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Chapter

Drugs for the Treatment of Muscle Atrophy

Linlin Chen, Hong Zhang, Mengyi Chi, Quanjun Yang and Cheng Guo

Abstract

Muscle mass is maintained through an interplay between anabolic and catabolic pathways. The ubiquitin-proteasome system plays an important role in the proteolysis progress during skeletal muscle atrophy which can be blocked by some proteasome inhibitors. But few studies have demonstrated the ability of these inhibitors to preserve muscle mass and architecture under catabolic condition in vivo. The insulin-like growth factor-1/phosphatidylinositide 3-kinases/protein kinase B/mammalian target of rapamycin (IGF-1/PI3K/Akt/mTOR) pathway was associated with anabolic pathways. The activation of IGF-1 causes muscle hypertrophy; however, it cannot be used as a drug target. Myostatin pathway maintains activation that can induce skeletal muscle atrophy involved with various transcriptional and genetic factors. Skeletal muscle atrophy is a debilitating consequence of multiple chronic diseases and conditions that involve starvation. It reduces treatment options and positive clinical outcomes as well as compromising quality of life and increasing morbidity and mortality. Though considerable research has been undertaken to find the drug target and the molecular mechanisms that improve skeletal muscle atrophy, no drug was approved to treat skeletal muscle atrophy. However, these years, the signaling pathways involved in muscle atrophy were clarified and some effective treatments were currently available to prevent, attenuate, or reverse muscle atrophy for experiment research.

Keywords: muscle atrophy, sarcopenia, cachexia, anabolic, catabolic

1. Introduction

The pathophysiology of skeletal muscle atrophy is multifactorial, with cancer, sepsis, renal and cardiac failure, acquired immune deficiency syndrome (AIDS) and chronic obstructive pulmonary disease (COPD) as well as inactivity or during aging [1–3]. These factors gradually lead to muscle wasting and weakness by decreasing protein synthesis and accelerating protein degradation, which are characterized by substantial decrease in myonuclear number, muscle fiber cross-sectional area, muscle strength and protein content while increasing in fatigability and resistance to insulin [4, 5]. Muscle atrophy is recognized as an independent predictor of mortality and is associated with functional impairment and poor quality of life [6].

Studies have revealed that different types of molecular mediators/catabolic players such as pro-inflammatory cytokines i.e. tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), interleukin-1 (IL-1), interferon gamma (IFN-γ) and

TNF-like weak inducer of apoptosis (TWEAK), eicosanoids and transforming growth factor-β (TGF-β) family effectors (such as activin A and myostatin) are involved in skeletal muscle atrophy under above mentioned clinical settings [7–9]. These cytokines binding to their respective receptor results in activation of several catabolic pathways including nuclear factor-kappa B (NF-κB), Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathways and small mothers against decapentaplegic homolog 2/3 (SMAD2/3). In addition to cytokines, growth factors such as insulin-like growth factor-1 (IGF-1) signal through anabolic pathway (phosphatidylinositide 3-kinases/protein kinase B/mammalian target of rapamycin; PI3K/Akt/mTOR) to mediate functional repression of the transcription factors fork-head box protein O1 (FoxO1) or FoxO3 by inhibiting their nuclear translocation and overall levels, which together inhibit the transcription of muscle atrophy genes [10].

In spite of many promising therapeutic targets for improving skeletal muscle atrophy, no treatment has been successful to date. In this chapter, we classify the potential drugs currently in laboratory/preclinical research into four categories and then discuss their mechanism of action.

2. Anabolic medications

2.1 Androgen/androgen receptor modulators

Testosterone treatments increase muscle protein synthesis and fat free mass, and its effects on muscle are modulated by nutrition and exercise [11]. Several studies have shown the beneficial effects of testosterone supplementation on sarcopenia characteristics such as decreases in the muscle mass [12] and grip strength [13]. A study recently demonstrated that testosterone administration for 3 years in older men (over 60 years old) significantly improved stair-climbing power, muscle mass and power [14, 15]. Similarly, lower doses of testosterone supplementation in women with hysterectomy or chronic heart failure significantly increases lean body mass, 6-m walk time, chest press power and maximal voluntary contraction [16]. Evident showed that the effect of testosterone in improving skeletal muscle atrophy is related to the positive regulation of IGF-1 [12], wnt [17] and myostatin [18]. Although testosterone and its analogs can induce muscle growth and increase muscle strength [19], its clinical use is substantially limited by severe side effects including the increased risk of developing prostate hypertrophy, cancer, sleep apnea, masculinization, thrombosis complication and behavioral abnormalities [20, 21].

Compared with testosterone, the selective androgen receptor modulator (SARM) binds to androgen receptors with differing levels of sensitivity [22], showed androgenic effects in some tissues (such as muscle and bone), and has no effect on other organs (such as prostate or skin), thereby limiting adverse reactions such as prostate hypertrophy or androgen production. Enobosarm (GTx-024), an orally bioavailable nonsteroidal SARM, has been shown to increase lean body mass in phase I and II clinical trials of cancer cachexia patients [23, 24]. Moreover, the stimulation of reproductive organs with enobosarm seems to be less pronounced compared to testosterone administration. However, the phase III clinical trial of enobosarm failed to meet its common primary endpoint of preserving lean body mass and physical function [25]. Phase I clinical trials using another SARM non-steroidal oral preparation LGD-4033/VK5211 also showed increased muscle mass, but there was no effect on fat mass [26]. The 4-aza steroidal drug MK0773 (TFM-4AS-1) is a dual SARM and an inhibitor of 5α-reductase. Studies have shown that it can improve IGF-1 levels and muscle function in women, however,

the trial was terminated due to increased cardiovascular risk [27]. GSK2881078, which is assessed for its impact on muscle growth and strength, has completed its phase I trial [28] and phase II trial for the treatment of weakness caused by COPD (NCT03359473). The development of SARM drugs still requires long-term follow-up and/or more effective and selective SARM trials to prove the safety and efficacy of SARM in improving physical function and health outcomes.

2.2 Ghrelin and its receptor agonist

Ghrelin is a growth hormone (GH)-releasing polypeptide that binds to the GH secretagogue receptor (GHSR-1α) and stimulates appetite by activating the neuropeptide Y (NY) in the hypothalamus and helps in regulation of body weight [29, 30]. Studies have shown that ghrelin can reduce dexamethasone, fasting, denervation, cancer and cisplatin-induced muscle atrophy [31, 32]. In cachexia induced by lung adenocarcinoma, ghrelin treatment can reduce the expression of TNF-α, IL-1β, IL-6 and C-reactive protein, and inhibit skeletal muscle atrophy by restoring the expressions of the p-Akt and p-FoxO1, and reducing the expressions of p-p38 mitogen-activated protein kinase and p-NF-κB in skeletal muscle of tumor-bearing mice [33]. A three-week clinical study of ghrelin therapy in cachexia patients with nausea, COPD and chronic heart failure (CHF) showed an increase in lean body mass and muscle strength [29, 34]. Although ghrelin plays a key role in stimulating appetite, gaining body weight and preventing muscle catabolism, its clinical efficacy is limited due to its half-life (0.5 h) and route of administration (intravenous) [35].

Ghrelin agonists (such as anamorelin) have the advantage of oral activity. Compared with ghrelin (0.5 h), it has a better half-life (7–12 h) [36]. A randomized, double-blind, placebo-controlled phase I clinical study showed that anamorelin gained body weight after 6 days of treatment [37]. In two phase II anamorelin trials in cachectic patients with advanced or incurable cancer [38] and two multinational phase III trials (ROMANA 1 and 2 trials) in cachectic patients with unresectable non-small cell lung cancer (NSCLC) [39], significant gains were recorded in lean body mass and body weight over 12 weeks, but there was no improvement in physical functions and hand-grip strength. Similarly, a multicenter, open-label, single-arm study investigated the efficacy and safety of anamorelin in advanced gastrointestinal cancer patients with cancer cachexia, and this study showed a positive effect of anamorelin on lean body mass, body weight, anorexia and patients' nutritional status [40]. Furthermore, anamorelin treatment was well tolerated over 12 weeks. Finally, two meta-analyses also strongly supported the positive effect of anamorelin on lean body mass and body weight [41, 42]. Recently, a single-center study on healthy young adults showed anamorelin elicited modest increases in hunger and achieved significant increases in hunger and caloric intake [43]. The findings are consistent with multi-center findings in cachectic cancer patients and expand the evidence supporting anamorelin as a potential intervention.

2.3 β-Adrenoceptor agonists

Muscle growth can also be stimulated by activation of G-protein coupled β2-adrenoreceptor (β2-AR), which causes protein kinase A activation [44] and thereby stimulating PI3K/Akt/mTOR signaling [45]. Formoterol is a β2-AR agonist, the administration of formoterol significantly increased the levels of follistatin and decreased the levels of myostatin and its receptors (activin receptor IIB, ActRIIB) in tumor-bearing rats, thereby regulating muscle mass loss [46, 47]. In addition to skeletal muscle, formoterol also shows a strong protective effect on the

heart muscle [48]. Clinical studies have also shown that formoterol treatment can increase the content of PGC-1α and mtDNA in skeletal muscle of COPD patients to enhance the oxidation process of skeletal muscle and improve exercise ability [49]. Clenbuterol is another β2-AR agonist and can improve skeletal muscle atrophy in a variety of muscle atrophy models dominated by denervation [50], immobilization [51] and spinal cord injury [52]. However, due to concerns about potential cardiovascular side effects [44, 53], such as cardiac arrhythmia, there has been little interest in the clinical applications of β2-AR agonists for muscle atrophy treatment. Among them, espindolol may be a potentially attractive compound. It is a β1 receptor antagonist, a partial β2 receptor agonist and also has 5-HT1a receptor activities. In old rats, espindolol has been shown to significantly increase muscle mass, while reducing fat mass without negatively affecting heart function [54]. In addition, it has also shown very promising results in phase IIa cancer cachexia studies leading to increased muscle mass and grip strength [55, 56].

3. Enzyme inhibitors

3.1 Cox2 inhibitors

Cox2 is a bifunctional enzyme with cyclooxygenase and peroxidase activities. Cyclooxygenase activity is responsible for the synthesis of prostaglandins (PGE2) from arachidonic acid, while peroxidase activity can produce adjacent carcinogens. Both Cox2 and PGE2 are downstream effectors of cytokine activity and mediate cachexia [57]. A placebo-controlled study of celecoxib (Cox2 inhibitor) on cachectic patients with either head and neck or gastrointestinal cancer showed a significant increase of body mass and the quality of life [58]. In addition, a phase II non-randomized trial examined the efficacy and safety of celecoxib on cancer cachexia. Celecoxib administered at 300 mg/day for 4 months induced a significant increase of lean body mass, a decrease of serum TNF-α levels, and a trend toward a reduction of fatigue symptom [59]. Moreover, side effects such as grade 1/2 anemia, neuropathy and epigastralgia have been observed in only a few patients, and no grade 3/4 adverse events have been observed. Recently, a randomized double-blind clinical trial of combined treatment with megestrol acetate plus celecoxib versus megestrol acetate alone in cachexia-anorexia syndrome induced by gastrointestinal cancers was performed, however, this study failed to show that adding celecoxib (200 mg/day) to megestrol (320 mg/day) could enhance anti-cachexic effects of megestrol [60]. Meloxicam is another Cox2 inhibitor, and can suppress the expression of Cox2, Atrogin-1 and MuRF1 induced by lipopolysaccharide (LPS), and regulate the loss of muscle mass in rats by attenuating protein degradation [61]. In addition to cachexia, the administration of meloxicam can also inhibit the upregulation of Atrogin-1 and MuRF1 in the muscles of arthritis rats and improve the loss of muscle mass [62].

3.2 Histone deacetylase inhibitors

Trichostatin A (TSA) is a well-known class I and II histone deacetylase inhibitor. Published data indicate that TSA regulates atrogenes level and controls muscle mass by reducing HDAC4 activity and myogenin expression, and increasing Dach2 level under denervation condition (neuromuscular disorders) [63]. TSA treatment can improve body weight, myofiber cross-sectional area and myofiber number [64]. Recent report shows that TSA inactivates FoxO by inhibiting HDAC activity,

which leads to atrophy of skeletal muscle atrophy and contractile dysfunction [65]. In addition, under nutrition-deprived atrophy on C2C12 myotubes, TSA treatment leads to the suppression of FoxO target genes, including Lc3 (autophagy marker), MuRF1 and Atrogin-1 [66]. Similarly, TSA treatment can regulate muscle depletion by inhibiting the levels of Atrogin-1 and MuRF1 in dexamethasone-induced atrophic mice [63]. However, study shows that TSA treatment increased the expression level of follistatin (a negative regulator of skeletal muscle development), without retaining or increasing muscle mass in tumor-bearing mice [67]. Recent studies have shown that TSA can inhibit skeletal muscle atrophy and histomorphological alterations induced by unloading [68] and cigarette smoke (the main risk factor for COPD) [69]. Due to the contradictory findings, further research is needed to confirm the use of HDAC blockers to regulate atrophy.

3.3 PDE inhibitors

Torbafylline (HWA 448) is a xanthine derivative which acts as a phosphodiesterase (PDE) inhibitor [70]. Torbafylline treatment down-regulates the mRNA expression of cathepsin L, calpain and E3 ligases, and regulates the proteolytic pathway in burn-induced injury. In addition, the anti-atrophic effects of torbafylline have been demonstrated in casting, denervation or cancer induced cachexia models [70–72]. Torbafylline inhibits PDE activity leading to stimulation of the anti-proteolytic effect in PDE4/cAMP/Epac/PI3K/Akt pathway-mediated muscle atrophy [73]. Pentoxifylline (PTX) is another xanthine derivative that is non-selective in inhibiting PDE. Published data indicate that the administration of PTX under various pathological conditions in animal models (diabetes, tumors, sepsis) can stimulate the formation of cAMP, and by down-regulating calpain, cathepsin L and proteasome proteolytic system activity [74–76]. Other selective inhibitors of PDE, including rolipram and cilomilast have also been shown to reduce muscle atrophy in denervation and casting animal models [77, 78].

3.4 Angiotensin-converting enzyme inhibitors

ANGII induces muscle atrophy through several mechanisms including suppresses protein anabolism by reducing IGF-1 level and appetite, and promotes protein catabolism by increasing reactive oxygen species (ROS) and intermediate molecules (TNF-α, IL-6, glucocorticoids) in skeletal muscle [79]. In ACE-Is, enalapril treatment can reduce the risk of weight loss by>19% and delay the occurrence of cachexia by about 8 months [80]. Studies conducted in an old rat model show that the administration of enalapril can increase muscle strength and has a protective effect on age-related muscle degeneration [81]. Perindopril (an ACE inhibitor) has shown especially in a double-blind randomized controlled trial, which evaluated the effect of perindopril on the elderly 6-minute walking distance, thereby improving physical function, especially the 6-minute walk distance and reduced the incidence of hip fractures [82]. In subjects with dysfunction, perindopril improved exercise capacity to the extent reported after 6 months of exercise training [83]. However, the use of the perindopril in cachectic mice bearing colon-26 tumors to inhibit this pathway does not reduce muscle atrophy, nor does it increase the production of maximum muscle strength. Nonetheless, treatment with ACE inhibitors did enhance physical function and reduce fatigue of respiratory muscles. These effects appear to be due to a shift to a more oxidized muscle phenotype, as evident from increased oxidative enzyme capacity in the muscle cross-section [84].

4. Anti-inflammatory drugs

4.1 Thalidomide

Thalidomide is a glutamic acid derivative with various pharmacological activities, such as anti-inflammatory, immunomodulatory, anti-angiogenic, anti-emetic and sedative effects. Report shows that thalidomide and its derivatives can inhibit Cox2 and PGE2 synthesis induced by LPS in murine macrophages [85], and control systemic inflammation. In addition, evidence shows that thalidomide can reduce serum IL-6 and CRP levels in patients with cancer cachexia [86, 87]. Another study showed that thalidomide can maintain the fast-twitch type myofibers by reducing the expression of TNF-α and TGF-β1 in soleus muscle of cholangiocarcinoma rats [88]. Down-regulation of NF-κB/iNOS pathway by chronic thalidomide treatment improves hepatopulmonary syndrome and skeletal muscle atrophy in rats with biliary cirrhosis [89]. In addition to anti-inflammatory and anti-cachectic activity, thalidomide treatment (Phase II trial) also showed an effect on appetite in 64% of patients with advanced stage of cancer [87]. Studies reported that thalidomide (100 mg/day and 200 mg/day) treatment showed a significant improvement in body weight and skeletal muscle atrophy in AIDS associated cachexia patients [90]. Similarly, another research team worked with pancreatic cachexia patients and observed a significant increase in body weight of patients treated with thalidomide [91]. The lack of benefits was mainly due to the drug toxicity of thalidomide including peripheral neuropathy, dizziness, constipation and rash, considering that 47% of patients receiving active treatment were unable to continue taking thalidomide due to side effects and disease-related morbidity [92].

4.2 Anti-IL-6/STAT3

Evidence has shown that antibodies against IL-6 or its receptor can effectively reduce skeletal muscle atrophy and cachexia in mouse models [93, 94]. Preliminary results of a phase II double-blind trial in patients with advanced NSCLC have shown that ALD518 (humanized IL-6 monoclonal antibody) can reverse fatigue and prevent muscle loss [95]. Tocilizumab is an IL-6 receptor (IL-6R) neutralizing antibody approved by the FDA for rheumatoid arthritis. It can destroy the binding of IL-6/IL-6R to GP130, and cause the decrease of JAK/STAT3 pathway activity, reduce B cell hyperactivity and lead to a dramatic normalization of the acute phase reactions [96, 97]. Pharmacologic inhibition of the IL-6R using tocilizumab antennas skeletal muscle atrophy and function loss during infection [98]. Recently, a case of 65-year-old man who underwent percutaneous coronary intervention for acute myocardial infarction received tocilizumab led to prompt remission of Takayasu arteritis activity and improvement of left ventricular function and skeletal muscle atrophy [99]. Ruxolitinib, a JAK1/2 inhibitor, may protect muscle through on-target effects because it significantly reduces IL-6-induced STAT3 activation and myotube atrophy in vitro [100]. However, due to the inability to recruit qualified patients, the clinical trial of cancer patient study (NCT02072057) that investigating whether blocking downstream signaling of IL-6 by ruxolitinib improves muscle atrophy were terminated. In addition, there is evidence that C188-9 (a small molecule of STAT3 inhibitor) can reduce skeletal muscle atrophy in tumor-bearing mice [101, 102], but there are no relevant clinical studies.

4.3 Anti-TNF-α

Studies have shown that the administration of anti-murine TNF IgG in rats bearing Yoshida AH-130 ascites hepatoma can reduce circulating TNF-α and

inhibit muscle protein degradation [103]. Similarly, injecting soluble TNF receptors (sTNFR1, a specific inhibitor of TNF-α) prevents the interaction of TNF-α with its receptor and attenuates ubiquitin transcription, reduce the waste of skeletal muscle and preserve body weight in cardiac cachexia [76]. A study reported the opposite effect of sTNFR1 on arthritic rat that it did not alter muscle mass and MuRF1 and Atrogin-1 gene expression [104]. Infliximab is a chimeric monoclonal antibody that blocks TNF-α action, thereby preventing its binding to cellular receptors and downstream immunological effects. A phase II study of the combined chemotherapy drugs gemcitabine and infliximab did not show the benefit of maintaining lean body mass or survival in pancreatic cancer cachexia patients [105]. Interestingly, in clinical trials of Crohn's disease patients with skeletal muscle atrophy or sarcopenia arising from chronic inflammation, significant gains were recorded in muscle volume and strength over 25 weeks of infliximab treatment [106, 107]. Etanercept is a recombinant fusion protein that acts as a decoy receptor to neutralize TNF-α, and has been used to treat inflammatory diseases including rheumatoid arthritis. In another study, significant weight gain was observed in rheumatoid arthritis patients who received etanercept twice a week for 12 consecutive months [108]. A phase I/II study compared the efficacy of etanercept with gemcitabine and gemcitabine alone for the treatment of advanced pancreatic cancer cachexia patients, and the results were also disappointing because the addition of etanercept did not improve symptoms of cancer cachexia [109].

4.4 Anti-IL-1α

MABp1 is a human antibody against IL-1α (a chronic inflammatory mediator) and has anti-tumor activity. Intravenous MABp1 treatment for 8 weeks in adults with metastatic solid cancer showed increased lean body mass and improved quality of life (fatigue, pain, and loss of appetite), and has no toxic; however, there was no control group in this study [110]. A randomized, double-blind, placebo-controlled phase III clinical study showed that MABp1 improved the lean body mass, anorexia, fatigue and pain scores in advanced colorectal cancer patients [111]. Another phase I dose-escalation study evaluating the IL-1α-targeted monoclonal antibody xilonix in patients with NSCLC showed increased lean body mass and improved symptoms, suggesting a clinically important response [112]. In view of this, a phase III placebo-controlled study of human antibodies against IL-1α has been conducted in patients with advanced colorectal cancer to assess the remission rate of the disease, muscle mass and appetite. Xilonix was very well tolerated by NSCLC patients, with the clinically significant reductions in pain, fatigue and improved lean body mass and appetite [113]. However, the primary limitation of this report is the small number of patients which made any comparisons statistically difficult.

4.5 TWEAK/Fn14 inhibition

The inflammatory cytokine TNF-like weak inducer of apoptosis (TWEAK) and its related receptor fibroblast growth factor-inducible 14 (Fn14) play multiple roles in proliferation, inflammation and wound repair. TWEAK/Fn14 signaling also negatively regulates muscle growth and function [8]. Report showed that TWEAK activates noncanonical NF-κB pathway and promotes myoblast fusion at low concentrations (10 or 100 ng/ml), and activates canonical NF-κB signaling to inhibit differentiation at high concentrations (500 ng/ml). Thus, TWEAK can maintain myoblast differentiation at physiological conditions; however, under pathological conditions (such as denervation and disuse), TWEAK/Fn14 system becomes activated and causes muscle atrophy [8]. Blocking antibodies against TWEAK antibody

can improve muscle function in mice caused by myotonic dystrophy and amyotrophic lateral sclerosis (ALS) [114, 115]. Consistent with these findings, colon-26 tumor-bearing mice treated with anti-Fn14 antibodies showed increased weight and muscle mass, improved muscle fatigue, and increased survival [116]. These results indicate that neutralizing antibodies against TWEAK and Fn14 should be further explored in various muscle atrophy models and clinical trials.

5. Other investigational drugs

5.1 Myostatin inhibition

Existing evidence indicates that members of the TGF-β superfamily, such as myostatin and activin A, are powerful catabolic stimuli that can inhibit muscle growth and promote muscle protein loss in various disease states [117]. It is reported that myostatin can improve the dystrophy phenotype of mdx mouse models, sarcopenia in aging mouse models and muscle atrophy in tumor-bearing mice [118, 119], which can significantly inhibit systemic inflammation and prolong the survival of tumor-bearing mice without affecting tumor growth [117]. There are currently two main strategies for targeting myostatin signals: First, neutralize myostatin directly by using humanized myostatin antibody (LY2495655), and second, block ActRII by using soluble ActRIIB (ACE-031) or ActRII antibody (bimagrumab/BMY338). LY2495655 treatment had mixed results in elderly subjects: the appendicular lean body mass and gait speed were slightly improved, and despite increased muscle mass, grip strength was not affected [120]. However, a randomized, phase II trial in patients with pancreatic cancer, LY2495655 treatment have no significant improvement in muscle volume or functional. Additionally, among possibly drug-related adverse events, fatigue, diarrhea, and anorexia were more common in LY2495655-treated than in placebo-treated patients [121]. Soluble recombinant ActRIIB and other "ligand trap" interventions can generally inhibit TGF-β signaling and affect other tissues and processes, including reproduction and angiogenesis, with some causing severe off-target effects. Therefore, new strategies that target myostatin receptors and thereby reduce the activity of other ligands seem more promising. For example, after ACE-031 treatment, a group of 48 postmenopausal women gained weight and increased lean body mass [122]. However, in the phase II clinical trial conducted by ACE031 with Duchenne muscular dystrophy (DMD) patients and healthy volunteers, some participants experienced bleeding gums, nosebleeds, and skin vasodilation, which led to the interruption of the trial [123]. Blocking ActRII by administering BMY338 can greatly increase muscle mass and prevent dexamethasone-induced muscle atrophy in mice [124], and significantly improve patient's lean body mass, muscle mass, and 6-minute walking test in patients with myositis after 8 weeks of treatment. However, no significant differences were observed after 24 weeks of treatment [125]. In addition, there are no beneficial effects on these treatments were reported in cancer patients, while in COPD patients, muscle volume increases without affecting functional indicators, which is similar to the effect of BMY338 in sarcopenia patients [126, 127]. Therefore, these treatments seem to improve muscle mass and have less effect on muscle strength and other functional parameters [128].

5.2 Appetite stimulants

The FDA approved megestrol acetate (MA) as the treatment of cachexia caused by cancer and AIDS in 1993. More than 15 clinical trials have shown that this drug

can significantly improve appetite and lean body mass at a dose of 160–1600 mg/day. MA can be used alone or as a supplement along with meloxicam in patients with cancer cachexia, showing a positive effect in controlling weight loss [129]. Although the mechanism of appetite stimulation/weight gain is unclear, studies have shown that it is related to the involvement of neuropeptide Y and the inhibition of pro-inflammatory cytokines such as IL-1, IL-6 and TNF-α [130, 131]. However, a newer meta-analysis started in 2015, which studied the use of non-cancer cachexia (HIV, COPD, renal failure and geriatric cachexia) and concluded that progesterone therapy (MA or medroxyprogesterone acetate) has a negligible effect on weight gain when treat of non-cancer cachexia [132]. MA treatment can also cause serious side effects such as thromboembolism, peripheral edema, hyperglycemia, hypertension, adrenal suppression and adrenal insufficiency [132].

Previous studies have shown that cannabinoids have the potential to improve appetite, body weight and fat mass, as well as amelioration of quality of life in several chronic diseases including cancer [133]. The results of a pilot study conducted in adult patients with advanced solid tumors showed that patients receiving delta-9-tetrahydrocannabinol (THC) treatment had a marked increase in appetite [134]. However, the study did not record changes in participants' body weight and lean body mass, and a larger trial was needed to study the effect of cannabinoids on skeletal muscle atrophy. A pilot study in patients with advanced NSCLC showed food intake and quality of life in patients treated with nabilone (a tetrahydrocannabinol) have improved significantly [135]. However, another randomized, double-blind placebo-controlled trial showed that nabilone did not improve the symptoms of nausea during radiotherapy in head and neck cancer patients, nor did it have significant benefits for the appetite and body weight [136].

5.3 Natural compounds

Recently, growing evidence has shown that natural products play a key role in the prevention and treatment of skeletal muscle atrophy. Numerous studies conducted in vitro and in vivo confirmed that resveratrol treatment can prevent proteolysis-inducing factor (PIF), angiotensin I and II, phorbol ester, 12-O-tetradecanoylphorbol 13-acetate (TPA), and dexamethasone-induced protein degradation [137]. In addition, resveratrol has been shown to protect muscle atrophy under various catabolic conditions, including cachexia and disuse [138, 139]. Salidroside is one of the main phenylpropane glycosides found in *Rhodiola rosea*. Research shows that salidroside treatment can effectively maintain body weight, reduce fat and gastrocnemius muscle loss in CT26 and LLC models. Additionally, in combination chemotherapy, salidroside can synergistically enhance the anti-tumor activity of cisplatin, especially reduce or eliminate cachexia caused by chemotherapy. Further analysis showed that salidroside can significantly increase the expression of p-mTOR and MyHC in the gastrocnemius muscle [140]. Matrine improves skeletal muscle atrophy in CT26 induced cachexia via inhibiting the production of TNF-α and IL-6 and activating the Akt/mTOR/FoxO3α signaling pathway [141]. Other natural medicines reported to improve skeletal muscle atrophy include imperatorin [142], parthenolide [143], ursolic acid [144] and cryptotanshinone [145], but more research is still needed to prove the anti-muscular atrophy effect of these compounds.

6. Conclusions

Up-regulation of muscle protein catabolic is a sign of atrophy, so most potential drugs target the proteolytic system to cure or prevent skeletal muscle atrophy.

Due to the multifactorial pathogenesis of muscle atrophy, combining new drugs with multimodal transport interventions including exercise methods and nutritional interventions may be the most promising approach; however, few clinical trials have investigated this approach. In this light, a better understanding of the contributing factors and underlying mechanisms of muscle atrophy is essential for the development of targeted therapies, and new methods of combination therapy for muscle atrophy treatment are needed.

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Conflict of interest

The authors declare no conflict of financial interest.

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