Picrosirius Red staining to assess alterations in muscle integrity and intramuscular lipid infiltration in high-fat high-sucrose diet-fed rats (Collins et al., 2016). They concluded that muscle fibrosis marked by compromised muscle integrity and increased intramuscular fat deposition was linked to fluctuations in gut microbiota composition, particularly exhibited by decreased abundance of *Bacteroides/Prevotella* species and systemic inflammation. Also, silk peptide administration in aged rats could protect against age-related decline in lean muscle mass and muscle strength through gut microbiota modulation (Park et al., 2021). Intestinal histology results show improved gut barrier integrity and alterations in gut microbiota. Additionally, Alcian Blue-Periodic acid (AB-PAS) staining indicates increased mucin content in intestinal tissues and preservation of the mucus barrier in silk peptide-treated groups compared to the aged group. The muscle protective mechanisms were associated with high serum concentrations of amino acids and SCFAs, post silk peptide intake, in addition to decreased insulin resistance and inflammation. Qi et al. demonstrated the effects of intestinal microbiota colonization by FMT on germ-free (GF) piglets (Qi et al., 2021). The absence of microbiota led to decreased muscle function and a reduction in myogenic transcription factors, MyoG and MyoD. The H&E staining of longissimus dorsi muscle sections revealed thinner muscle fibers in the GF piglets as compared to FMT and normal piglets. Immunohistochemical analysis exhibited a reduced proportion of slow-twitch muscle fibers in GF piglets promoted by a significant decrease in SCFA levels. Their results, along

with histological assessments, confirmed the contribution of gut bacteria in the maintenance of growth and development of host muscle tissues. These findings emphasize the correlation between the gut microbiome and muscle histology, highlighting the potential of interventions or mechanisms targeting the gut-muscle axis to alleviate age-related muscle decline. Moreover, they demonstrate that muscle histology could serve as a gold standard in studying the correlation between gut microbiota and muscle health.

Future directions and possible intervention strategies

Dietary intervention

Food intake declines with progressing age due to various geriatric factors like physiological anorexia, drug interactions, impairment in masticatory function, and changes in food preferences from energy and protein-rich foods to energy-dilute foods like fruits, grains, and vegetables (Liguori et al., 2018). Dietary insufficiencies are the main reason for metabolic diseases related to gut dysbiosis. Amino acids like leucine, casein and whey proteins (from milk), creatine monohydrate, and vitamin D have been most commonly studied for their role in muscle protein generation through the mTOR signalling pathway by regulation of myogenic regulatory factors (Snijders et al., 2018; Liao et al., 2022). Nutrient supplementation, a significant modulator of intestinal microbiota composition, has been a helpful intervention strategy to increase muscle protein synthesis (Picca et al., 2018; Liao et al., 2022). Dietary interventions for sarcopenia patients can be planned to meet essential requirements. It should consider adequate calorie consumption, metabolic profile and health status of the patient, physical activity level, provision of nutrients quality- and quantity-wise concerning physiological needs, and concomitant therapies. This should be extended for sufficient time to impact muscle health (Calvani et al., 2013). Research has evidenced the beneficial effects of the following nutritional supplements on ageing muscle physiology.

Proteins

The complex interplay of a wide range of factors maintains skeletal muscle health; however, it is mainly governed by the equilibrium between protein synthesis and breakdown. Proteins and amino acids derived from dietary sources play a pivotal role in maintaining optimal muscle protein metabolism. In the fasting state, such as the postabsorptive, skeletal muscle proteins are catabolised to release free amino acids, which can serve as energy substrates, be utilised in the synthesis of immune system, enzymes, peptide hormones and plasma proteins, and can also aid in gluconeogenesis (Carbone and Pasiakos, 2019). Also, the postprandial increase in amino acid levels after dietary protein ingestion stimulates muscle protein synthesis (Kouw et al., 2019). Increased protein consumption above 0.8 g/kg/day (the recommended dietary allowance) can effectively counter skeletal muscle loss. It can result in an increased appetite for food in the older population (Muscariello et al., 2016). With increased protein consumption, more proteins reach the intestine, increasing the production of bacterial metabolites like BCAAs and SCFAs, both of which are essential mediators of muscle protein anabolism (Prokopidis et al., 2020). Recent studies stress the quality of proteins is a significant factor in promoting muscle health. Proteins rich in essential amino acids (EAAs) induce muscle protein anabolism in older subjects. Leucine, a crucial BCAA, induces molecular mechanisms promoting muscle hypertrophy (Perna et al., 2020). It is considered the principal dietary modulator of muscle protein anabolism as it can inhibit proteasomes by activating the mTOR pathway (Landi et al., 2016). Therefore, dietary sources rich in EAAs like lean meat, dairy-based products, lentils, peanuts, soybeans, and cowpeas are advised for older individuals suffering from sarcopenia (Landi et al., 2016). β-hydroxy β-methyl butyrate (HMB) is an active amino acid metabolite of leucine, responsible for activating the mTOR signalling pathway in muscle (Oktaviana et al., 2019). However, following absorption, only 5% of dietary leucine is metabolised to HMB, implying the need for direct administration of HMB to reach pharmacological levels to mediate its efficacy against sarcopenia. Recent evidence also proves that milk-derived proteins, whey and casein, are effective proteins against sarcopenia as they stimulate myogenesis, and their combination prolongs muscle protein synthesis (Kanda et al., 2016). Clinical studies link high dietary protein consumption and progressive resistance training to improved muscle function in older populations. These findings support the need for a personalised diet plan with proteins rich in EAAs to be consumed in adequate amounts to boost muscle health and function in gut dysbiosis-induced sarcopenia.

Vitamin D

Decreased levels of vitamin D are linked to disease conditions like osteomalacia, osteoporosis, and osteopenia since it is an important mediator of bone homeostasis (Perna et al., 2020). Apart from bone-related pathologies, several studies have linked vitamin D status with sarcopenia and musculoskeletal pain; also, there are reports of a positive correlation of vitamin D levels with muscle mass and strength in the older population (Yang et al., 2020). Vitamin D supplementation for eight weeks combined with BCAAs improved muscle strength in sarcopenia patients (Gkekas et al., 2021). Gut microbiota is known to stimulate calcium and vitamin D absorption. Vitamin D aids in the translocation of microbial metabolites to the host by maintaining intestinal epithelial barrier integrity (Li et al., 2021). This regulation of gut microbiota homeostasis

by vitamin D also modulates immune responses at multiple levels and minimises inflammation (Farré et al., 2020). This immunoregulatory role also makes vitamin D a nutrient of significance in reducing muscle damage. Vitamin D is known to regulate muscle cell proliferation and differentiation, potentiate muscle protein synthesis, and transport calcium and phosphorus inside the cells via the Vitamin D receptor (Caballero-García et al., 2021). Vitamin D promotes skeletal muscle regeneration by reducing apoptosis in muscle cells, balancing the production of pro-inflammatory cytokines, like IFN-γ and IL-1, and anti-inflammatory cytokines, like IL-10 and IL-13. It also increases calcium transport into the sarcoplasmic reticulum to facilitate muscle contraction. Based on growing evidence of the muscle-protective role of vitamin D, it is recommended that the concentration of 25-hydroxy vitamin D be measured in all patients suffering from sarcopenia, and vitamin D supplements (800 IU [20 μg]/day) be prescribed to all patients with serum concentrations below 100 nmol/L (40 ng/mL) (Liguori et al., 2018). Vitamin D supplementation also elevates the gene expression of vitamin D receptors in muscle tissues (Pojednic et al., 2015), which ultimately improves muscle fibre size in the older population (Cruz-Jentoft et al., 2020). A vitamin D-rich diet can also be consumed by sarcopenic patients. Dietary sources of vitamin D3 (cholecalciferol) include liver oils from cod, shark, and tuna, and oily fish like herring, sardines, and salmon, egg yolk, and meat; whereas dietary sources of vitamin D2 (ergocalciferol) include, wild mushrooms and UV-exposed fungi and yeast (Ljubic et al., 2020). However, in the absence of exposure to the appropriate amount of sunlight, vitamin D supplementation serves as a suitable alternative to recover impaired muscle health in sarcopenia.

Fatty acids

Omega-3 fatty acids, like eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and α-linoleic acid (ALA), are recognised as possible dietary counter-measures for sarcopenia, mainly owing to their anti-inflammatory properties (Calvani et al., 2013; Dupont et al., 2019). The primary sources of omega-3 long-chain fatty acids, EPA, and DHA, are seafood, fish oils, krill oil, and algal oils; they can also be bio-synthesised from ALA (Bird et al., 2021). Since increased inflammatory responses are a hallmark of sarcopenia (Liguori et al., 2018), oral nutrient supplementation of EPA and DHA could contribute to immunoregulation and affect the gut microbiota. An increase in the content of SCFAs mediates the muscle-protective action by affecting gut microbiota, as indicated by increased SCFAs in omega-3, PUFA-treated *Salmonella*-infected mice due to an increase in *Bacteroidetes* and *Bifidobacterium* spp. (Machate et al., 2020). Another study reported that consuming an omega-3 PUFA-rich diet (4 g of EPA and DHA in combination daily) led to a significant increase in SCFAs, particularly butyrate-producing species like *Blautia*, *Coprococcus*, *Bacteroides*, and *Roseburia* (Ochoa-Repáraz and Kasper, 2016). Butyrate has been evidenced to induce protection against muscle atrophy and elevate muscle mass in sarcopenia patients (Kang et al., 2021). Omega-3 PUFAs can also be effective in gut dysbiosis-induced sarcopenia by mitigating the effect of LPS-induced pro-inflammatory cytokines and increasing the levels of anti-inflammatory cytokines (Liu et al., 2015). They inhibit nuclear factor kappa (NF-κB) signalling pathways induced by LPS and decrease the expression of pro-inflammatory cytokines like TNF-α. They also increase the production of anti-inflammatory factors like IL-10, decrease IL-17 production, which is a pro-inflammatory mediator, and increase Treg differentiation, thus, mediating an overall anti-inflammatory response that contributes to its protective role in sarcopenia (Fu et al., 2021).

CLAs are a group of 18-carbon PUFA isomers derived from linoleic acid, which can be obtained from meat and dairy products from ruminant animals like lamb and beef (Polidori et al., 2019). The exact mechanism of its muscle-protective action through modulation of gut microbiota is unknown to date, however, there is enough evidence demonstrating its positive role in skeletal muscle metabolism. Dietary supplementation of 1.2-2.0% CLA in pigs significantly elevated the expression of oxidative slow-twitch type I myofiber (Huang et al., 2014). CLA is associated with enhanced muscle endurance in mice and the upregulation of molecular biomarkers in skeletal muscle, which potentiate muscle growth (Kim et al., 2016).

Antioxidants

Increased oxidative stress from the reduction in enzymatic antioxidant protection and a surge in reactive oxygen species is one of the pathophysiological mechanisms contributing to sarcopenia-associated muscle loss (Bellanti et al., 2020). Chronic exposure to ROS can lead to microbial dysbiosis, which leads to inflammation and muscle atrophy. The administration of antioxidative agents through dietary modification can thus be a possible strategy to protect muscle tissue from oxidative damage in sarcopenia patients. Recent studies have proven that food-derived antioxidant compounds increase the composition of beneficial microbes like *Bacteroidetes* in the gut, which in turn protects the muscle cells of the host against oxidative stress (Rajoka et al., 2021). Consumption of natural antioxidants from fruit, vegetables, and medicinal plants increased the *Bacteroidetes* to *Firmicutes* ratio, which decreased inflammation, oxidative stress, and intestinal barrier dysfunction (Ni et al., 2019a). Dietary polyphenols obtained from food sources like cocoa, tea, coffee, spices, wine, fruit, and vegetables like berries, broccoli, carrots, spinach, beetroot, potato peel, etc., are also well-known antioxidants, and their interaction with gut microbiota is being widely investigated (Aravind et al., 2021; Rajoka et al., 2021). Polyphenols exert their

beneficial effect by increasing the abundance of beneficial bacteria, *Lactobacillaceae* and *Bifidobacteriaceae*, and lowering the count of pathogenic bacteria, like *Escherichia coli*, *Helicobacter pylori*, and *Clostridium perfringens* (Plamada and Vodnar, 2022). Thus, their antioxidant properties can be traced to their ability to improve the gut structure and balance through increased production of SCFAs. An antioxidant can also protect against oxidative damage in muscle cells by inhibiting free radical production and scavenging existing free radicals, thereby protecting against the oxidative chain reaction, which leads to muscle cell death (Eke et al., 2017; Rajoka et al., 2021). Both fat-soluble vitamins (vitamin E) and water-soluble vitamins (vitamin C) inhibit oxidation. Dietary carotenoids are also important lipid-soluble sources of antioxidants, which act by scavenging free radicals, inhibiting lipid peroxidation, regulating transcription factors like NF-κB, and quenching singlet oxygen (Cerullo et al., 2012). The primary sources of dietary carotenoids are eggs, salmon, fish, fruit, and vegetables like bell peppers, carrots, mangoes, oranges, etc. (Toh et al., 2021). Many studies have proven the beneficial effect of antioxidant supplementation in sarcopenia (Liu et al., 2021). Chronic antioxidant intake increases locomotor activity, elevates the expression of antioxidant enzyme-related genes, and improves the metabolic profile of muscles in mice with age-related muscle atrophy (Nonaka et al., 2019; Tsukamoto-Sen et al., 2021).

Creatine

Creatine is obtained endogenously by a reaction involving the amino acids methionine, glycine, and arginine (Dinesh et al., 2020) and exogenously from food sources like salmon, tuna, and lean red meat. Recently, the International Society of Sports Nutrition (ISSN) concluded that, with regards to muscle uptake and the capability to boost high-intensity exercise capacity, creatine monohydrate is the form of creatine that has been the most thoroughly investigated and clinically proven to be useful in dietary supplements (Kreider et al., 2022). Approximately 95% of creatine is stored in muscles, where two-thirds of it gets converted into its high-energy metabolite - phosphocreatine, and one-third is available as free creatine (Kreider et al., 2017). There is plenty of evidence of the effectiveness of creatine supplementation on ageing muscle and bone. A recently conducted meta-analysis showed a significant increase in fat-free muscle mass and strength in ageing subjects supplemented with creatine (Chilibeck et al., 2017). These results were consistent with another meta-analysis study conducted by Devries and Philips (Devries and Phillips, 2014), concluding that creatine supplementation increased physical performance, lean tissue mass, and strength in 357 older subjects aged between 55-71 years when compared with placebo. The increase in lower body strength mediated by creatine in these studies is of particular importance as the muscle tissues of the lower body are more prone to wasting during the ageing process (Candow et al., 2019). Multiple cellular mechanisms can be involved to enhance muscle mass and function in response to creatine supplementation. An increase in the expression of genes related to myogenesis, like Myogenin and MRF-4 and other downstream protein kinases of the IGF-1/mTOR pathway (muscle protein synthesis pathway), protection against mitochondrial oxidative stress, increase in intracellular osmolarity, and potential anti-inflammatory action can be the possible mechanisms of the muscle-protective action of creatine (Candow et al., 2019). Gut microbiota is known to produce specific enzymes like creatinine deaminase and creatine amidinohydrolase, which breakdown creatine. Thus, gut microbiota potentiates the metabolism of creatine, which is essential for its action of supporting intestinal barrier function and shaping host immunity and metabolism. These findings have been correlated with the positive impact of creatine supplementation on muscle mass and health. The positive influence of gut microbiota on creatine metabolism may be a reason behind the protective action of creatine against age-related muscle wasting and its positive role in promoting muscle strength and hypertrophy (Kitzenberg et al., 2016). Creatine supplementation can also compensate for the intestinal barrier. The compromised integrity of the intestinal barrier due to gut dysbiosis can also be recovered by creatine supplementation, thus mediating its anti-inflammatory action, and putting a check on the altered immune responses that ultimately lead to sarcopenia.

Other nutritional supplements

Nutrients and nutritional supplements have ancillary effects on gut microbiome status to enhance muscle mass and strength in sarcopenia patients, thus proving to be a multimodal strategy for treating sarcopenia-induced muscle wasting (Banerjee et al., 2021). A high microbiome-accessible carbohydrate diet can promote gut microbiota diversity, diminish harmful bacteria, increase SCFA production (Xu et al., 2021a), and enhance muscle mass and function (Okamoto et al., 2019; Liu et al., 2021). Curcumin enhances muscle mass and function in addition to sharing a symbiotic relationship with gut microbiota. It increases the number of beneficial gut microbial bacteria like *Bifidobacteria*, *Lactobacilli*, and butyrate-producing bacteria and decreases the number of pathogenic bacteria like *Prevotellaceae*, *Enterobacteria*, *Coriobacterales*, and *Rikenellaceae*. Also, relevant gut microbial strains like *Bifidobacteria*, *Lactobacilli*, and *Enterococcus* mediate the biotransformation of curcumin by various metabolic pathways like reduction, acetylation, demethylation, hydroxylation, and demethoxylation. The resulting metabolites mediate curcumin's antioxidant, anti-inflammatory and muscle-protective action (Scazzocchio et al., 2020; Liu et al., 2021). Depleting magnesium stores with ageing also leads to sarcopenia, suggesting its significant role in muscle contraction and its

interactions with calcium to promote muscle health (Cruz-Jentoft et al., 2020). Its mechanisms of muscle-protective action include enhanced muscle protein synthesis, increased ATP generation, maintaining electrolyte balance, increased oxygen uptake in muscle cells (Perna et al., 2020), and positive modulation of the intestinal microbiota (Bielik and Kolisek, 2021). Supplementation with kefir, which is acidic fermented milk with a trace amount of alcohol and lactic acid bacteria, changed the gut microbial composition and shifted it towards *Bacteroidetes* (beneficial bacteria) and reduced the proportion of harmful bacteria, *Firmicutes* and *Clostridia* (Hsu et al., 2018). Subsequently, the study also reported increased muscle strength and physical performance following kefir supplementation. Ursolic acid also has similar beneficial effects on gut microbiota as it decreases the *Firmicutes* to *Bacteroidetes* ratio and promotes the growth of SCFA-producing bacteria in the gut (Hao et al., 2020). Several studies report the suppression of skeletal muscle wasting, stimulation of skeletal muscle synthesis, and increase in muscle strength following ursolic acid treatment through downregulation of skeletal muscle atrophy markers, MuRF 1 and Atrogin 1, or through upregulation of muscle protein synthesis stimulation via the Akt/mTOR pathway (Sakuma and Yamaguchi, 2012b; Yu et al., 2017; Seo et al., 2018). The primary dietary sources of ursolic acid include apple peel, peppermint, basil, thyme, rosemary, plum, oregano, cranberries, and bilberries (Aprotosoaie et al., 2019). Oyster polypeptides have also shown muscle-protective properties by attenuating muscle atrophy. They regulate muscle protein turnover by reducing the expression of markers associated with protein degradation and mediating mitochondria biogenesis (Jeon and Choung, 2021). They have prominent anti-fatigue effects attributed to their ability to regulate the abundance of gut microbiota and maintain a balance between the harmful and beneficial taxa (Xiao et al., 2020).

Pharmacological intervention

Non-steroidal anti-inflammatory drugs (NSAIDs)

The chronic low-grade inflammation mediated by the alteration in gut microbial composition can be attenuated by NSAIDs, which can be therapeutic in preventing muscle strength loss and subsequent progression of sarcopenia. In a study conducted on aged rats, treatment with ibuprofen, an NSAID, increased muscle protein synthesis and decreased proteolysis (Xu et al., 2021b). Chronic inflammation generally has detrimental effects on the regeneration process mediated by satellite cells of skeletal muscle and can potentiate cell death pathways in myocytes (Walston, 2015; Howard et al., 2020). NSAIDs can also protect against inflammation either by their direct effect on the intestinal microbiome, i.e., by increasing the abundance of beneficial bacteria like *Bacteroidetes* and *Enterobacteriaceae*, or by recovering intestinal barrier integrity (Maseda and Ricciotti, 2020).

Ghrelin and ghrelin mimetics

Ghrelin is an orexigenic hormone that causes the secretion of growth hormone (GH) and increases appetite (Devesa, 2021). A study showed that ghrelin-null mice exhibited a reduction in butyrate-producing bacteria, with an upregulation of muscle atrophy marker MuRF1 and a decrease in expression of the myogenic gene *MyoD* (Wu et al., 2020). At therapeutic doses, ghrelin has actions resembling GH, which is known to positively regulate the growth and differentiation of muscle cells via the GH/IGF axis. Therefore, ghrelin and ghrelin mimetics are potential therapies against sarcopenia and related muscle atrophy (Ali and Garcia, 2014). Phase III clinical trials of anamorelin, a ghrelin receptor agonist, have shown significant improvement in the muscle mass of sarcopenia patients (Liguori et al., 2018).

Angiotensin-converting enzyme inhibitors (ACEIs)

Studies have shown that the gavage of ACEIs reverses intestinal microbiota dysbiosis and increases the abundance of SCFA-producing bacteria, which positively influence muscle growth by favouring skeletal muscle mass retention (Xie et al., 2022). ACEIs have also proven effective in countering sarcopenia by promoting muscle blood flow, inhibiting endothelial apoptosis, and antioxidant activity (Ekiz et al., 2020). The muscle-protective mechanisms of ACEIs, along with their positive influence on gut microbiota, make this drug class an intriguing therapeutic option in gut dysbiosis-induced sarcopenia.

Monoclonal antibodies (MABs)

MABs like bimagrumab, infliximab, and tocilizumab have also appeared as promising candidates against sarcopenia by reversing skeletal muscle loss (Molfino et al., 2016). They positively influence gut microbiota as they improve intestinal microbiota dysbiosis and have a potent anti-inflammatory action (Garito et al., 2017; Seong et al., 2020; Zaragoza-García et al., 2020). Bimagrumab is an antibody against ActRIIB, a mediator in the muscle degradation pathway. This antibody has been shown to check the binding of myostatin and increase lean mass in animal models (Garito et al., 2017). Therefore, the efficacy of these monoclonal antibodies against gut dysbiosis-induced sarcopenia warrants further investigation as they could prove to be potential therapeutic candidates owing to their mechanistic role against muscle atrophy and enhancement of gut microbiota composition.

Regenerative medicine strategies

Another emerging therapeutic option being investigated in treating sarcopenia is regenerative

medicine strategies. Stem/progenitor cells, e.g., satellite cells, perivascular, muscle-derived, embryonic, and induced pluripotent stem cells, are delivered exogenously to compensate for the loss of contractile myofibrillar units by stimulating myogenesis (Naranjo et al., 2017; Neves et al., 2017; Liguori et al., 2018; Bengal et al., 2017). This strategy has already progressed to preclinical studies in mediating skeletal muscle repair; however, it still needs to be investigated in the clinical setting (Naranjo et al., 2017). Chronic inflammation is the major contributor to the reduced regenerative capacity of ageing tissues. In light of this, regenerative cell therapies are also being studied as possible modulators of inflammaging (inflammation progressing with age) caused by altered gut microbiota composition in sarcopenia (Chhetri et al., 2018).

Probiotic and prebiotic therapies

Preclinical and clinical studies have emphasised the administration of prebiotics and probiotics as supplements to recover age-related gut microbiota dysbiosis (Bischoff, 2016). Probiotics are defined as "live microorganisms, when administered in adequate amounts, show a health benefit on the host" and act by improving intestinal barrier integrity, anti-inflammatory action, and promoting microbiota homeostasis (Picca et al., 2018). On the other hand, prebiotics are "selectively fermented ingredients which allow specific changes both in the composition and/or activity in the gastrointestinal microbiota which benefits upon host well-being and health" (Picca et al., 2018). Their effect on gut microbiota includes an increase in butyrate-producing bacteria, thus positively impacting skeletal muscle health in aged people (Liao et al., 2020). Many studies have shown that oral supplementation of probiotics modulates gut microbiota, induces protection against ROS and inflammatory cytokines, and, most importantly, increases the production of SCFAs. Supplementation with multiple *Lactobacilli* probiotics decreased muscle atrophy markers and inflammatory cytokines (Bindels et al., 2012). *Lactobacillus casei* Shirota, a unique probiotic bacterium, was recently proven to induce healthy gut microbiota composition, increased SCFA production, and improved muscle health, in addition to their well-established anti-ROS and anti-inflammatory effects (Joseph et al., 2019; Cervantes-Tolentino et al., 2020). A recently conducted study also evaluated the efficacy of this strain in reversing muscle impairment caused by gut microbiota dysbiosis in aged mice (Chen et al., 2022). The results proved that it successfully attenuated the onset and progression of sarcopenia via the gut-muscle axis. Administration of prebiotic formulations containing *Faecalibacterium prausnitzii*, a prominent producer of SCFAs, reduced systemic inflammation in mice (Munukka et al., 2017). Comparatively, there is little evidence of links between prebiotics and muscle health. One of the studies involved the supplementation of prebiotic curcumin as a nano-bubble showed an increase in grip strength and physical performance in test subjects via changes in gut microbiota composition (Chen et al., 2020b). Another study proved that prebiotic consumption (galactooligosaccharides and inulin combination) led to an increase in lean body mass, demonstrating their positive impact on muscle mass (Desbuards et al., 2012). Apart from these animal studies, a prominent example of prebiotic supplementation was Darmocare Pre®, consisting of inulin and fructooligosaccharides, which positively influenced parameters of muscle strength like endurance capacity and grip strength in frail aged people (Buigues et al., 2016). The efficacy of prebiotics has also been evaluated in combination with other strategies like faecal microbiota transplantation and dietary intervention (Okamoto et al., 2019). Such studies have also proven their positive role in improving muscle function via gut microbiota.

Faecal Microbiota Transplantation (FMT): Restoration of intestinal microbiota

The findings of Picca et al. have shown that there is an increase in *Bifidobacteriaceae*, *Eggerthella*, *Pyramidobacter*, and *Dialister* and a decrease in *Slackia* and *Eubacterium* in the faecal microbiota of older individuals, supporting the gut-muscle axis hypothesis and stressing the importance of restoration of faecal microbiota composition to improve muscle health (Picca et al., 2019). FMT mainly involves the administration of donor faeces to patients to improve their skeletal muscle mass and function (Qi et al., 2021). Increased grip strength and muscle mass were seen upon FMT from healthy human subjects to mice, proving the significance of the gut-muscle axis in sarcopenia and the efficacy of this strategy in countering it (Fielding et al., 2019). The importance of faecal microbial composition was further proved by shotgun metagenomics sequencing study performed between two groups of people belonging to the older community and varying in muscle mass and limb performance (Ticinesi et al., 2020). Microbiome depletion downregulates ubiquitin- mediated proteolysis in skeletal muscle cells in sarcopenic patients. In another exciting study along similar lines, the FMT from obese pigs to germ-free mice resulted in the replication of the fibre type and metabolic profile of the skeletal muscle of the recipients, further implying the positive impact of FMT on muscle health (Yan et al., 2016a). FMT has been considered a more radical option than supplementation with prebiotics/probiotics (Steves et al., 2016; Liao et al., 2020).

Lifestyle and environmental interventions

Exercise

There is a lack of effective pharmacological agents to treat sarcopenia induced by alterations in gut

microbiota. To date, there has not been a single therapeutic approach that has shown satisfactory results. The most effective treatment option suggested in numerous studies is physical therapy or exercise to strengthen muscles. Exercise positively influences gut microbiota via an increase in beneficial microbial metabolites through increased biodiversity of the intestinal microbiome (Bressa et al., 2017; Ticinesi et al., 2019a). Physical activity and targeted nutritional supplementation together hold a promising therapeutic approach to sarcopenia in older patients. The Sarcopenia and Physical fRailty IN older people: multi-componenT Treatment strategies (SPRINTT) project was a multicentre evaluator-blinded randomised controlled trial (NCT02582138) to evaluate the beneficial role of physical activity and nutritional support in older adults with sarcopenia (Bernabei et al., 2022). The results of this multicomponent intervention showed a marked reduction in the incidence of mobility disability in older patients, proving the therapeutic efficacy of this combination in sarcopenia-induced muscle wasting. Also, there are reports from many animal studies that exercise training improves intestinal microbiota composition and functional capacity, independent of diet (Allen et al., 2015; Mika et al., 2015; Campbell et al., 2016; Denou et al., 2016; Mailing et al., 2019). It has been proven to increase the abundance of SCFAs, like butyrate-producing bacteria, which improve gut barrier integrity and modulate the host's immune system (Mailing et al., 2019). Exercise training also reduces the ratio of *Firmicutes* to *Bacteroidetes*, which is otherwise harmful to muscle health (Mika et al., 2015; Denou et al., 2016). Human cross-sectional and longitudinal studies have also made similar observations. Recently, a survey conducted by Bressa et al. (Bressa et al., 2017), proved that three hours of weekly exercise increased the number of *Faecalibacterium prausnitzii*, *Roseburia hominis*, and *Akkermansia muciniphila*, which improves metabolic health and lean body mass index (Dao et al., 2016). Similar results were obtained by Munukka et al. (Munukka et al., 2018), which showed that six to eight weeks of endurance exercise increased the levels of A. muciniphila and decreased the abundance of harmful Proteobacteria. Exercise and physical activity can prove to be a possible strategy in sarcopenia as it improves the homeostatic equilibrium in skeletal muscle through modulation of gut microbial diversity, along with multiple other mechanisms, including increased production of antioxidant enzymes, protein synthesis, anti-inflammatory functions, and levels of anabolic hormones (Gizard et al., 2020).

Lifestyle changes

Lifestyle habits, like reduced physical activity and exercise, impaired nutrition, tobacco smoking, and alcohol consumption, could have detrimental effects on skeletal muscle and accelerate the progression of sarcopenia (Rom et al., 2012). An inactive and sedentary lifestyle, which becomes more prominent with progressing age, leads to increased muscle atrophy and lowered muscle function and quality. A similar adverse impact is caused by dietary insufficiencies like excess calorie intake, and insufficient (< 20 μg/day) intake of vitamin D and protein. Older people are more likely to experience reduced appetite, leading to decreased food intake, which leads to reduced muscle protein synthesis and increased loss of skeletal muscle mass, aiding muscle wasting in sarcopenia. The role of nutrition and physical activity in modulating gut microbiota composition and subsequently contributing to improved muscle health has already been discussed in previous sections. Recently, a study evaluated the impact of daily lifestyle behaviours like food selection, time spent sitting, physical activity, and sleep duration in sarcopenic and non-sarcopenic subjects (Tzeng et al., 2020). This study found all these lifestyle parameters linked to a higher risk of sarcopenia, stressing the importance of a balanced dietary intake, increased physical activity, and reduced sitting time in sarcopenia patients. There is direct evidence of the detrimental effects of alcohol consumption on the intestinal barrier and gut microbiota (Bajaj, 2019). Alcoholism promotes gut microbiota dysbiosis, increasing the taxa involved in compromising gut barrier integrity and promoting the release of inflammatory mediators (Day and Kumamoto, 2022), which warrants the progress of sarcopenia-induced muscle wasting. Alcohol and its metabolites also disturb protein homeostasis in skeletal muscle, which leads to sarcopenia (Dasarathy et al., 2017). Tobacco or cigarette smoking has manifested similar effects on gut microbial status. Cigarette smoking is known to increase the permeability of intestinal mucosa, which increases inflammation and insulin resistance in skeletal muscle (Gui et al., 2021). Cigarette smoking is associated with an increased chronic obstructive pulmonary disease (COPD) incidence. Enhanced cytochrome oxidase (CytOx) activity in peripheral lymphocytes, in turn, increases CytOx activity in skeletal muscles in COPD patients, leading to muscle atrophy (Polverino et al., 2009). It has also been stated that each cigarette consumed daily increases the risk of developing sarcopenia (Locquet et al., 2021), as smoking elevates the expression of genes related to impaired muscle protein syntheses, like myostatin and MAFbx (Petersen et al., 2007).

Water intake

Inadequate dietary water consumption in old age subjects leads to dehydration and its associated complications, which include sarcopenia-induced muscle wasting (Yoo et al., 2018). Water is considered a quintessential nutrient linked to sarcopenia, comprising approximately 76% of muscle mass (Lorenzo et al., 2019). Drinking an adequate amount of water also has a significant role in shaping the human intestinal microbiome and is regarded as a potential source of

abundant and beneficial microbial diversity (Vanhaecke et al., 2022). However, no studies have been conducted to date deciphering the exact mechanism by which increased water intake can reverse sarcopenia and related muscle degradation via alterations to gut microbiota.

Environmental factors

Environment-related factors can also accelerate the progression of sarcopenia by alterations to the gut microbial community. These factors include environmental extremes like heat waves, cold or high altitude, ecological toxicants and pathogens, dust and pollutants, noise, and stress induced by external factors (Karl et al., 2018). The bi-directional relationship between the host and gut microbiota is mediated by the host's availability of a hospitable environment and nutrients. This shapes a favourable gut microbiota composition, which boosts the host's metabolic health by strengthening the gut barrier and potentiating the host's immune system and function (Cani, 2012; Hooper et al., 2012; Karl et al., 2018). Environmental stressor factors disturb this relationship, causing an imbalance between harmful and beneficial taxa of intestinal microbiota. Exposure to high altitudes (≥ 2500 m) causes hypobaric hypoxia, which induces alterations in the gut microbiota population, oxidative stress, and inflammation (Adak et al., 2014; Xu et al., 2014). Exposure to cold has also been evidenced to induce alterations in murine gut microbiota. Chevalier et al. (2015) reported an increased abundance of multiple taxa associated with muscle loss, as well as an increased ratio of *Firmicutes* to *Bacteroidetes* (Chevalier et al., 2015). They reduced the

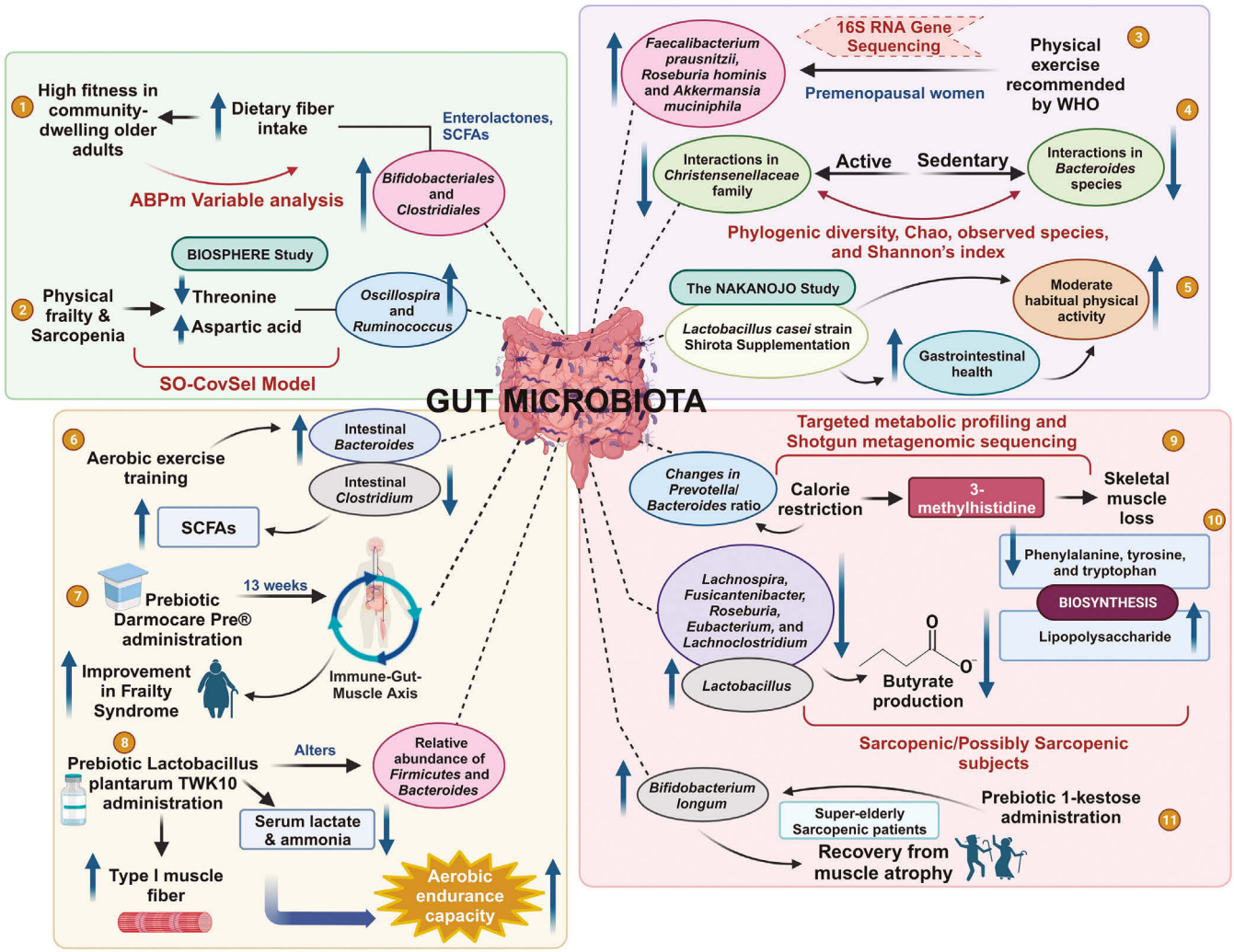

Fig. 3. Gut microbiota targeted in clinical trials. The figure summarises major clinical trials that indicate the role of gut microbiota composition in maintaining physical fitness and skeletal muscle health in the elderly population. Prebiotic or probiotic supplementation used in the trials boosts healthy gut microbiota composition, which positively impacts on muscle recovery in sarcopenia patients. Created in BioRender.com.

count of *Akkermansia muciniphila*, which positively influences muscle health. Heat stress is also detrimental to the gut microbiome (Dokladny et al., 2016) by decreasing microbial diversity and impairment of the intestinal epithelium barrier (Pearce et al., 2014; Sohail et al., 2015), all of which have harmful effects on skeletal muscle cells. Long-term exposure to environmental toxicants and pollutants common to urban environments (soil, air, or water) has been shown to impact adversely on human health. Apart from causing respiratory illness (Sly and Bush, 2019) and cognitive impairments (Sullivan et al., 2018), increasing evidence suggests that these harmful chemicals also have an impact on the gut microbiota of the host (Karl et al., 2018). These effects include increased serum levels of LPS and altered gut microbiota composition. Over eight weeks, exposure to cadmium and lead decreased the abundance of butyrate-producing bacteria (Breton et al., 2013). Mice orally exposed to Benzo[a]pyrene for 28 days resulted in a shift in the microbial community in mice by reducing the count of *Lactobacillus* and *Akkermansia*, potentially anti-inflammatory taxa that promote muscle health, and by decreasing the quantity of the pro-inflammatory bacteria *Turicibacter* (Ribière et al., 2016). Exposure to high levels of particulate matter, a component of air pollution, resulted in increased production of pro-inflammatory cytokines, reduced butyrate production, and increased the ratio of *Firmicutes* to *Bacteroidetes* (Karl et al., 2018). The detrimental effect of toxic environmental factors on gut microbiota promotes sarcopenia-induced muscle wasting. Efforts to minimise exposure of older individuals to these toxins are required to prevent muscle degradation.

Conclusion and Outlook

Sarcopenia, owing to its multifactorial pathogenesis, has significant adverse implications on the quality of life of the older population, which extends to the social and economic front. Many studies have been conducted to date to find an ultimate treatment strategy to recover muscle wasting and improve the physical status of patients. However, the wide array of mechanisms involved in its pathogenesis makes it difficult to target a specific marker and achieve therapeutic efficacy. The gut microbiota has a significant role in mediating multiple mechanisms of sarcopenia like anabolic resistance and chronic inflammation. The association between intestinal microbiota composition and muscle health highlights many novel possible mediators, which may be targeted to reverse the metabolic implications of sarcopenia. Further extensive research is required to understand the significance of the gut-muscle axis in the pathophysiology of age-related sarcopenia. Large sample-size studies need to be conducted to decipher the therapeutic potential of microbiota-based treatment strategies. Combinatorial strategies can be effective in improving muscle health via a multimodal approach by addressing gut-muscle crosstalk rather than individual treatment options, such as dietary supplementation, pharmacological intervention, or exercise alone. The use of novel pharmacological interventions, such as FMT, can be implemented in patients with sarcopenia, along with regular exercise, dietary supplements, and pre/probiotics. Furthermore, patients with sarcopenia can accelerate their recovery process with a comprehensive understanding of lifestyle and environmental factors. Fig. 3 summarises the clinical studies previously conducted to study the correlation between gut microbiota composition, physical fitness, and muscle health. A significant amount of research is necessary to understand how these other factors can modulate gut microbiota, which will enable physicians to make a well-informed decision when treating age-related sarcopenia patients.

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