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LEADING ARTICLE

The Current Landscape of Pharmacotherapies for Sarcopenia

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Abstract
Sarcopenia is a skeletal muscle disorder characterized by progressive and generalized decline in muscle mass and function. Although it is mostly known as an age-related disorder, it can also occur secondary to systemic diseases such as malignancy or organ failure. It has demonstrated a significant relationship with adverse outcomes, e.g., falls, disabilities, and even mortality. Several breakthroughs have been made to find a pharmaceutical therapy for sarcopenia over the years, and some have come up with promising findings. Yet still no drug has been approved for its treatment. The key factor that makes finding an effective pharmacotherapy so challenging is the general paradigm of standalone/single diseases, traditionally adopted in medicine. Today, it is well known that sarcopenia is a complex disorder caused by multiple factors, e.g., imbalance in protein turnover, satellite cell and mitochondrial dysfunction, hormonal changes, low-grade inflammation, senescence, anorexia of aging, and behavioral factors such as low physical activity. Therefore, pharmaceuticals, either alone or combined, that exhibit multiple actions on these factors simultaneously will likely be the drug of choice to manage sarcopenia. Among various drug options explored throughout the years, testosterone still has the most cumulated evidence regarding its effects on muscle health and its safety. A mas receptor agonist, BIO101, stands out as a recent promising pharmaceutical. In addition to the conventional strategies (i.e., nutritional support and physical exercise), therapeutics with multiple targets of action or combination of multiple therapeutics with different targets/modes of action appear to promise greater benefit for the prevention and treatment of sarcopenia.

1 Introduction

Sarcopenia is a skeletal muscle disorder characterized progressive and generalized decline in muscle mass and function. Although it has been mostly recognized as an age-related disorder, it can also result from secondary factors such as bed rest or inflammatory diseases [1, 2]. It has come into the foreground more in recent years, as plenty of solid evidence accumulated on its high prevalence and significant relationship with adverse outcomes like falls, fractures, increased hospitalizations, and mortality [3]. Sarcopenia stands out from other geriatric syndromes because of being a common denominator of the most important geriatric giants such as frailty, malnutrition, or disabilities [4].

Key Points

Currently there is no approved pharmacological treatment for sarcopenia. Exercise and ideal nutritional intake covering optimal/adequate energy, protein, vitamin D, and other nutrients (in particular omega-3 fatty acids and essential micronutrients) are the mainstay of treatment.

Complex multifactorial pathogenesis is one of the main reasons for the failure to find an effective pharmacotherapy for sarcopenia.

Novel interventions or combination therapies that are able to concurrently act on multiple targets seem necessary to elicit an effective treatment for sarcopenia.

Testosterone is the therapeutic agent with the most accumulated evidence regarding its anabolic effects on muscle and safety profile.

The mas receptor agonist BIO101 is at the forefront of having the potential to be a therapeutic agent for sarcopenia.

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Since 1931, the year when Critchley came up for the first time with the concept of "age-related loss of muscle mass," several definitions have been proposed for sarcopenia [5]. More recently, "muscle strength" has replaced "muscle mass" as the central focus of the sarcopenia concept for almost all guidelines [1, 6, 7]. Because, the decline in strength has been reported to precede loss of mass and predicts adverse outcomes better. However, decreased muscle mass is still an important component of sarcopenia that confirms the diagnosis. Sarcopenia was recognized as a disease with an International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) code: (M62.84) for the first time in 2016 [8]. Of note, the 11th revision of ICD was introduced in 2022, and the ICD code for sarcopenia has been revised as FB32.Y. However, a global consensus definition of sarcopenia does not exist, yet. Consequently, the use of different definitions and diagnostic algorithms make reported prevalences, and outcomes of sarcopenia highly variable and inconsistent in the literature, hindering advances in the field. To this end, an international initiative called "Global Leadership Initiative in Sarcopenia (GLIS)," including all the consensus groups that have proposed currently used definitions [Australian and New Zealand Society for Sarcopenia and Frailty Research (ANZSSFR), Asian Working Group for Sarcopenia (AWGS), European Working Group on Sarcopenia in Older People (EWGSOP), and Sarcopenia Definitions and Outcomes Consortium (SDOC)], has been launched very recently to overcome this conflict by producing an inclusive definition that can be widely accepted by all global consensus groups [9, 10].

While waiting for a single valid definition, there have been several attempts to find a pharmacological cure for sarcopenia. However, only a few resulted in promising findings [11]. Unfortunately to date, there is no US Food and Drug Administration (FDA) or European Medicines Agency (EMA)-approved pharmacological treatment for sarcopenia. To date, the only management means to counteract the effects are adequate, high-quality protein intake, adequate energy and nutritional intake covering essential micronutrients, and physical exercise [12, 13]. However, these means are not always easily applicable when the case is "older adults." Not all older adults are candidates for a sound exercise program, and/or trained therapists and special equipments are not readily available in most settings. In addition, anorexia of aging and other common causes of anorexia, such as polypharmacy and comorbid diseases are common and frequently hamper adequate protein, energy, and overall nutritional intake. Furthermore, there is certainly room for better management, even if the current management strategies can be applied efficiently. To this end, effective pharmacological agents are required to prevent the burden of sarcopenia and related outcomes in the aging world.

The most important reason for failing to find an effective therapeutic is probably that the complex multifactorial pathway underlying the disorder, sarcopenia, does not fit the standalone/single disease paradigm adopted in medicine [14, 15]. Various trials targeted single or few mechanistic points or pathways, which were reported or likely involved in the pathogenesis of sarcopenia and came up with conflicting results [16]. In this article, we aimed to detail the complex pathophysiological pathway of sarcopenia, thereby outlining the possible targets or pathways for effective treatment(s). We review the completed and/or ongoing trials for pharmacological treatments so far and present future directions of therapeutic options.

2 Pathophysiology of Sarcopenia

Sarcopenia is a complex multifactorial geriatric syndrome. The underlying etiological factors and pathways are not fully understood. Both intrinsic factors within the muscle (e.g., apoptosis or autophagy) and systemic factors (e.g., hormonal changes and inflammatory status) can lead to the development of structural and functional deterioration in muscle [17–19]. The etiological factors of sarcopenia are detailed below (Fig. 1).

2.1 Imbalance in Muscular Protein Turnover

2.1.1 Muscle Protein Synthesis

Muscle protein synthesis is triggered by anabolic stimulants like insulin, insulin-like growth factor-1 (IGF-1), branched-chain amino-acids (BCAA) (i.e., leucine, isoleucine, and valine), and exercise [20]. These anabolic stimulants provoke protein synthesis by activating a complex signaling pathway in muscles. The key molecule of this pathway is the mammalian/mechanistic target of rapamycin (mTOR). Two biochemically and functionally distinct mTOR complexes exist: mTORC1 and mTORC2. Both complexes include mTOR as their common catalytic subunit and each has unique components and actions. mTORC1 promotes and controls protein synthesis and mTORC2 regulates cell survival and metabolism [21].

Upon binding to the IGF receptor, insulin and IGF-1 cause the IGF receptor to phosphorylate and promote several steps of reactions leading to the activation of phosphoinositide 3-kinase (PI3K) and Akt (protein kinase B) thereafter. Akt phosphorylates tuberous sclerosis complex (TSC) 1–2, leading to activation of mTORC1 [22]. The other effective anabolic agents like BCAA and acute resistance exercises can directly activate mTOR, without the requirement of activation by Akt [23, 24]. mTORC1 triggers translation and

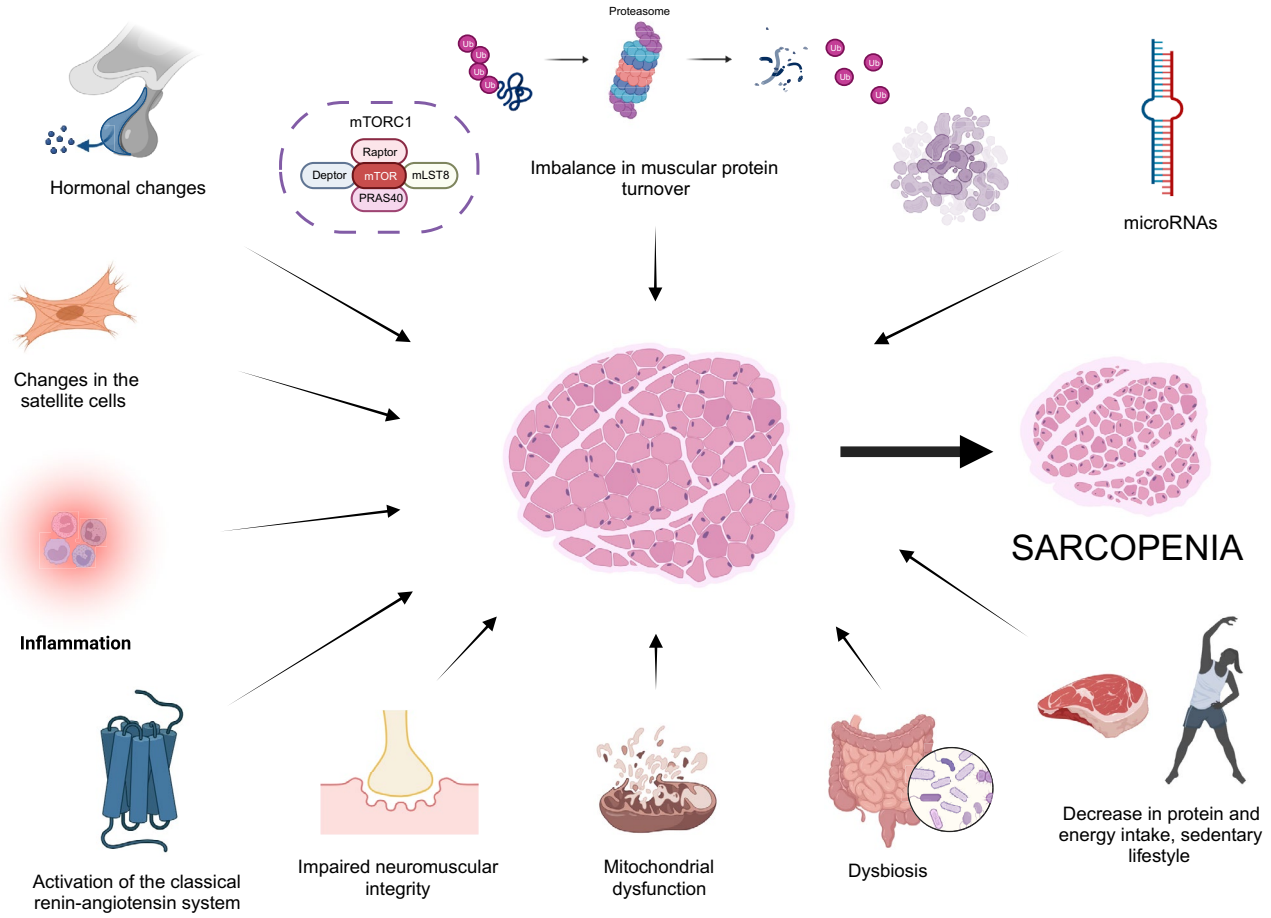

Fig. 1 The pathophysiology of sarcopenia. *Fig. 1 was created with BioRender.com

protein synthesis by activating the downstream kinase S6 kinase 1 (S6K1) and inhibiting eukaryotic translation initiation factor 4E-binding protein 1 (4E-BP1) [25], by the action of its three core components: mTOR, raptor (regulatory protein associated with mTOR), and G protein β-subunit-like protein (GβL) [also known as mammalian lethal with Sec13 protein 8 (mLST8)] [26]. Akt also decreases protein degradation by phosphorylation and inhibition of the *forkhead box protein O (FOXO) family of proteins*. When active, FOXO translocate from cytosol to nucleus to promote transcription of atrophy-related genes [i.e., *atrogin-1 (also called muscle atrophy F-box; MAFbx)* and *muscle RING finger protein-1 (MuRF-1),* the two muscle-specific *E3-ubiquitin ligases* that are increased transcriptionally in skeletal muscle under atrophy-inducing conditions] [27, 28] (Fig. 2).

Several studies conducted on both humans and rodents reported that the initiation of translation with the abovementioned anabolic stimuli is hampered in older samples. This blunted response was thought to be caused by diminished mTOR signaling with increased age [29–31]. Reduced circulatory IGF-1 and IGF-1 mRNA levels, and increased IGF-binding proteins with increased age consequently cause lesser activation of Akt signaling, and thereby, decreased muscle synthesis and increased muscular breakdown [24, 32, 33]. On the other hand, some recent studies reported contradicting results on the activity of Akt/mTORC1/S6K1 in aged muscles as well. Accordingly, hyperphosphorylation of *mTORC1* was also observed in aged muscles, and contrary to expectation, this hyperactivation did not induce protein synthesis, because it ended up with "dysregulated *mTORC1*" [34, 35]. The dysregulated *mTORC1* creates a complex process of anabolism and catabolism, and this imbalance causes muscle fiber damage and loss [36]. Of note, chronic *mTORC1* activation was reported to be caused by defective amino acid and growth factor sensing in senescent cells [37].

Hyperphosphorylation of *mTORC1* might be a reason for anabolic resistance seen in older adults, as anabolic stimuli (nutrients or resistance training)-induced mTOR activation is reduced in aged muscle compared with young muscle [38]. Moreover, reduced mTOR signaling has been linked to longevity, shown to reduce age-related pathologies in model organisms (and in some human studies), and may

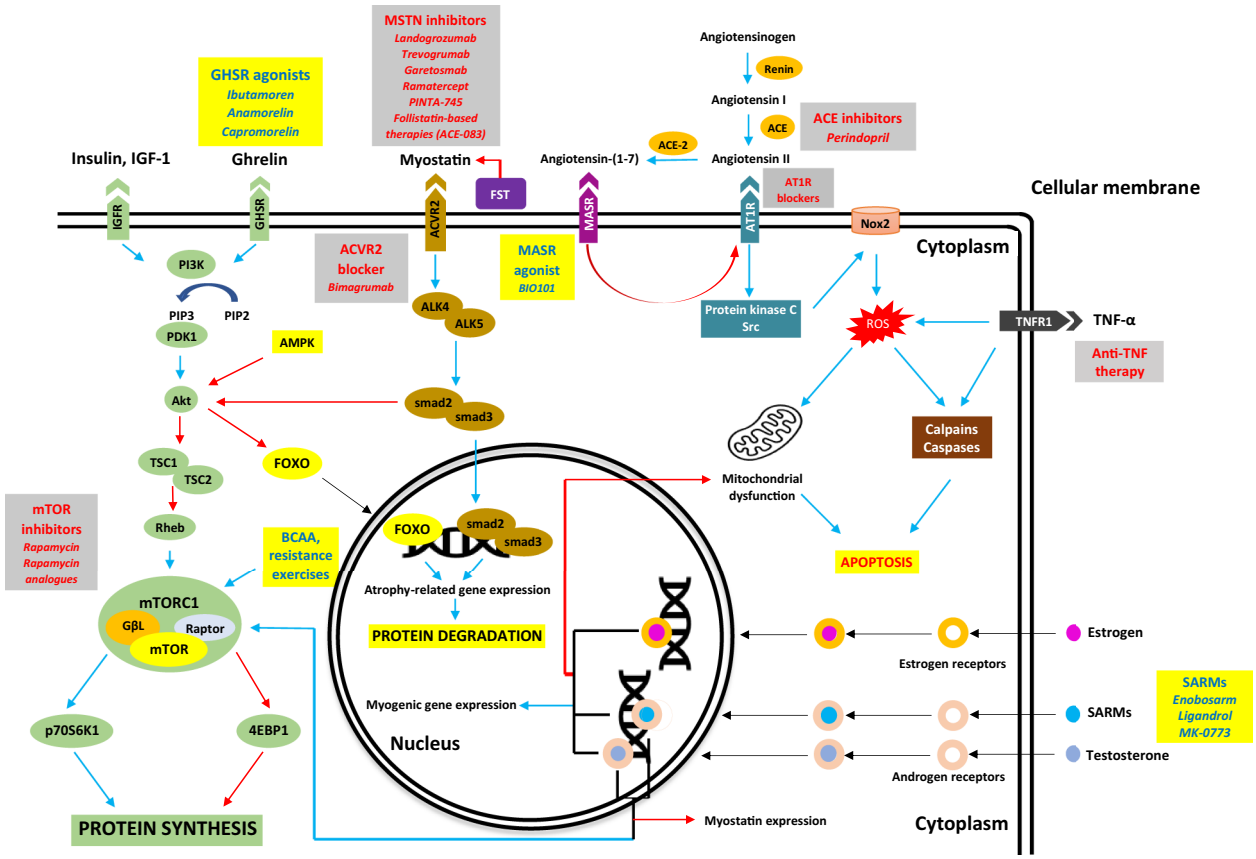

Fig. 2 Signaling pathways in sarcopenia and potential therapeutic agents targeting them. The blue and red arrows indicate promoting and inhibiting effects to the next step, respectively. *4EBP1* eukaryotic translation initiation factor 4E-binding protein 1, *ACE* angiotensin-converting enzyme, *ACVR* activin receptor type 2, *Akt* protein kinase B, *ALK* activin receptor-like kinase, *AMPK* AMP-activated protein kinase, *ARB* angiotensin type 1 receptor blocker, *AT1R* angiotensin type 1 receptor, *BCAA* branched-chain amino acids, *GβL* G protein β-subunit-like protein, *GHSR* growth hormone secretagogue receptor/ghrelin receptor, *FOXO* forkhead BOX O, *FST* follistatin (activin-binding protein), *IGF-1* insulin-like growth factor, *IGFR* insulin-like growth factor receptor, *MASR* mas receptor, *MSTN* myostatin, *mTOR* mammalian target of rapamycin, *mTORC1* mammalian target of rapamycin complex 1, *Nox2* NADPH oxidase II, *p70S6K1* ribosomal protein S6 kinase 1, *PDK* phosphoinositide-dependent protein kinase, *PI3K* phosphoinositide 3-kinase, *PIP2* phosphatidylinositol 45-bisphosphate, *PIP3* phosphatidylinositol 345-trisphosphate, *Raptor* regulatory associated protein of mTOR, *Rheb* Ras homolog enriched in brain, *ROS* reactive oxygen species, *SARMs* selective androgen receptor modulators, *Src* non-receptor tyrosine kinase, *TNFR1* tumor necrosis factor receptor 1, *TNF-α* tumor necrosis factor-α, *TSC* tuberous sclerosis complex

have similar beneficial effects on age-related sarcopenia [21, 39].

2.1.2 Muscular Breakdown

Ubiquitin-proteasome system (UPS) regulated protein degradation is essential to maintain the quality control of proteins in muscle [40]. This system is activated by *transforming-growth factor β (TGFβ)* and *myostatin* (also known as *growth differentiation factor-8*; *GDF-8*); the cytokines which are known to increase with aging. Upon binding to their receptors, they activate *activin receptor-like kinase* (*ALK-4 or ALK-5*), induce the activation of *smad2 and smad3* (the transcription factors that regulate the expression of genes responsible for protein degradation), and *TAK1/p38 mitogen-activated protein kinase (MAPK)* (which regulate the activity of related transcription factors); leading to increased expression of *E3-ubiquitin ligases* called *atrogin-1* and *MuRF-1* in skeletal muscle [41].

Atrogin-1 and *MuRF-1* polyubiquinate target proteins and cause their destruction by proteasomal systems. *Smad2/3* also inhibits *PI3K* and *Akt* pathway, leading to inhibition of protein synthesis (Fig. 2) [41, 42]. Although reports of elevated levels of ubiquitin-conjugated proteins and intramuscular myostatin (GDF-8) with increased age suggest that UPS likely contributes to sarcopenia in humans [33, 43, 44], there are conflicting reports regarding the molecular mechanisms that regulate ubiquitin-mediated proteolysis in sarcopenia. Accordingly, some reports did

not find any increase [33, 45], while others have come up with decreased UPS activity in sarcopenic muscle in animal and human studies [46]. Therefore, it is difficult to draw any firm conclusions about the relationship between UPS and sarcopenia as with many other wasting conditions [47].

Calpain-mediated protein degradation is another way of muscular breakdown. Calpains are calcium-dependent, non-lysosomal cysteine proteases that cleave myofibril proteins that anchor actin and myosin. Calpastatin, the endogenous inhibitor of calpains regulates the activity of the calpain system [48]. Age-related increases in reactive oxygen species (ROS) and proinflammatory cytokines like tumor necrosis factor (TNF) may upregulate calpain-mediated degradation [49]. Oxidative damage leads to impaired calcium (Ca^{2+}) reuptake via sarcoplasmic reticulum and higher intracellular Ca^{2+} concentrations, which promote the activity of calpain system to cause proteolytic cleavage of sarcomeric and cytoskeletal proteins such as titin, dystrophin, nebulin, and desmin. Calpains are also involved in apoptosis (Fig. 2) [47].

Caspases, non-calcium-dependent cytoplasmic cysteine proteases constitute another proteolytic pathway involved in the pathophysiology of sarcopenia. Caspases, particularly caspase-3, play an important role in apoptosis, and this appears to be its main action in the context of sarcopenia (Fig. 2) [47, 50]. Caspases were also reported to prompt the degradation of the actin–myosin complex and thereby muscular breakdown [48].

The other way of muscular breakdown is autophagy. Autophagy is a protective mechanism of cells to survive in response to stress like starvation or exercise [51]. During fasting, *Akt* is suppressed, and *AMP-activated protein kinase (AMPK)* is activated, leading to suppression of the mTOR pathway, which allows the *Unc-51-like autophagy activating kinase 1 (ULK1)* complex to initiate autophagy [51, 52]. *AMPK* also activates *FOXO3*, leading to increased expression of several autophagy-related (Atg) proteins, and *atrogin-1* and *MuRF-1* [53]. Although it was believed that increased autophagy might be one of the causes of increased muscular breakdown with aging, there are conflicting reports on the role of autophagy in sarcopenia today. Because recent studies also reported that autophagy maintains muscle mass by promoting the selective degradation of misfolded proteins and dysfunctional organelles and that this function declines with aging [54].

2.2 Impaired Neuromuscular İntegrity

With aging, a progressive loss of muscle fibers, especially fast and glycolytic type II fibers, and a decrease in number of motor neurons that innervate muscles occur [55]. Both the nerve terminal areas and the postsynaptic folds at neuromuscular junctions (NMJ) decrease, leading to an impairment in postsynaptic responses, and ending up with lower quantities of neurotransmitter release during depolarization [56]. The dysfunction of Schwann cells that contribute to the maintenance and regeneration of peripheral nerves with aging causes impairment in the reinnervation of denervated muscle fibers [57]. The gradual atrophy and decrease in size and volume of muscles are replaced with the accumulation of fat and fibrous tissue, which interfere with both the quantity and quality of the muscles [58].

2.3 Changes in the Satellite Cells

Satellite cells (or muscle stem cells) are responsible for muscle regeneration, by supporting the repair and remodeling of the muscle fibers to maintain healthy muscle mass. *Pax7* is a transcriptional factor that is essential for regulating the expansion and differentiation of satellite cells. The number of *Pax7* transcription factors expressing satellite cells decreases with age [59]. Also, histone modification of myogenic transcription factors, and chromatin status changes with aging, leading to impaired functioning of satellite cells [60]. Increased myostatin *(GDF-8)* levels and deprivation of *growth differentiation factor-11 (GDF-11)* with aging also deteriorate satellite cell functions [61–63].

Myogenesis takes place by the coordination of transcription factors like *myoblast determination protein (MyoD)*, *myogenic factor 5 (Myf-5)*, and *myogenin* in satellite cells, leading to differentiation to myoblasts [64]. The activity of these transcription factors is enhanced by *myocyte enhancer factor 2 (MEF2)*. All these factors are regulated by *histone deacetylases (HDACs)*, which, in the end, repress the differentiation of myoblasts [65, 66]. Several studies reported elevated levels of HDACs in aged muscle [67, 68]. Likewise, various signaling pathways that take a role in myogenic differentiation like *p38 α/β MAPK* and *fibroblast growth factors (FGF)* become hyperactive and aberrant with aging, which is associated with impaired asymmetric division, depletion of cell pool, and impaired self-renewal capacity of satellite cells [69].

2.4 Mitochondrial Dysfunction

Mitochondrial functions gradually deteriorate as age takes toll. Mitochondria is a major source of cellular energy and free radical signaling, and they can activate apoptotic mechanisms. Impaired mitochondrial biogenesis and function results in reduced ATP production in high energy-consuming muscle cells, increased ROS due to reduction in antioxidant enzyme levels (ending up with mitochondrial DNA mutations), and impaired mitochondrial homeostasis with imbalance in mitochondrial fusion and fission [63, 70]. Increased mitochondrial fusion to complement damaged mitochondria results in giant mitochondria, which are difficult to remove from cells [71]. As the number of damaged mitochondria accumulates, the healthy and

functional mitochondria to complement the damaged ones gradually decrease, resulting in damage in mitochondria membrane potential and leakage of the mitochondria content in the cell cytosol, and this triggers apoptosis (Fig. 2) [72]. As a result of these deregulations, about 27% reduction in the motor unit pool takes place [73–75].

2.5 Inflammation

Aging is associated with an increase in dysfunctional proinflammatory molecules [i.e., TNF-α, interleukin-1 (IL-1), C-reactive protein (CRP), chemokines, etc.] [76] and increased oxidative stress, causing chronic systemic low-grade inflammation known as "inflammaging" [77, 78]. This condition predisposes not only diseases like type 2 diabetes mellitus (T2DM) and osteoarthritis, but also sarcopenia by impairing muscle protein synthesis by reducing the anabolic effect mediated by IGF-1 and increasing proteolysis via stimulating apoptotic pathways and *UPS* (Fig. 2) [79]. Immune cells and factors change the muscle microenvironment, affecting muscle regeneration [78]. The inflammation-induced activation of the *NLRP3* inflammasomes results in "*pyroptosis*," which is an inflammatory mode of regulated cell death. *NLRP3* inflammasomes and pyroptosis cause changes in the muscle synthesis environment and a decline in myofiber size, leading to sarcopenia [80].

Moreover, aging and chronic inflammatory status stimulate the differentiation of fibro-adipogenic progenitor (FAP) cells into fibrocytes and adipocytes, causing inter- and intramuscular infiltration of fat and fibrotic tissue, and causing sarcopenia [81].

Cellular senescence is closely related to inflammaging. It is defined as a permanent cell cycle arrest, and characterized by telomere shortening, increased ROS and DNA damage, and the secretion of inflammatory molecules such as IL-1α, IL-6, IL-8, and NF-KB, causing the *senescence-associated secretory phenotype* (*SASP*) [82, 83]. The accumulation of senescent cells and SASP contribute to sarcopenia by an increase in muscle degradation, and hampered muscle regeneration by affecting the normal functioning of satellite cells [84, 85].

2.6 Hormonal Changes

Aging brings hormonal alterations that have significant effects on muscle mass and functions [86]. Sex hormones [e.g., testosterone, dehydroepiandrosterone (DHEA), and estrogens], growth hormone, and IGF-1 decrease with aging leading to changes in body composition, i.e., decrease in lean body mass (LBM) and bone mineral density (BMD) and increase in visceral adiposity [87, 88]. Testosterone levels decline by about 1% each year after 30 years of age and are associated with a decrease in muscle strength and mass [89, 90]. The decline in estrogen levels appears to trigger apoptotic pathways to contribute loss of muscle mass [91]. The decline in ghrelin with aging is suggested as one of the etiological factors in sarcopenia [92]. In addition, the decrease in vitamin D levels, which is frequently encountered in older age, is significantly associated with decline in muscle functions [88]. On the contrary, aging is also associated with rising levels of cortisol, which may contribute to an increase in visceral adiposity and fat mass, insulin resistance, and decreased LBM and BMD [93, 94]. These changes in body composition may cause sarcopenic obesity, that is considered as a unique condition different from sarcopenia or obesity alone in terms of its pathogenesis and related outcomes [95].

When the chronic low-grade inflammatory status that aging brings is superimposed on the body composition changes seen with aging, anabolic resistance to the effects of insulin takes place. Increased adiposity also aggravates the chronic inflammatory state, and creates a vicious cycle, leading to further loss of skeletal muscle reserves, and causing sarcopenia and sarcopenic obesity [94, 96].

2.7 Renin–Angiotensin System (RAS)

RAS system is far more complex than previously conceived as if it was a linear hormonal system involved in blood regulation and fluid homeostasis [97]. Angiotensinogen is synthesized in the liver and converted to angiotensin I (Ang I) by renin. Today we know that two distinct pathways develop after this step, namely classical and non-classical RAS. In the classical pathway, Ang I is converted to Ang II by the Ang converting enzyme (ACE), and Ang II binds to Ang II receptor type 1 (AT1R) or 2 (AT2R), demonstrating opposite actions on peripheral blood flow and metabolism. In the non-classical pathway, Ang I or Ang II is converted to Ang-(1-7), and it binds to another G-protein coupled receptor *mas (masR)*, acting opposite to the axis of Ang/AT1R actions on blood flow and metabolism [97, 98] (Fig. 2).

The classical pathway is the major effector of atherosclerosis, and its activation triggers inflammation, oxidative stress, and endothelial dysfunction. Aging and several diseases such as hypertension, congestive heart failure, and chronic kidney disease were demonstrated to induce muscle atrophy through activation of the classical RAS pathway [99]. Ang II binds AT1R and activates the downstream *protein kinase C* and/or *Src* pathway. This leads to the activation of *nicotinamide adenine dinucleotide phosphate* (*NADPH*) *oxidase II* (*Nox2*), which upregulates the production of ROS [16]. This process contributes to protein degradation, decreased protein synthesis, increased fibrosis, and apoptosis [16, 98, 100]. On the contrary, the

non-classical pathway was shown to exhibit protective effects by inhibiting ROS-mediated effects and myonuclear apoptosis and stimulating the anabolic processes of the protein synthesis in skeletal muscle [101], hence emerging as a potential therapeutic target (Fig. 2).

2.8 MicroRNAs (miRNAs)

miRNAs are small, non-coding RNAs that inhibit the function of targeting mRNAs by destabilization and inhibition of translation [102]. miRNAs play a pivotal role in sarcopenia as they regulate satellite cell quiescence and renewal, the function of the IGF-1/PI3K/Akt pathway, mitochondrial function, and fat infiltration in muscles [71, 103]. Various miRNAs have shown to increase or decrease in muscles and blood in sarcopenia [104–107]. Moreover, overexpression of different miRNAs has been demonstrated to affect sarcopenia in either a positive or negative way, depending on studied miRNAs in in vitro or in vivo models [106, 107]. Therefore, miRNAs are claimed to be potential biomarkers and targets of gene therapy for sarcopenia [108].

2.9 Dysbiosis

A limited number of studies suggest that the gut–muscle axis is involved in the pathogenesis of sarcopenia [109, 110]. An altered diet, reduced physical activity, and medications contribute to age-associated dysbiosis [111]. It has been suggested that dysbiosis affects protein metabolism by hampered cleavage of undigested peptides by healthy gut microbes, which are reduced in number and by increased protein fermentation through an abundance of unhealthy species, causing reduced postprandial delivery of amino acids for muscle protein synthesis [109]. Moreover, age-associated dysbiosis and thinning of the mucin layer increase mucosal permeability, which permits *pathogen-associated molecular patterns* (*PAMPs*) to translocate into the circulation and trigger a low-grade systemic chronic inflammation [111]. Decreased abundance of certain microbial communities producing anti-inflammatory short-chain fatty acids (SCFA) like acetate, butyrate, and propionate promotes insulin resistance and mitochondrial dysfunction and supports intramuscular fatty acid deposition, contributing to sarcopenia [112].

2.10 Behavioral Factors

Aging brings loss of appetite and reduced oral intake, which is termed "anorexia of aging." Anorexia of aging is a multifaceted condition that results from diminished hunger and satiety control mechanisms (i.e., reduced ghrelin and neuropeptide Y and increased leptin, cholecystokinin, peptide YY, and insulin levels), age-related gastrointestinal motility changes (decreased stomach compliance and delayed gastric emptying causing early and postprandial satiety), and other factors such as alterations in taste and smell sensation, neuropsychiatric problems, drugs, financial problems, etc. [113, 114]. The decline in protein and energy (calorie) intake causes a decrease in muscle protein synthesis and contributes to muscle degradation, leading to sarcopenia [94, 115]. Likewise, physical activity gradually decreases by about 40–50% with the aging process, thereby more sedentary lifestyle increases the likelihood of older individuals developing sarcopenia [116]. Decreased activity contributes to a decrease in appetite by causing fewer calorie needs [117].

3 Current Treatment of Sarcopenia

The basic treatment of sarcopenia at present depends on non-pharmacological strategies, i.e., exercise, optimum energy (calorie), and protein intake/protein supplementation, and optimum intake of vitamin D and essential micronutrients [13, 118–121]. Resistance training is accepted as the most effective way to improve muscle mass and functions [118]. Likewise, aerobic training is also known for its beneficial effect in not only improving muscle mass and functions but also endurance and cardiovascular well-being [119].

Adequate protein, calorie, and vitamin D intake is essential to maintain muscle health. To prevent muscle loss, the recommended daily protein intake for healthy older adults is 1.0–1.2 g/kg body weight (BW), for older individuals with acute or chronic diseases it is 1.2–1.5 g/kg BW, and for older individuals with critical illness or malnutrition it is up to 2.0 g/kg BW [120]. Vitamin D replacement is especially recommended for individuals suffering its deficiency since it is reported to improve muscle functions, falls, and mortality in older people with deficiency [121, 122]. The benefit of vitamin D supplementation on muscle functions has been reported, particularly in older women with very low vitamin D levels (< 25 nmol/L or < 10 ng/mL) and without oversupplementation (< 1000 IU/day) [121, 123]. Omega-3 (n3-polyunsaturated fatty acids; n3-PUFA) supplementation was also reported to be beneficial for muscle mass and volume, with more evident effects with higher doses (> 2 g/day) [124]. Omega-3 may positively affect muscle protein synthesis response to anabolic stimuli, alleviating age-related anabolic resistance. It also seems to improve muscle strength and physical performance, although the evidence is conflicting and comes from meta-analysis with high protocol heterogeneity [125]. Selenium, magnesium, and inorganic nitrate have also been studied as dietary intake or supplements in clinical studies and appear to have a potential association with muscle performance and physical activity in older adults, but the evidence is limited compared with omega-3 [13, 126]. Creatine intake during resistance

training is also suggested to increase the ability to exercise at high intensities and enhance postexercise recovery and adaptation in older adults [124]. Overall, healthier diets of higher quality across adulthood are linked not only to lower risks of noncommunicable diseases like diabetes or cancer, but also to the preservation of muscle mass and function [127].

4 Pharmacological Therapy of Sarcopenia

Apart from the mentioned conventional approaches, several pharmacological interventions for sarcopenia have been tested over the years, without providing evidence as solid and consistent as exercise and nutrient support. At the time this article was written (March 2023), there were 60 clinical trials registered in ClinicalTrials.gov that explored/exploring different pharmacological interventions for sarcopenia, with 28 articles published on these studies (Supplementary Table 1) [128–155]. As research continues, new potential treatments have emerged giving prospects for the treatment of sarcopenia. We are going to summarize the pharmacotherapeutic options for sarcopenia with the latest knowledge, by categorizing the potential interventions according to the abovementioned pathophysiological pathways. For this purpose, we performed a non-systematic literature review on the databases PubMed and Google Scholar until March 2023 for clinical trials, observational studies, reviews, meta-analyses, and editorials published in English and that have an abstract and full-text. We used keywords such as "sarcopenia (MeSH)," "therapeutics (MeSH)," "drug therapy (MeSH)," "pharmaceutical preparations (MeSH)," "pharmacotherapy," and names of the pharmacotherapeutic options mentioned in the literature for sarcopenia [i.e., "testosterone (MeSH)," "androgens (MeSH)," "selective androgen receptor modulators," "selective estrogen receptor modulators (MeSH)," "dehydroepiandrosterone (MeSH)," "insulin (MeSH)," "metformin (MeSH)," "glucagon-like peptide-1 receptor agonist," "sodium-glucose co-transporter-2 inhibitor," "thiazolidinediones (MeSH)," "growth hormone (MeSH)," "insulin-like growth factor-1," "ghrelin (MeSH)," "ghrelin receptor agonist," "myostatin inhibitor," "activin receptor inhibitor," "renin-angiotensin system inhibitor," "mas receptor agonist," "mTOR inhibitor," "espindolol," "indoxyl sulphate," "fast skeletal muscle troponin activators," "elamipretide," and "anti-TNF"] during our search. We did not include supplemental interventions in our research. We performed our search without any limitation for the publication year. The earliest report cited in this article was published in 1990 (with the exception of age-related loss of muscle mass concept proposed by Critchley in 1931).

4.1 Hormonal Therapies

4.1.1 Testosterone

Androgen receptors (AR) are expressed in satellite cells and myoblasts. Upon binding to the AR in cytoplasm, testosterone translocates AR to the nucleus to promote myogenic gene expression [156]. Testosterone promotes protein synthesis by stimulating Akt/mTOR and inhibits protein degradation by suppressing FOXO-targeted gene expression in cellular and animal models [28]. Moreover, testosterone stimulates the entrance of satellite cells into the cell cycle and their proliferation by suppressing myostatin expression [157, 158]. Testosterone also improves the fusion of myoblasts and increases the utilization of amino acids from muscle breakdown [159–161]. Furthermore, testosterone also co-regulates mitochondrial biogenesis, dynamics, and autophagy with estradiol to maintain mitochondrial function in skeletal muscle [162].

Testosterone is the therapeutic option with the most accumulated evidence of an anabolic effect on muscle, particularly in older men with low testosterone levels (< 200–300 ng/dl) [94, 121, 163]. The anabolic effects of testosterone are reported to be dose dependent to a certain extent. In lower doses, testosterone increases protein synthesis and thereby, increases muscle mass [164, 165]. In higher doses, it activates satellite cells and reduces adipose stem cells [158]. The dose-dependent anabolic effects were reported not only for hypogonadal men but also for eugonadal older men and healthy young men [166]. Alongside its almost ubiquitous, dose-dependent anabolic effect on muscle mass, the effects of testosterone replacement on muscle strength and function are also supported by recent studies. A recent meta-analysis showed that testosterone significantly increased lean body mass of 2.54 kg, increased handgrip strength of 1.58 kg, and concluded that testosterone replacement therapy improved sarcopenia components, i.e., primarily muscle mass, then strength and physical performance in middle-aged and older men [167]. Testosterone trials (TTrials) were a set of placebo-controlled, double-blind trials conducted on 788 older men with low testosterone levels [168]. The Physical Function Trial was one of seven TTrials and showed that 1-year testosterone gel administration did not increase the distance walked in 6 min in men whose gait speed was low. However, in all TTrial participants, testosterone increased the distance walked [169]. In fact, the methodology of the studies, the study populations, treatment regimens, route of administration, duration of treatments, and even the ester of testosterone and pharmaceutical formulation vary widely among testosterone trials in the literature. Therefore, outcomes show moderate-to-high heterogeneity [167]. Therefore, additional studies are still needed to elucidate the muscle–testosterone relationship.

It is well known that testosterone is associated with some adverse effects like erythrocytosis, fluid retention, exacerbation of sleep apnea, and potential growth of prostate cancer [170, 171]. However, there are a growing number of studies demonstrating no increase in prostate cancer incidence among men on testosterone replacement [172]. Moreover, there are studies with prostate cancer reporting no significant increase in disease progression with testosterone replacement [173, 174]. Of note, the poor evidence in the literature regarding the safety of testosterone replacement in terms of progression and recurrence in prostate cancer survivors is mostly deriven from the studies including low risk patients with Gleason score < 8 [175]. Therefore, the safety of its use in prostate cancer has not yet been established.

The cardiovascular side effects such as increased risks of myocardial infarction and stroke are still controversial, as some recent meta-analyses did not demonstrate any significant association between testosterone and cardiovascular events [176, 177]. Moreover, some studies reported that testosterone replacement in androgen-deficient men resulted in a lower risk of cardiovascular outcomes [178, 179]. Testosterone supplementation resulting in physiological levels of testosterone (i.e., 280–873 ng/dL or 9.6–30 nmol/L) [175] is generally well-tolerated [121]. Adverse effects such as increased risk of prostate cancer, erythrocytosis, and fluid retention are dose dependent and more frequent with doses producing supraphysiological levels [71, 180] (Table 1). *In summary, testosterone is the therapeutic agent embodying the richest evidence for improving muscle mass and strength, while worrisome adverse effects like increased cardiovascular events and prostate cancer should be considered especially with supraphysiologic doses. The ideal treatment regimen (dosage, formulation, and duration) promising the optimum risk-benefit balance between effectiveness and adverse effects of testosterone for older adults with sarcopenia is still under investigation.*

4.1.2 Selective Androgen Receptor Modulators (SARMs)

SARMs are a class of androgen receptor ligands developed to eliminate androgenic effects on skin and prostate and specify them to certain tissues and organs like muscles and bones. Several steroidal and nonsteroidal SARMs have been produced and undergone clinical trials. MK-0773 (TFM-4AS-1) is a steroidal, orally active dual-SARM that also has the action of inhibiting 5α-reductase [an enzyme that converts testosterone into its more potent form, dihydrotestosterone (DHT) in skin and prostate], thereby further reducing unwanted androgenic effects of DHT [181, 182]. In a phase II randomized controlled trial (RCT), MK-0773 showed a significant improvement in lean body mass (LBM) but did not improve muscle strength and functions in older women with sarcopenia [145]. In another phase II RCT, enobosarm (GTx-024), an orally bioavailable nonsteroidal SARM, showed a dose-dependent improvement in LBM and stair climb in 120 older men and postmenopausal women [183]. In another phase III trial, enobosarm significantly increased LBM in male and postmenopausal female patients with cancer [184]. Another novel nonsteroidal SARM ligandrol (LGD-4033, VK5211) also showed dose-dependent improvement in LBM in a phase I clinical trial including 76 healthy young men [185]. Concerning their hepatotoxicity and unpredictable post-dose prognosis, safety warnings were released by the FDA. Hence, SARMs have not yet been approved under any clinical condition including sarcopenia [186] (Table 1). *Overall, although they were developed as alternative anabolic agents to testosterone due to safety concerns, the effects of SARMs on muscle still need to be solidified with further evidence. Therefore, long-term follow-up trials are needed to demonstrate the long-term safety and efficacy of SARMs.*

4.1.3 Dehydroepiandrosterone (DHEA)

DHEA is a steroid hormone produced mainly in the adrenal gland and also a prohormone precursor that is converted to testosterone in men and estrogen in women. Serum DHEA levels are associated with bone and muscle health and decline steadily by approximately 80% between ages 25–75 years [187]. Therefore, over-the-counter oral DHEA supplementations have been consumed to increase both DHEA and testosterone levels. Several reports on DHEA supplementation have come up with the enhancement of physical and psychological well-being, sexual functions, and insulin sensitivity [188–190]. In terms of sarcopenia components, a recent meta-analysis has shown that 50–90 mg/day DHEA supplementation significantly improved lean body mass in older women [191]. According to another study reporting pooled analysis of clinical trials about sex-specific effects of 50–75 mg/day DHEA supplementation on body composition parameters, it was shown that DHEA did not cause any significant improvement in LBM in either older men or women [192]. A phase III, randomized controlled trial with 64 older men and women reported that 50 mg/day DHEA alone did not result in improvement in muscle mass or strength. However, it potentiated the effect of resistance training exercises on muscle strength and volume [136]. Side effects of DHEA are generally mild and transient; androgenic side effects are the most common. DHEA supplementation is contraindicated in patients with sex steroid-dependent prostate, breast, and endometrial cancers [187] (Table 1). *The positive effect of DHEA on sarcopenia components is inconclusive and*

Table 1 Pharmacotherapeutic options for sarcopenia: details on their target, action, benefit, adverse effects and concluding remarks

Drug	Target	Action	Benefits on sarcopenia components	Adverse effects	Remarks
Testosterone	Androgen receptor	Exerts a dose-dependent effect: in lower doses, it increases protein synthesis by stimulating Akt/mTOR. In higher doses, it activates satellite cells and reduces adipose stem cells	Alongside its dose-dependent anabolic effect primarily on muscle mass, it also improves muscle strength and physical performance	Erythrocytosis, fluid retention, exacerbation of sleep apnea, conflicting reports on increased risk of cardiovascular diseases and prostate cancer	Testosterone is the agent with the most accumulated evidence regarding its effects on skeletal muscle. The anabolic effects are dose-dependent and was demonstrated primarily in hypogonadal older men. The ideal treatment regimen (dosage, formulation and duration) for use in the indication of sarcopenia remains to be elucidated
SARMs	Androgen receptor	Upon binding to androgen receptor, SARM+AR complex translocates to nucleus to promote myogenic gene expression	The anabolic effect of SARMs seems to be mostly dose dependent and pronounced on mass component	Hepatotoxicity, increased risk of heart failure or stroke	SARMs are safe regarding androgenic side effects compared to testosterone. More evidence is needed to demonstrate its anabolic effects on sarcopenia components and its safety profile
DHEAs	Androgen receptor, estrogen receptor	DHEA induces acceleration of steroidogenesis and improves glucose and lipid metabolism in skeletal muscle	Data regarding its effect on muscle mass and function are inconsistent	Androgenic side effects (acne, hirsutism, etc), contraindicated in sex steroid-dependent cancers	DHEAs may improve muscle mass and function in older patients when combined with exercise. However, more evidence is needed to recommend its use in sarcopenia
Estrogen-based treatments	Estrogen receptors	Estrogen promotes muscle regeneration and repair and prevents protein degradation and apoptosis	Controversial effect on muscle function, small but insignificant positive effect on mass component in postmenopausal women	Increased risk of breast and endometrial cancer, cardiovascular disease, and deep vein thrombosis	Not recommended for sarcopenia treatment due to insuffient evidence on their anabolic effect and potential adverse effects
SERMs	Estrogen receptors	Exerts estrogen-agonistic effect on muscle through ERα receptors	Little evidence of positive effect on FFM, with no demonstrated effect on muscle function	Leg cramps, hot flushes	Maintanence of weight and increase in FFM in older postmenopausal women requires further research, especially as it has promise for use in chronic diseases accompanied by weight loss and sarcopenia

Table 1 (continued)

Drug	Target	Action	Benefits on sarcopenia components	Adverse effects	Remarks
Growth hormone	GH receptor	Stimulates the production of IGF-1 from many tissues, mainly the liver	Little evidence regarding its anabolic effect on muscle mass. Available evidence does not suggest any benefit in terms of muscle function	Gynecomastia, carpal tunnel syndrome, soft tissue edema, hyperglycemia, arthralgia	Unfavorable benefit/risk balance makes GH an inappropriate intervention for sarcopenia
IGF-1	IGF-1 receptor	Stimulates PI3K/Akt pathway, leading to muscle hypertrophy through the promotion of anabolic effects.	Limited evidence regarding its anabolic effects on muscle. High doses were reported to improve muscle strength in older women with hip fracture	Lipohypertrophy and erythema at the injection site, headaches, myalgia, jaw pain, edema, hypoglycemia, seizures, altered liver function	Positive effect on muscle strength was shown with high doses. Further studies are warranted to elucidate its effect on sarcopenia and its components
Insulin	Insulin receptor, IGF-1 receptor	Stimulation of PI3K/Akt pathway for anabolic response, muscular blood flow, and amino acid delivery	Insulin treatment may overcome blunted anabolic response in patients with DM by preservation of increase in muscle mass. Evidence is scarce for its effect on muscle function	Hypoglycemia, weight gain, injection site reactions	No indication for its use in sarcopenia in patients without DM. Chronic use appears to help preserve muscle mass reserve in the course of DM. More studies are needed on its net effect on sarcopenia
Metformin	Multiple targets	Effects on autophagy, inflammatory pathways, and mitochondrial biogenesis	Metformin 1500 mg/day resulted in significant increase in physical performance in older adults with prefrailty. Conflicting results regarding its effect on mass component	Loss of appetite, risk of malnutrition and weight loss, vitamin B12 deficiency, lactic acidosis	Its anorectic effect and conflicting evidence on sarcopenia components suggest that metformin is not an ideal drug for the treatment of sarcopenia
GLP-1RA	GLP-1 receptor	Stimulates insulin secretion, improves endothelial function, reduces inflammatory factors and myostatin expression	Conflicting results on its effect on mass component. No potential positive effects on muscle function was reported	GI intolerance (nausea, vomiting, diarrhea), weight loss, increased risk of malnutrition and dehydration, injection site reactions, nasopharyngitis	Although GLP-1RA can be useful in sarcopenia treatment in a theoretical basis, evidence is very limited. Since it has a high weight loss effect, it has the potential to have a negative impact on muscle health by causing muscle loss
SGLT-2 inhibitors	SGLT-2	Enhance fatty acid oxidation and ketogenesis, reduce RAS activity	Evidence shows that SGLT-2i use causes decline in SMM and SMMI in follow-up	Modest–intermediate weight loss, ketoacidosis, dehydration, postural hypotension, increased risk of falls, and urogenital infections	Since their weight loss effects are not as strong as GLP1-RA, the effects of lipolysis and fatty acid oxidation may be beneficial to muscle, especially in obese sarcopenics, but there is no evidence compatible with this theory

Table 1 (continued)

Drug	Target	Action	Benefits on sarcopenia components	Adverse effects	Remarks
Thiazolidinediones	PPARγ	Enhance insulin sensitivity, reduce apoptosis, NF-κB transcription, and muscle lipid content	There is no solid evidence regarding its anabolic effect on muscle mass. It may potentiate the effect of resistance training in obese/overweight women on muscle power	Weight gain, fluid retention and edema, increased risk of bone fractures, potential risk of bladder cancer	The effect of lowering muscle lipid content may be more pronounced in sarcopenic obesity treatment with combined resistance training. Still, further well-designed trials are required to elucidate the effects on sarcopenia
Ghrelin receptor agonists	GHSR	Promote protein synthesis by activating PI3K/Akt/mTOR pathway and mitochondrial biogenesis, inhibit inflammatory factors	Anabolic effect on muscle mass was reported mostly in small scale trials. The effect on muscle function is mixed	Hyperglycemia, lower extremity edema, muscle pain	Increase in muscle mass and body weight by ghrelin receptor agonists make them a favorable option in catabolic conditions like cancer cachexia. Evidence should be supported with large scale trials
Myostatin and activin II receptor inhibitors	Myostatin, ACVR2	Block myostatin's action on ACVR2 to inhibit protein degradation and promote protein synthesis	Bimagrumab and landogrozumab were shown to increase LBM while decreasing total body fat mass in individuals with overweight/obesity. The anabolic effect of ACE-031 and ACE-083 on mass component was reported in small scale studies. The effect of these drugs on muscle function is yet to be elucidated	Injection site reactions, muscle spasms, myalgia, diarrhea, epistaxis, and telangiectasia*	The dual effects of bimagrumab and landogrozumab in increasing muscle mass and decreasing fat mass indicate that they are promising drugs for the treatment of sarcopenic obesity. Large scale studies are needed to support current evidence
ACEI, ARB	ACE, AT1R	Reduce inflammation, fibrosis, endothelial and mitochondrial dysfunction, and increases the formation of Ang-(1-7), which induces activation of protein synthesis and prevention of protein degradation. ACEI also increases IGF-1 levels	Although there is data showing that perindopril improves 6MWD in patients with heart failure or mobility limitation, its beneficial effect on other sarcopenia components have not been demonstrated ARBs were reported to improve muscle mass in limited number of studies and the effect on muscle function is inconsistent	Dizziness, headache, fatigue, hyperkalemia, acute kidney injury, cough, and angioedema with ACEI	ACEI and ARB may improve sarcopenia components in vulnerable patient groups during use for other indications. More studies are needed to identify their effect on muscle mass and function

Table 1 (continued)

Drug	Target	Action	Benefits on sarcopenia components	Adverse effects	Remarks
BIO101	MasR	Promotes protein synthesis and energy production in muscle	High-dose BIO101 showed a clinically meaningful improvement in the 400MWT in older adults with sarcopenia	Backpain, muscle spasms, myalgia, gastroinestinal symptoms (abdominal discomfort, constipation or diarrhea, etc.)	Since BIO101 was able to improve physical performance in the older adult population with sarcopenia with no serious adverse events, it seems to have a potential for approval for use with a sarcopenia indication. The results of the phase III trial will allow a clear conclusion to be reached
mTOR inhibitors	mTORC1	Long-term administration of mTOR inhibitors was hypothesized to prevent muscle damage caused by chronic, persistent activation of mTORC1 in aged muscle	There is no evidence regarding beneficial effect of long-term mTOR inhibitor administration on sarcopenia components. Contrarily, long-term use of rapamycin analogs ended up with a decrease in muscle mass in patients with cancer	Nausea, diarrhea, anemia, leukopenia, thrombocytopenia, hyperglycemia, hyperlipidemia	Long-term use of mTOR inhibitors failed to improve muscle mass and function in different study groups
Espindolol (MT-102)	β1/β2 adrenergic receptors, $5HT_{1A}$ receptor	Effect on three potential targets that may be relevent for cancer cachexia (reduced catabolism through non-selective β-blockade, reduced fatigue and thermogenesis through 5HT1A receptor antagonism, and increased anabolism through partial β2 receptor agonism)	Four-month high-dose espindolol treatment was reported to increase muscle mass and body weight in patients with cancer. Muscle strength was significantly and 6MWT was nonsignificantly in favor of high-dose espindolol	Anemia, cough, dyspnea were seen more common with espindolol treatment compared with placebo	Espindolol stands out as a potential drug candidate for the treatment of cancer cachexia. Large scale studies are needed to support the available evidence
AST-120 (Renamezin)	Indoxyl sulfate	IS increases inflammatory factors and oxidative stress in muscle. AST-120 adsorbs IS and maintains mitochondrial function, suppresses muscular breakdown, and recovers Akt phosphorylation	The 48-week AST-120 administration improved gait speed in patients with CKD, but caused no significant effect on muscle strength or mass. The proportion of individuals with sarcopenia showed a decreased tendency in AST-120 group	Mostly gastrointestinal side effects (heartburn, diarrhea, constipation, etc.)	Besides its potential effect to slow the progression of CKD and improvement of uremic symptoms, AST-120 may be useful to treat secondary sarcopenia or its components. Further studies are needed to reach a definitive conclusion

Table 1 (continued)

Drug	Target	Action	Benefits on sarcopenia components	Adverse effects	Remarks
FSTA	Fast skeletal muscle troponin	FSTA sensitizes fast skeletal muscle troponin to Ca^{2+}, slows the rate of its release, amplifies the muscle cell response to neural inputs, and increases force generation at submaximal levels	Although preclinical studies reported that FSTA improves strength, power, and exercise performance, their effect on muscle functions is mixed in diseases characterized by muscle weakness. There is no evidence regarding their effect on muscle mass and function in patients with sarcopenia	Dizziness, nausea, fatigue, headache, gait disturbances	Troponin activation may provide a new therapeutic approach to improve muscle functions in sarcopenia with future clinical studies
Elamipretide	Mitochondria	Increase in ATP production and reduction in ROS	Elamipretide was primarily studied in primary mitochondrial myopathies, with disappointing results in terms of improvement in muscle function. No trials have been conducted on sarcopenia	Injection site reactions, dizziness, falls	Although it has not been tested on individuals with sarcopenia before, elamipretide has a potential to treat sarcopenia and its components
Anti-TNF	TNF-α	Reduces inflammation, protein degradation, and apoptosis	Prevention of age-related atrophy and improvement in muscle functions in preclinical studies. Increase in muscle mass or decrease in proportion of sarcopenic patients in rheumatological diseases	Increased risk of infections, malignancies (especially lymphomas), injection site reactions.	The beneficial effect of anti-TNF therapy on sarcopenia only reported in preclinical studies of rheumatological diseases with promising results. Further studies are needed to reach firm conclusions

$5HT1_{RA}$ serotonin 1A receptor, *6MWD* 6-minute walking distance, *400MWT* 400-meter walking test, *ACVR* activin receptor type 2, *ACE* angiotensin-converting enzyme, *ACEI* angiotensin-converting enzyme inhibitor, *Akt* protein kinase B, *AR* androgen receptor, *ARB* angiotensin type-1 receptor blocker, *AT1R* angiotensin type 1 receptor, *ATP* adenosine triphosphate, *CKD* chronic kidney disease, *DHEA* dehydroepiandrosterone, *DM* diabetes mellitus, *ER* estrogen receptor, *FFM* fat-free mass, *FSTA* fast skeletal muscle troponin activator, *GH* growth hormone, *GHSR* growth hormone secretagogue receptor/ghrelin receptor, *GI* gastrointestinal, *GLP-1* glucagon-like peptide-1, *GLP-1RA* glucagon-like peptide-1 receptor agonist, *IGF-1* insulin-like growth factor-1, *IS* indoxyl sulfate, *LBM* lean body mass, masR mas receptor, *mTOR* mammalian target of rapamycin, *mTORC1* mammalian target of rapamycin complex 1, *NF-κB* nuclear factor kappa B, *PI3K* phosphoinositide 3-kinase, *PPARγ* peroxisome proliferator-activated receptor gamma, *ROS* reactive oxygen species, *SARM* selective androgen receptor modulator, *SERM* selective estrogen receptor modulator, *TNF* tumor necrosis factor

*Epistaxis and telangiectasias were reported with the use of ACE-031 in Duchenne muscular distrophy. The study was terminated early due to potential safety concerns [259]

needs to be elucidated by large-scale randomized controlled trials.

4.1.4 Estrogen-Based Treatments and Selective Estrogen Receptor Modulators (SERMs)

The anabolic effect of estrogens on muscle is less pronounced compared with androgens. Estrogens (mainly the most potent and ubiquitous type, 17β-estradiol) bind to nuclear and membrane estrogen receptors (ERs) [estrogen receptor α (ERα), estrogen receptor β (ERβ), and G-protein-coupled ER (GPER)] and regulate gene expression through genomic and non-genomic pathways [162]. Thereby, it promotes muscle regeneration and repair by stimulating the activation and proliferation of satellite cells [193]. Estradiol also inhibits the inflammation-mediated release of proinflammatory cytokines and inflammatory stress damage, which can cause protein degradation [194]. Moreover, estradiol regulates mitochondrial functions and thereby leads to mitochondrial protection and prevention of apoptosis [162, 193]. All these actions suggest estrogens have anabolic effect on muscle and thus, may be used as a treatment option for sarcopenia.

The effects of estrogen therapy on muscle health are controversial. According to a meta-analysis comparing muscle strength in postmenopausal women who were and were not on estrogen-based hormone therapy, estrogen therapy caused a small beneficial effect on muscle strength (~ 5% greater muscle strength compared with the control group) [195]. On the contrary, a recent meta-analysis including 2476 postmenopausal women has reported that estrogen-based hormone therapy was not associated with improvement in muscle strength [196]. In terms of the effects on mass component, a meta-analysis published in 2019 reported that postmenopausal women using estrogen-based hormone therapy lost 0.06 kg [95% confidence interval (CI), − 0.05 to 0.18) less LBM compared with control group in a median follow-up of 2 years, but this benefit did not reach statistical significance [197]. Estrogen-based therapies require caution due to potential complications such as increased risk of breast cancer, endometrial cancer, cardiovascular disease, and deep vein thrombosis [198] (Table 1). *In summary, estrogen-based therapies are not recommended to prevent or treat sarcopenia, due to conflicting and insufficient benefits on muscle mass and functions and their potential risks.*

The effect of *SERMs* on muscle was also investigated, with a similar motive to SARMs. Accordingly, 12-month raloxifene (a selective estrogen receptor modulator) 60 mg/day treatment ended up with a significant increase in fat-free mass, but without an improvement in muscle strength or power in healthy older women, compared with the placebo group [199]. Furthermore, 5-year raloxifen treatment maintained muscle mass and body weight with fewer side effects in postmeopausal women [200]. *Nonetheless, further research is necessary to determine the efficacy of SERMs in adults with sarcopenia, since the current evidence is insufficient to support its use in sarcopenia* (Table 1).

4.1.5 GH/IGF-1/Insulin and Drugs For Type 2 Diabetes Mellitus as Potential Pharmacological Treatments for Sarcopenia

GH signaling promotes the expression of IGF-1 by the liver and adipose tissue to induce PI3K/Akt/mTOR anabolic pathway. As a potential treatment strategy for sarcopenia, injectable GH therapy in healthy adults ≥ 50 years was shown to increase LBM, but not muscle strength, with significant adverse effects such as gynecomastia, carpal tunnel syndrome, and hyperglycemia [201] (Table 1). *Although it may have anabolic effects on muscle mass, the benefits on muscle functions have not been demonstrated to date. Moreover, its side effect profile raises concerns about its use with sarcopenia indication.*

Clinical trials evaluating the efficacy of *IGF-1* on muscular disorders showed promising results in improving LBM [202, 203]. In older women with recent hip fracture, a 2-month high dose (1 mg/kg/d) subcutaneous administration of recombinant human IGF-1/IGF-binding protein-3 resulted in an 11.4% increase in handgrip strength at 6 months, compared with placebo [204]. In terms of safety, both low and high levels of IGF-1 are associated with increased risk of cardiovascular disease: a study conducted on frail older patients demonstrated that the magnitude of increase in IGF-1 after administration was a significant predictor of severe orthostatic hypotension, myalgias, and drug-induced hepatitis [205] (Table 1). *In summary, further clinical studies are needed to make firm conclusions on whether IGF-1 could be a safe and effective therapeutic strategy for sarcopenia.*

Insulin has been shown to stimulate anabolic response in young healthy nondiabetic adults [206], but the same effect was not encountered in healthy nondiabetic older adults [30, 138]. Studies have reported that insulin's anabolic effects on muscle proteins were mediated by stimulation of endothelial-dependent increases in blood flow, muscle perfusion, and amino acid delivery to the muscles, and this mechanism might become impaired in older adults [30, 138, 207]. The difference in the muscle protein anabolic response to increased levels of insulin between age groups was defined as true insulin resistance and it could be overcome by elevating insulin to supraphysiologic concentrations [208]. However, in the case of T2DM, insulin concentrations are often already supranormal, and treatment with exogenous insulin did not appear to increase protein synthesis [209]. Nonetheless, the Multicenter Study for Clarifying Evidence for Sarcopenia

in patients with Diabetes Mellitus (MUSCLES-DM), which was a longitudinal 1-year follow-up study including 588 patients with T2DM with a mean age of 70 years, revealed that the patients with a decrease of ≥ 1% in HbA1c exhibited a significant increase in skeletal muscle index (SMI) (appendicular lean mass adjusted for height squared) and gait speed, but not hand grip strength (HGS). The most striking finding of this study was the insulin use showing an independent and positive correlation with an increase in SMI [210]. Likewise, the KORA-Age study, which was a 3-year follow-up study including 731 older adults, revealed that T2DM was independently associated with a decline in skeletal muscle index (adjusted for height^2), and insulin therapy was associated with preserved muscle mass, but not muscle function parameters like gait speed or Timed Up-and-Go Test [211]. *Although it does not seem likely to be used for the treatment of sarcopenia in individuals without DM (due to the risk of hypoglycemia), insulin therapy in DM may be used to take advantage of its anabolic effect in muscles as well as hyperglycemia treatment. Nevertheless, it is clear that more work is needed to be more conclusive* (Table 1).

Metformin has been recommended as the first-line drug for the treatment of type 2 diabetes mellitus for years, and its potential for treating sarcopenia has been explored. It has effects on autophagy, stress resistance, and stimulating mitochondrial biogenesis by activating AMPK and inhibiting mTOR signaling [212, 213]. It also inhibits proinflammatory cytokines and inflammatory pathways by inhibiting NF-κB and precipitating changes to the gut microbiota [214, 215]. Metformin was shown to extend the lifespan and improve physical performance in several models [216]. Although metformin was hypothesized to augment the effects of exercise on muscles in older adults [217], contradictory results have been published: the MASTERS trial reported that a 14-week treatment of 1700 mg/metformin blunted muscle hypertrophy in response to progressive resistance exercises in older adults [218]. In another RCT including 120 older adults with prefrailty, metformin 1500 mg/day ingestion resulted in a significant increase in gait speed by 0.13 m/s, which exceeds the minimal clinically important difference (MCID) for this measure, but no significant benefits on handgrip strength were observed [219]. In another trial with 120 older adults with prediabetes, 3-year metformin 850 mg twice a day (b.i.d.) treatment did not end up with a reduction in loss of LBM or appendicular lean body mass or improvement in 400 meter walk speed. Although the preliminary results of this study were provided at ClinicalTrials.gov [220], they were not published elsewhere yet. The anorectic effect of metformin should not be overlooked when considering its effects on muscle health, as it might reduce the anabolic stimulus on muscles by reducing protein intake and thus exacerbating sarcopenia [221]. A recent trial named "MET-PREVENT" will study the effect of 4-month metformin 500 mg three times daily (t.i.d.) versus placebo ingestion on 4 m walking speed in older adults with probable sarcopenia and physical frailty [222]. *Although metformin exhibits multiple pleiotropic effects on sarcopenia pathogenesis, available evidence regarding its effects on muscle health is contradictory. Further studies are needed to elucidate its role in the treatment of sarcopenia and whether its potential benefits outweigh its risks, considering adverse effects on appetite and body weight.*

Glucagon-like peptide-1 receptor agonists (GLP-1RA) are novel antidiabetics with multiple pleiotropic effects [223]. GLP-1RA are reported to improve endothelial functions, reduce myostatin expression, and inflammatory factors, stimulate insulin secretion, and thereby show potential to be an effective therapeutic agent to improve muscle health [224]. However, clinical trials studying the effect of 6-month liraglutide treatment in different study populations (in patients with congestive heart failure and T2DM) did not exhibit any significant benefit of the drug on physical performance or endurance [225, 226]. Evidence is contradictory on their effect on mass component; as some studies reported decrease in SMI in follow-up [227], others reported no significant change [228] or increase in muscle mass in patients with T2DM [229]. Further studies are needed to elucidate the net effect of GLP-1RA on different components of sarcopenia. Of note, GLP-1RA has a high potential for weight loss, and up to 50% was attributed to the loss of lean mass [223, 230]. *Whether or not it is indicated for sarcopenia in the future, the use of GLP-1RA will require close monitoring and ensuring adequate protein intake in older adults in order not to lose the muscle reserve they already have* (Table 1).

Sodium-glucose co-transporter 2 inhibitors (SGLT-2i) are another novel antidiabetic agents proven to have multiple cardiorenal benefits in diabetes mellitus [223]. SGLT-2i increase lipolysis and ketogenesis, reduce RAS activity, and inhibit the inflammatory environment by reducing inflammatory factors in the liver [224]. Although preclinical studies have reported positive effects of SGLT-2i on muscle strength and mass [231, 232], these beneficial effects have not yet been demonstrated in human studies. SGLT-2i lead to reductions in lean mass and fat mass, but lean mass has been reported to account for 20–50% of the weight loss observed with these agents [230]. The effects of SGLT-2i on SMI tend to be negative and this result may be due to the fact that the adjustment of measured SMM is almost always made with height square [233]. Of note, while using SGLT-2i or other drugs with potential weight-loss (such as metformin and GLP-1RA), absolute SMM or LBM values or their adjustment for height square are not appropriate to evaluate the actual effect of weight loss caused by these drugs on

skeletal muscle [223, 234]. In overweight and obese people, there may be a "relative decrease in muscle mass" compared with increased fat mass. The total muscle mass will decrease with weight loss, and according to the absolute values or adjustment for height square, this will always be interpreted as absolute loss of muscle mass. However, the "relative decrease in muscle mass" may be overcome by the weight loss effect of these drugs and the net effect on muscle may be positive, but misinterpreted due to the inappropriate adjustment method [235]. In this case, whether treatment-related weight loss has a positive effect on muscle can only be interpreted correctly when the measured muscle mass is adjusted for body weight [235] or BMI [223, 234]. This point should be taken into consideration in future studies evaluating whether weight loss agents cause an actual loss of muscle mass. *In summary, more studies are needed to determine whether SGLT-2i are beneficial especially in sarcopenic obesity and sarcopenic individuals without diabetes mellitus* (Table 1).

Thiazolidinediones bind to peroxisome proliferator-activated receptor gamma (PPARγ) and improve insulin sensitivity in parallel with changes in fat metabolism, including a substantial reduction in circulating free fatty acid and increased fatty acid storage in subcutaneous adipocytes. The potential anabolic effect of thiazolidinediones comes not only from increase in the action of insulin, but also from decrease in intra-myocellular lipid content and improved skeletal muscle fatty acid metabolism [236]. Clinical trials on the effect of thiazolidinediones on muscle were reported mostly in T2DM and the results are contradictory. Neither 16-week pioglitazone nor 1-year rosiglitazone use resulted in a significant change in muscle tissue areas measured via magnetic resonance imaging (MRI) or computerized tomography (CT), respectively [237, 238]. Nevertheless, pioglitazone was reported to potentiate the effect of resistance training on muscle power in older women with obesity [239]. *Although the limited data available show that the positive effects of thiazolidinediones on muscle are not satisfactory, it is obvious that more studies are needed to make a clear claim* (Table 1).

4.1.6 Ghrelin and Ghrelin Receptor Agonists

Ghrelin is an orexigenic hormone secreted from the fundus of the stomach during fasting and has various physiological functions like controlling energy metabolism, insulin secretion, inflammation, and GH secretion. Ghrelin exhibits anabolic properties by promoting protein synthesis by activating the PI3K/Akt/mTOR signaling pathway, inhibiting the production of inflammatory factors IL-1β, IL-6, and TNF-α, and promoting mitochondria activity. Studies have shown that ghrelin can increase appetite and reduce fasting, denervation, and cancer-induced muscle atrophy [240, 241]. MK-0677 (ibutamoren mesylate), an oral ghrelin mimetic was shown to enhance GH and IGF-1 levels in healthy older adults to those of healthy young adults. In an RCT, oral intake of 25 mg MK-0677 (ibutamoren mesylate) was shown to increase LBM over 1 year, but no significant improvement in muscle strength or function was observed [143]. Another RCT conducted on older adults with unilateral hip fracture revealed that 25 mg/day *MK-0677* (ibutamoren mesylate) treatment significantly improved gait speed and ended up with fewer falls; however, it was terminated early due to increased risk of congestive heart failure [144].

Another ghrelin receptor agonist, anamorelin was shown to be beneficial in improving LBM and body weight in patients with cancer cachexia; however, no improvement in muscle strength and performance was observed [242, 243]. Of note, similar to drugs that cause weight loss, it would be appropriate to adjust measured muscle mass for body weight or BMI, to accurately assess the net effects of therapeutics that cause weight gain on muscle mass [223, 234, 235]. A phase I RCT studying the effect of daily administration of anamorelin 100 mg on total body muscle mass via the D_3-creatine dilution method in individuals with sarcopenia has just been completed but the results have not yet been published [244].

Oral administration of capromorelin in older adults at risk for functional decline revealed that LBM, gait speed, and stair climb significantly increased at the end of 12 months of treatment [245]. Reported side effects with ghrelin receptor agonists were mostly mild such as muscle pain, lower extremity edema, and hyperglycemia; except for congestive heart failure episodes seen with the use of MK-0677 (Table 1). *Indeed, ghrelin mimetics attract attention as a therapeutic group that can be useful especially in catabolic conditions such as cancer cachexia, due to their effects on increasing LBM and total body weight. However, their effects on muscle functions are questionable, and more clinical studies are needed on their long-term efficacy and safety*.

4.2 Myostatin and Activin II Receptor İnhibitors

Myostatin is an endogenous regulator of skeletal muscle growth by binding to activin receptors type IIb (ActRIIb) on myofiber membranes. It has drawn wide attention as a novel target for diseases related to muscle health. Several approaches have been experimented with to attenuate myostatin/ActRIIb, like ligand traps, monoclonal antibodies, or gene therapeutics [246].

The most extensively tested one is bimagrumab (BYM338), which neutralizes the ligand-binding domains of ActRIIb. It has been tested in various disease animal models resulting in activation of mTOR, attenuation of

smad 2/3 signaling, suppressing MuRF1/MAFbx expression, and improvement in muscle mass [247–249]. In an RCT including 40 older adults with low appendicular skeletal muscle index, bimagrumab 30 mg/kg intravenous infusion resulted in significant improvement in thigh muscle volume, appendicular lean mass, and grip strength, and significant improvement in gait speed among slow walkers [250]. In another study including 180 older adults with sarcopenia, monthly infusion of a top dose of bimagrumab (700 mg) with nutritional support and home-based exercises resulted in more improvement in LBM in the intervention group, but improvement in physical performance did not differ significantly compared with the placebo group [131]. Recently, bimagrumab 10 mg/kg every 4 weeks versus placebo in individuals with overweight/obesity and T2DM was reported to decrease total body fat mass (− 22.2% versus − 0.3%) and increase appendicular lean mass (+ 0.5 versus − 0.3 kg) significantly at week 48 [251]. Bimagrumab's dual effect of decrease in fat mass and increase in LBM makes it a potential therapeutic agent for sarcopenic obesity. In line, a study of bimagrumab in obesity without T2DM is ongoing.

Myostatin monoclonal antibodies are another group whose therapeutic effects have been under investigation. Landogrozumab (LY2495655) sequesters myostatin in circulation, and clinical trials have come up with promising results in terms of improvement in muscle mass and decrease in fat mass in older adults with hip arthroplasty and falling history, but conflicting results on muscle functions [252, 253]. Another myostatin monoclonal antibody is trevogrumab (REGN1033, SAR391786), which was originally developed for treating sarcopenia and inclusion body myositis (IBM) [246]. The sarcopenia trial of trevogrumab was completed in 2015; however, the results have not been posted [254]. An IBM trial testing trevogrumab in combination with garetosmab (REGN2477), an activin-A monoclonal antibody, was withdrawn by the company in 2019, with an internal decision that this combination was not the best approach [255]. Indeed, trevogrumab is no longer listed as a pipeline drug in the sarcopenia arena, and its development status is not clear at present [246].

A ligand trap ACE-031 (ramatercept), a recombinant fusion protein of the extracellular domain of ActRIIB and the Fc domain of IgG (ActRIIB-Fc), was shown to increase total LBM and thigh muscle volume in healthy 48 postmenopausal women, with a single subcutaneous dose at day 29 [256]. Another ligand trap is ACE-083, which is derived from follistatin (activin-binding protein), an endogenous myostatin antagonist. ACE-083 is a recombinant fusion protein consisting of a modified form of human follistatin and the Fc domain of IgG. ACE-083 was tested on 58 healthy postmenopausal women as local administration as 1 or 2 doses 3 weeks apart. Accordingly, the volume of rectus femoris and tibialis anterior muscles exhibited a significant increase after injection in magnetic resonance imaging (MRI), but no significant improvement in muscle strength was observed [257]. The clinical trials of another myostatin antibody PINTA-745 (AMG-745), a fusion protein with a human Fc and a myostatin-neutralizing bioactive peptide, were terminated after disappointing results were encountered regarding the increase in muscle mass in pancreatic cancer and end-stage kidney disease [246, 258]. The development of these tested drugs for sarcopenia is suspended at present.

Myostatin and activin II receptor inhibitors are generally well tolerated. That said, myostatin and other members of the TGF-β family have high similarities in their recognition sites, and several myostatin inhibitors have cross-reactivity with activin, bone-morphogenetic protein (BMP) and GDF-11, which may cause unwanted adverse effects in other tissues. Supportive of this, a phase II trial on Duchenne muscular dystrophy was terminated early due to safety concerns of epistaxis and telangiectasias that were encountered after the second dose, which was attributed to binding and inhibition of BMP activity [259] (Table 1). *In summary, among myostatin and activin II receptor inhibitors, bimagrumab stands out as an important therapeutic candidate, especially for sarcopenic obesity. Precise targeting seems to be more helpful in the case of developing myostatin-related drugs to narrow the spectrum of side effects* [260].

4.3 Therapeutics with Actions on RAS

ACE inhibitors (ACEI) have been primarily used for primary and secondary prevention of cardiovascular diseases. Apart from hemodynamic effects, ACEI are reported to increase IGF-1 levels and the number of mitochondria, thus having the potential to have a therapeutic action in sarcopenia. These therapeutic effects can be achieved via simultaneous actions on classical and nonclassical pathways: inhibition of Ang II formation in the classical pathway causes an increase in Ang I. Ang I can be directly converted to the vasodilator peptide Ang-(1-7) in the nonclassical pathway. Moreover, the metabolism of Ang-(1-7) can be inhibited by ACEI as well [98]. Besides ACEI, angiotensin II type 1 receptor blockers (ARB) can also lead to increased formation of Ang-(1-7) through ACE2, and shunt Ang II to the AT2R pathway that shares similar properties to the Ang-(1-7) system [261].

Perindopril treatment was reported to increase 6-min walking distance (6MWD) significantly in very old patients with left ventricular systolic dysfunction [262]. Furthermore, 20-week perindopril treatment in older adults "without underlying heart failure or left ventricular systolic dysfunction," but with mobility or functional impairment, significantly improved 6MWT compared with placebo, with a degree of improvement equivalent to 6 months of exercise training. However, it exhibited nonsignificant

improvement in other tests measuring physical performance [i.e., Timed Up-and-Go Test (TUG) and sit-to-stand tests] [263]. Recently, Leucine or Angiotensin Converting Enzyme inhibitors for sarcopenia (LACE) trial aimed to determine if 12-month therapy with perindopril or leucine supplementation improved physical performance in 145 older adults with sarcopenia, in a placebo-controlled parallel-group double-blind randomized trial. At the end of 12 months, no significant treatment benefits were seen in either the perindopril or leucine group compared to placebo, in terms of Short Physical Performance Battery (SPPB) scores, appendicular skeletal muscle index, 6MWT, gait speed, and grip and quadriceps strength [264]. In another recent trial, the effect of increasing doses of losartan, an angiotensin receptor blocker (ARB) versus placebo on isokinetic strength, frailty status, and other muscle function parameters were studied in 37 older participants with prefrailty, and 24 weeks of losartan treatment did not demonstrate a significant difference in bilateral knee concentric strength, grip strength, and physical performance compared with the control group, but ended up with significantly lower odds of frailty [141]. The Singapore Longitudinal Ageing Study reported that the use of ARBs is associated with a reduction in frailty and age-related loss of muscle mass and strength in a mean follow-up period of 4.5 years in older adults [265]. *Further studies are needed to better clarify the effects of the agents for the classical RAS pathway on skeletal muscle* (Table 1).

As the anabolic and protective role of non-classical RAS on skeletal muscles has become clearer in years, activation of this pathway has been a novel therapeutic target recently. In line with this, a recent phase II study has come up with striking findings: SARA-INT trial was a phase II randomized placebo-controlled multicentered study to evaluate the efficacy and safety of a mas receptor activator, BIO101, in patients over 65 years suffering from sarcopenia and at high risk of mobility disability [132]. In cellular and animal studies, BIO101 activated the mas receptor on muscle cells thereby triggering two important mas receptor downstream signaling pathways in myocytes: PI3K/Akt/mTOR pathway and AMPK/Acetyl CoA carboxylase (ACC) pathway, and this resulted in protein synthesis and energy production [266, 267]. In the SARA-INT trial, a total of 233 participants were recruited and randomized to three arms: BIO101 175 mg b.i.d. versus BIO101 350 mg b.i.d. versus placebo for 6 months, and the primary endpoint was mobility disability measured by the gait-speed over the 400 m walk test (400MWT). After 6 months of treatment, BIO101 350 mg b.i.d. showed a clinically meaningful improvement of 0.09 m/s for the 400MWT in the full analysis dataset (FAS) population (not significant), and of 0.10 m/s in the per-protocol (PP) population (significant, $p = 0.008$), compared with placebo. This effect was close to the minimal clinically important difference (MCID) in sarcopenia (0.1 m/s) known to be associated with a reduction in mobility disability in older adults [268]. BIO101 at 350 mg b.i.d. demonstrated a promising effect on 400MWT in subpopulations at higher risk of mobility disability such as slow walkers (0.07 m/s, $p = 0.015$ in PP population), obese subgroup (0.09 m/s, $p = 0.004$ in PP population), and chair stand subscore ≤ 2 of the SPPB (0.09 m/s, $p = 0.004$ in PP population). A trend of dose-dependent effect was observed on the secondary endpoints like handgrip strength (HGS) and 6MWT, although statistically insignificant. BIO101 also showed a very good safety profile after up to 9 months of dosing, with no significant differences between treatment arms and placebo for adverse events [269] (Table 1). The company has obtained FDA authorization to start a phase III trial in 2024, which will be conducted with BIO101 350 mg b.i.d. dose versus placebo for at least 12 months on 600–900 patients over 65 years old with low handgrip strength and low physical performance [270, 271]. *BIO101 is now considered to have the potential to become the first drug approved for the treatment of sarcopenia.*

4.4 mTOR Inhibitors

The longstanding knowledge of "the activity of mTOR pathway stimulates an anabolic response in muscles" has passed through an evolution. Short-term activation of mTORC1 is essential for cell growth, regeneration, and maintenance of muscle mass, thereby preventing muscle atrophy. In contrast, chronic/persistent activation of mTORC1 appears to trigger muscle degradation and atrophy, through feedback inhibition of Akt, and the consequent activation of FOXO leading to increased muscle catabolism [36]. In animal studies, inhibition of mTORC1 protected aging muscle from atrophy [272]. In line with the findings from animal studies, an early preventive treatment (maybe starting in middle age when mTORC1 activity increases) with mTORC1 inhibitors may help preventing sarcopenia [36].

Rapamycin, a natural macrocyclic lactone produced by the bacterium *Streptomyces hygroscopicus*, binds to the immunophilin FK binding protein-12 (FKBP-12) in mammalian cells to generate a complex that binds to and inhibits mTOR activation. Rapamycin analogs (rapalogs) have been developed to provide more favorable outcomes with optimal pharmacokinetics [273]. A small number of studies investigated the effects of acute rapamycin ingestion on skeletal muscle anabolic signaling, which developed our understanding of the role of mTORC1 in muscle protein synthesis in response to exercise and nutrients. Accordingly, short-term rapamycin administration was shown to only impair the increase in human skeletal muscle mTORC1 signaling and protein synthesis that occur as a response to an anabolic

stimulus, i.e., resistance training or increased amino acid availability [150, 274–276].

The effects of long-term rapamycin/rapalog intake on skeletal muscle health in humans were also investigated. In a special patient group with advanced solid tumors, weekly intravenous administration of temsirolimus (a rapalog) showed no significant changes in skeletal muscle tissue [SMT; measured at the level of the third lumbar vertebra (L3) in computerized tomography images] and skeletal muscle index (SMI; adjusted for height squared) from baseline over 8 weeks [277]. In another retrospective study conducted on patients with cancer who received everolimus or temsirolimus over 6 months, long-term use of these rapalogs ended up with a decrease in SMT and SMI (SMT at L3 level adjusted for height squared). Although cancer cachexia might be considered as a confounding factor, authors indicated that there was no significant loss of body weight and the loss of muscle mass observed here was most likely due to the drug itself [278]. In another RCT conducted on healthy older adults, at least 8 weeks of rapamycin ingestion did not improve but also did not worsen handgrip strength and walking speed [279]. There is an ongoing rapamycin trial that was designed to include individuals older than 50 years old and is searching to see whether 16-week rapamycin ingestion will help to reduce the negative impacts of excessive mTOR signaling on muscle size and function in older adults [280]. *There are limited number of clinical trials on the effect of rapamycin or other rapalogs on muscle health in the literature, with findings showing that there is still a long way to go to elucidate whether this pathway can be used in the treatment of sarcopenia* (Table 1).

4.5 Miscellaneous Drugs

Espindolol (MT-102) (*S*-isomer of pindolol) is a non-selective β-blocker with central 5-HT_{1A} antagonist and partial β2 receptor agonist effects. It reduces catabolism through non-selective β blockade, increases anabolism through partial β2 receptor agonism, and reduces fatigue and thermogenesis through central 5-HT_{1A} receptor antagonism [281]. The ACT-ONE trial studied the effect of espindolol in 87 patients with stage III or IV colorectal cancer or non-small cell lung cancer-related cachexia. Over 16-week treatment, high dose espindolol (10 mg twice daily) caused a significant weight gain and increase in LBM, with neutral changes in fat mass. HGS and physical performance tests were also in favor of espindolol treatment. Safety signals and survival did not differ with placebo, although dyspnea was seen more frequently in the treatment group [282]. *It is clear that further large-scale studies are needed. That said, espindolol has a potential for use in cancer cachexia* (Table 1).

Elevated serum levels of uremic toxin indoxyl sulfate are associated with low muscle mass in patients with chronic kidney disease (CKD) [283]. Tailored dosing of AST-120 (renamezin), an oral spherical activated carbon, which can adsorb uremic toxins like indoxyl sulfate, may delay the need for renal replacement treatment and improve uremic symptoms. A systematic review and meta-analysis showed that AST-120 (renamezin) represented an optimal treatment strategy for CKD because it resulted in lower rates of composite renal outcomes (clinical outcomes related to disease progression, such as dialysis initiation, kidney transplantation, and doubling of serum creatinine levels) [284]. RolE of AST-120 in sarCOpenia preVEntion in pRe-dialYsis chronic kidney disease patients (RECOVERY) trial aimed to determine the effects of AST-120 (renamezin) on muscle health on the basis of CKD. According to this 48-week randomized controlled multicentered trial including 150 participants with CKD, AST-120 (renamezin) did not succeed in achieving the primary outcome of gait speed difference $\geq$ 0.1 m/s between intervention and placebo groups, although gait speed significantly increased in the AST-120 (renamezin) arm at the end of the trial. AST-120 (renamezin) also did not improve HGS and SMI (skeletal muscle mass adjusted for height squared), but the proportions of participants with low muscle mass or sarcopenia according to the Asian Working Group for Sarcopenia (AWGS) 2019 showed a decreasing tendency in the AST-120 (renamezin) group [130]. *This study shows that AST-120 (renamezin) has a potential to improve sarcopenia in patients with CKD, but should be supported with further evidence* (Table 1).

Fast skeletal muscle troponin activators (FSTA) are small molecules that selectively sensitize fast skeletal muscle troponin to Ca^{2+} and slow the rate of Ca^{2+} release from the regulatory troponin complex of fast skeletal muscle. This action promotes amplification of the response to nerve inputs and increases force generation at submaximal levels. When preclinical studies showed that they reduce muscle fatigue and increase muscle strength, power, and exercise performance [285, 286], their potential use in diseases with muscle weakness created a new field of research. Although tirasemtiv (CK-2017357) and reldesemtiv (CK-2127107) did not achieve significant improvement in muscle strength in patients with amyotrophic lateral sclerosis [287, 288], they caused improved physical performance in patient groups with spinal muscular atrophy [289] or peripheric artery disease [290]. *Future studies will reveal whether this potential novel drug group will be an effective and safe choice for sarcopenia. At present, there is no ongoing trial studying the effects of FSTA on sarcopenia* (Table 1).

Elamipretide (SS-31, MTP-131, Bendavia) is a mitochondrial-targeting agent in development for treating patients with various mitochondrial diseases. Elamipretide

targets mitochondria via cardiolipin where it has been shown in animal models to improve ATP production and decrease ROS, possibly by stabilizing the mitochondrial membrane and cytochrome c in several organs, including skeletal muscles [291]. Although elamipretide treatment did not improve physical performance in patients with primary mitochondrial myopathy [292], its effect in sarcopenic individuals is intriguing. *Thus, elamipretide is considered a novel class of drugs with potential for the treatment of sarcopenia* (Table 1).

Pharmacological blockade of TNF-α, which is a prominent proinflammatory molecule causing apoptotic cell death, was reported to prevent the loss of muscle fibers and improve muscle functions in animal models [293]. The anabolic effect of anti-TNF therapy was studied in different patient groups with rheumatological diseases (i.e., spondyloarthropathies or rheumatoid arthritis) [294, 295]. Longitudinal studies exhibited promising results for secondary sarcopenia, with an increase in LBM [295] or a decrease in the proportion of sarcopenic patients in follow-up [294]. There is an ongoing trial of MyMD1, a synthetic derivative of the alkaloid myosmine capable of suppressing TNF-α production. The trial will investigate the efficacy, tolerability and pharmacokinetics of MyMD1 in participants with chronic inflammation associated with sarcopenia/frailty [296]. *Further studies will reveal whether anti-TNF therapy will get approval for the treatment of sarcopenia in the coming years* (Table 1).

5 Challenges in the Development of Drugs for Sarcopenia and Future Directions

Although significant research efforts have contributed to our understanding of sarcopenia in years, the prevention and treatment of sarcopenia are still based on lifestyle interventions, i.e., nutrition and physical exercise, and no pharmacological treatment has yet been approved among the aforementioned treatment candidates. The International Conference on Frailty and Sarcopenia Research (ICFSR) Task Force presented a report on the challenges faced in the development of a drug for the prevention and treatment of sarcopenia and frailty in 2022. According to the Task Force, the lack of treatment options is mainly caused by the paradigm of standalone/single diseases traditionally adopted in medicine [14, 297]. Age-related conditions like sarcopenia and frailty are complex, and this complexity makes the study of pharmacological interventions more challenging. Sarcopenia is not a disease caused by a single pathophysiological factor or pathway. Probably, the presence of more than one causative factor necessitates multiple targets to be handled at one time for therapeutics to be successful. Many confounders and mediators affect the findings of the studies, their interpretation, and their generalizability to real life. Although some animal studies have come up with promising results, some of the findings have not translated to humans, and have not been replicated in large-scale studies [14]. Moreover, the action of improvement in muscle mass does not always bring improvement in strength, physical performance, or functionality, which are generally determined as "the outcome of interest" in sarcopenia studies. Hence, an increase in muscle mass alone may not be sufficient to reduce incident disabilities caused by sarcopenia.

Older adults are a very heterogeneous population and present with different profiles of comorbidities and physiological reserves. This heterogeneity may impose limited response potential to sarcopenia treatments, considering those with significant comorbidity burden and frailty [14]. In fact, the potential targets of drug therapies may not be the same for different patient profiles, even if they are all categorized as sarcopenic. In 2016, an expert working group was convened under the auspices of the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) with the concern that a drug treatment for sarcopenia might have been overlooked because the appropriate trial for this purpose has not been designed yet. They have come up with several recommendations for standardization of designs and outcomes to contribute to an improvement of the methodological robustness and comparability of clinical trials, but acknowledging the remaining uncertainties at the same time [298]. Of note, the working group provided a further position paper aiming to update their previous recommendations inaccordance with the latest evidence in 2021[15].

Since sarcopenia is a multifactorial disorder with more than one potential target of action for pharmacotherapeutics, novel interventions that can concurrently act on more than one target may be necessary to elicit an effective treatment for sarcopenia [63]. In line with this, stem cell therapy can be a novel therapeutic intervention due to its regenerative capabilities and ability to produce antiinflammatory cytokines that transform the microenvironment into the one at which reinnervation and regeneration take place. It was reported that as few as seven satellite cells associated with one transplanted myofiber can generate over 100 new myofibers with thousands of myonuclei. Furthermore, these transplanted satellite cells vigorously self-renew and expand in number and repopulate the host muscle, showing the efficacy and feasibility of stem cell transplantation [299, 300]. Of note, stem cell transplantation has some limitations ranging from ethics, rejection, and production limitations [63]. Gene therapy is another promising novel treatment option for sarcopenia, as recent preclinical studies have reported beneficial effects on muscle mass or functions [301,

302]. miRNAs are considered as potential targets for gene therapy, as their modulation demonstrated promising effects on sarcopenia [108]. However, clinical studies are needed to confirm their utility as potential therapeutics for sarcopenia.

Constructing novel drug delivery systems to repair skeletal muscles can be another potential therapeutic intervention for sarcopenia. Nano-carrier drug delivery technology is an emerging area that may provide an ultimate solution for the treatment of age-related muscle loss [303]. A muscle-targeting delivery system, which requires a targeted motif combined with a delivery system to specifically deliver drugs to skeletal muscles, acts directly on targeted tissue and can concurrently eliminate the side effects related to systemic administration of drugs [304]. Moreover, extracellular vesicles (EVs), including exosomes, may also be ideal drug carriers with promoting muscle regeneration and protein synthesis. It has been proposed that EV-based delivery systems might be potential strategies for age-related muscle loss in the future, but many safety and effectiveness issues still need to be elucidated [305].

6 Conclusion

There has been an enormous effort to find an effective pharmacotherapeutic solution for sarcopenia over the last decades, and research still continues with some promising agents being in the current pipeline. Despite various therapeutic interventions being explored in a timely manner over the last decades, the effective options available against sarcopenia to date are still restricted to nutritional and exercise interventions. Among the drug candidates for sarcopenia, testosterone has the most accumulated evidence of anabolic effects on skeletal muscle and its safe profile in physiological doses. Bimagrumab (BYM338) is a promising drug candidate for especially sarcopenic obesity, showing dual effects of an increase in LBM and a decrease in fat mass. Ghrelin receptor agonists and espindolol are other promising drug groups for cancer cachexia with their reported beneficial effects on muscle mass and body weight. However, large-scale studies are needed. BIO101 is one of the most promising drug candidates in recent years with its positive effect on muscle functions in sarcopenic patients, and the results of its phase III trial will be followed with interest. The one lesson learned from so many years of experience in pharmaceutical trials is probably not to overlook the complexity and the fact that more than one mechanistic pathway is involved in the pathophysiology of sarcopenia. The multiple pathophysiological pathways probably create a "sarcopenia spectrum," ending with individuals having different etiological factors underlying the same outcome (namely sarcopenia), and seem to generate different treatment needs depending on which etiological factor(s) and pathway(s) are dominant. Analogous to sarcopenia, one can consider T2DM since it has also complex multifactorial pathogenesis similar to sarcopenia. Although all patients with T2DM are classified under the same diagnostic name, some present with insulin resistance and obesity, while some others present with weight loss and insulin deficiency and accordingly they need different treatment strategies (weight loss with insulin sensitizers for the former group and insulin treatment and sometimes weight gain for the latter group) [223]. In the case of sarcopenia, as a simple example, one can expect different treatment strategies in patients with sarcopenia along with cancer and malnutrition than those having sarcopenia and obesity (sarcopenic obesity). Therefore, revealing which pathway is dominant in sarcopenia on an individual basis with more advanced future diagnostic methods and creating taylored treatment strategies will most probably be a breakthrough in the future of pharmacotherapy in sarcopenia. Novel therapeutics with more than one potential target of action or an approach of combining pharmacotherapies with other existing modalities (such as nutritional support and exercise) or emerging modalities appear to be more effective in obtaining promising results from ongoing and future drug trials.

Take Home Messages
Although many pharmacotherapeutic agents have been studied over the years, there is no approved drug for sarcopenia so far.
Complex multifactorial pathogenesis of sarcopenia seems to be the major cause of disappointment encountered in the field of pharmacotherapies for sarcopenia. Novel therapeutics (single or in combination) with more than one potential target of action may finally enable pharmacological prevention or treatment of sarcopenia.
Different molecules or pathways may be more prominent in the pathophysiology of age-related sarcopenia and in a variety of secondary sarcopenia subtypes. As in the treatment of many other diseases with complex/multifactorial pathogenesis (e.g., type 2 diabetes mellitus), individualized/tailored pharmacotherapy is expected to come to the fore in the context of sarcopenia in the coming years.

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the investigation, writing—original draft preparation, and writing—reviewing and editing.

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Consent for publication Figure 1 (Pathophysiology of sarcopenia) was created with BioRender.com. We have been granted a license which permits the content to be sublicensed for use in journal publications.

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