

**COMPREHENSIVE REVIEW OF THE THERAPEUTIC POTENTIAL FOR THE
PREVENTION AND TREATMENT OF SKELETAL MUSCLE ATROPHY****Harsita Verma¹, Dr. Shobhit Prakash Srivastava^{2*}**¹Research Scholar, Dr. M C Saxena College of Pharmacy Lucknow Uttar Pradesh 226101, India.²Professor & Director, Dr. M C Saxena College of Pharmacy Lucknow Uttar Pradesh 226101, India.***Corresponding Author: Dr. Shobhit Prakash Srivastava**

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ABSTRACT

The progressive loss of muscle mass, strength, and functional ability is the hallmark of skeletal muscular atrophy, a crippling medical condition. Prolonged glucocorticoid therapy, physical inactivity, cancer cachexia, ageing (sarcopenia), and chronic diseases constitute some of the physiological and pathological circumstances that cause it to develop. Chronic inflammation, oxidative stress, mitochondrial dysfunction, impaired protein homeostasis, and activation of proteolytic pathways, such as the ubiquitin–proteasome, autophagy–lysosomal, and apoptotic systems, are some of the interrelated mechanisms involved in the pathogenesis of muscle atrophy. There is mounting evidence that bioactive substances produced from nature may provide useful treatment approaches to prevent muscle atrophy. Among these, ostivone has drawn notice for its strong anti-inflammatory and antioxidant effects as well as its capacity to control anabolic signalling pathways

KEYWORDS: Skeletal muscle atrophy; Ostivone; Muscle wasting; Ubiquitination; proteasome degradation pathway.**1. INTRODUCTION**

Skeletal muscle comprises approximately 40% of total body mass and is essential for movement, glucose regulation, metabolic control, and physical performance.^[1] Maintenance of muscle mass depends on a precise balance between protein synthesis and degradation.^[2] Disruption of this balance results in atrophy, characterised by a reduction in myofiber size, strength, and function. Common etiologies include sarcopenia, cancer cachexia, chronic inflammatory diseases, prolonged immobility, denervation, malnutrition, and glucocorticoid exposure.^[3] Muscle atrophy results from complex cellular and molecular processes. Activation of proteolytic systems, particularly the autophagy-lysosome pathway and the ubiquitin–proteasome system (UPS), plays a central role.^[4] Atrophic conditions upregulate muscle-specific E3 ubiquitin ligases, including MuRF-1 and Atrogin-1 (MAFbx), which accelerate myofibrillar protein breakdown. Suppression of anabolic pathways such as PI3K/Akt/mTOR further reduces protein synthesis.^[5] Chronic inflammation, oxidative stress, mitochondrial

dysfunction, and altered myokine signalling also contribute to muscle protein loss and impaired regeneration.^[6]

Muscle atrophy is associated with increased mortality, diminished quality of life, delayed recovery, and elevated morbidity.^[7] Despite its significant impact, effective pharmacological interventions remain limited. Current management strategies, including resistance training, nutritional supplementation, and hormonal modulation, are frequently insufficient, particularly in patients with severe inflammation or chronic disease.^[8] There is a critical need for multi-target therapies that simultaneously address inflammation, anabolic signalling, oxidative stress, and proteolytic pathways.^[9] Ostivone has emerged as a promising bioactive compound with anti-atrophic properties. Preliminary evidence suggests that ostivone modulates key signalling pathways involved in muscle protein turnover and demonstrates both anti-inflammatory and antioxidant activities.^[10] By targeting multiple mechanisms underlying muscle degeneration, ostivone may represent

a novel therapeutic strategy for the prevention and treatment of skeletal muscle atrophy.^[11] This review evaluates the therapeutic potential of ostivone for preserving muscle mass and function and provides an overview of the molecular pathways implicated in muscle atrophy.

2. Pathophysiology of atrophy in skeletal muscles

2.1 Protein Homeostasis Imbalance

Skeletal muscle atrophy primarily results from disrupted protein homeostasis, where degradation exceeds synthesis. Under normal conditions, growth factors like IGF-1 activate the PI3K/Akt/mTOR pathway, promoting protein synthesis and inhibiting atrophy-related gene transcription by keeping FoxO transcription factors inactive.^[12,13] In atrophic states caused by inflammation,

glucocorticoid excess, cachexia, denervation, or disuse, Akt signalling is suppressed, reducing mTORC1 activity and protein synthesis.^[14] Dephosphorylated FoxO (notably FoxO1 and FoxO3) enters the nucleus and induces muscle-specific E3 ubiquitin ligases, Atrogin-1 (MAFbx) and MuRF-1, which tag myofibrillar proteins for degradation by the ubiquitin–proteasome system. FoxO activation also upregulates autophagy-related genes, increasing lysosomal protein breakdown.^[15] Pro-inflammatory cytokines such as TNF- α and IL-6 further exacerbate atrophy by activating NF- κ B and increasing MuRF-1 expression.^[16] The combined inhibition of anabolic signalling and activation of proteolytic pathways leads to net protein loss, reduced fibre size, mitochondrial dysfunction, and progressive muscle weakness.^[17]

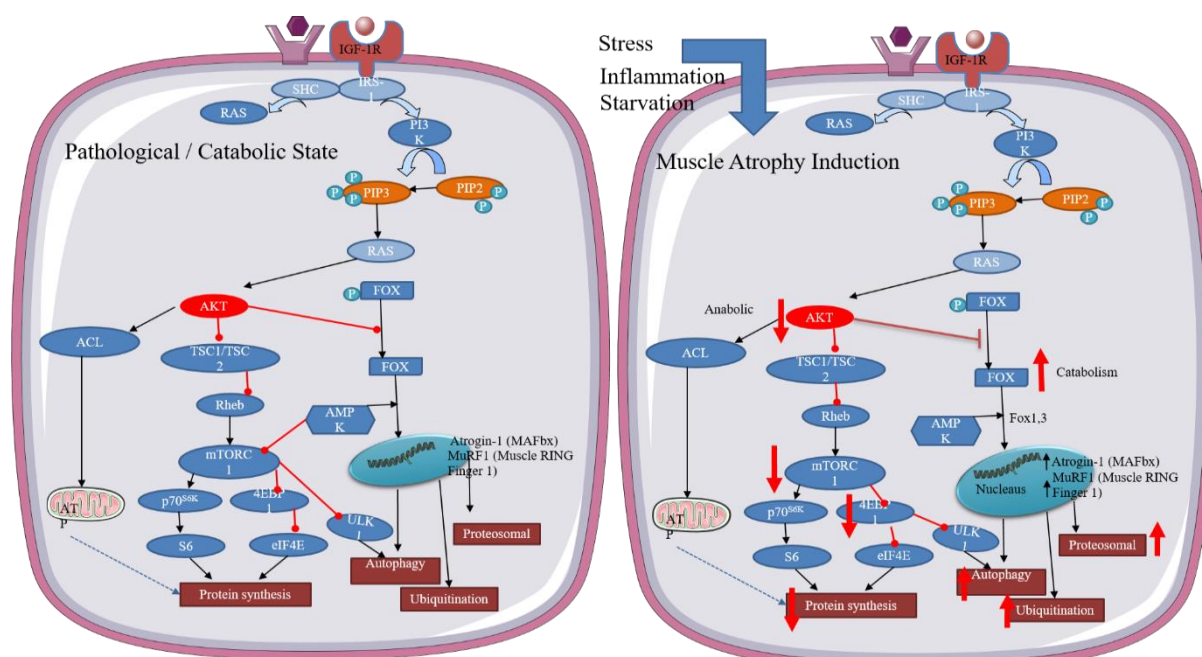
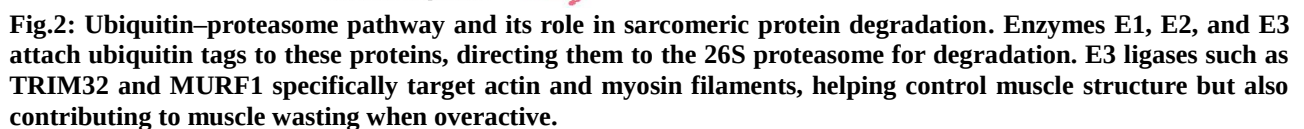


Fig. 1: Schematic depiction of IGF 1/PI3K/Akt signalling in skeletal muscle, comparing the pathological/catabolic condition (left) with stress-induced muscle atrophy (right), emphasising modifications in mTORC1 activity, protein synthesis, autophagy, and ubiquitin-proteasome-mediated proteolysis.

The ubiquitin-proteasome system (UPS) is the primary and most rapid mechanism for the selective degradation of myofibrillar proteins during muscle atrophy. This ATP-dependent process targets regulatory and contractile proteins through ubiquitination. In atrophic conditions such as cancer cachexia, denervation, ageing, glucocorticoid exposure, and disuse, suppressed Akt signalling permits FoxO transcription factors to enter the nucleus.^[18] These factors significantly increase the expression of the muscle-specific E3 ubiquitin ligases MuRF-1 and Atrogin-1 (MAFbx).^[19] These ligases provide the ubiquitination cascade with substrate specificity and catalyse the attachment of polyubiquitin chains to structural proteins such as myosin heavy chain, titin, troponin, and Z-disc components, primarily via Lys48.^[20] The 26S proteasome then recognises and

degrades polyubiquitinated proteins after its 19S regulatory cap unfolds the substrates and delivers them to the 20S catalytic core for proteolysis. Crucially, calpains and caspase-3 first degrade myofibrillar proteins, allowing the UPS to consume them. A molecular hallmark of muscle atrophy is the sustained activation of Atrogin-1 and MuRF-1, which is directly correlated with the rate of muscle protein loss and the decrease in fibre cross-sectional area.^[21]



Cellular quality control depends on autophagy, a lysosome-dependent breakdown mechanism. By eliminating malfunctioning mitochondria, misfolded proteins, and damaged organelles, it preserves muscle homeostasis at resting levels.^[22] Muscle wasting results from autophagy becoming overly active under prolonged stress, such as nutritional scarcity, denervation, or systemic illness. By activating autophagy-related genes,

including LC3, Bnip3, Beclin-1, and Gabarapl1, FoxO3 plays a crucial regulatory role.^[23] This results in the formation of double-membraned autophagosomes, which engulf cytoplasmic debris and fuse with lysosomes for enzymatic breakdown. Selective mitochondrial autophagy, or excessive mitophagy, lowers mitochondrial content and hinders ATP synthesis and oxidative phosphorylation.^[24,25]



2.4 Oxidative Stress and Dysfunction of Mitochondria.

Defective mitochondria and NADPH oxidases are the main sources of elevated reactive oxygen species (ROS), which oxidatively modify proteins, lipids, and DNA.^[26] Oxidised myofibrillar proteins are more vulnerable to proteasomal degradation and ubiquitination. Additionally, ROS are signalling molecules that increase the production of Atrogin-1 and MuRF-1 by activating redox-sensitive transcription factors, including NF- κ B and FoxO. Furthermore, oxidative stress increases the expression of catabolic genes by activating the p38 MAPK and JNK pathways.^[27] Reduced membrane potential, decreased ATP synthesis, and impaired electron transport chain activity are all signs of mitochondrial malfunction. This energy shortage triggers AMPK, which in turn inhibits mTORC1 and suppresses protein synthesis. In addition to causing myonuclear loss and fibre shrinkage, persistent oxidative stress also stimulates the opening of mitochondrial permeability transition pores, the release of cytochrome c, and the activation of caspase-mediated apoptotic pathways.^[28]

2.5 Inflammation

A major systemic cause of skeletal muscle atrophy is chronic inflammation, especially in diseases like cancer cachexia, obesity, chronic illness, and sepsis. TNF- α , IL-6, and IL-1 β are pro-inflammatory cytokines that trigger intracellular signalling cascades that promote proteolysis and inhibit regeneration.^[29] To hinder myogenic differentiation, TNF- α triggers NF- κ B signalling, which, in turn, directly increases MuRF-1 transcription and inhibits MyoD. IL-6 triggers the JAK/STAT3 pathway, leading to mitochondrial dysfunction and muscle breakdown.^[30] Additionally, inflammatory cytokines cause insulin resistance by inhibiting IGF-1/Akt signalling, which in turn inhibits mTOR-mediated protein synthesis. Furthermore, inflammation increases ROS production, forming a feedback loop that maintains NF- κ B and FoxO activation.^[31] Long-term exposure to these cytokines causes progressive loss of muscle mass and function by accelerating protein breakdown, inhibiting satellite cell activation, and impairing muscle repair.^[32]

3. Pharmacological Treatments for Atrophying Muscles

Pharmacological treatments for muscle atrophy aim to restore the balance between protein synthesis and degradation by targeting underlying molecular processes. Because atrophy is driven by oxidative stress, inflammation, mitochondrial dysfunction, activated proteolytic systems, and suppressed anabolic signalling, effective therapies often require multi-pathway regulation rather than single-target approaches.^[33] Increasing anabolic signalling, especially by activating the IGF-1/PI3K/Akt/mTOR pathway, is one such tactic. By boosting mTOR activity and preventing FoxO-

mediated transcription of atrophy-related genes, substances such as testosterone, selective androgen receptor modulators (SARMs), and IGF-1 analogues promote protein synthesis and muscle growth.^[34] Supplemental nutrients like β -hydroxy β -methylbutyrate (HMB) and essential amino acids, particularly leucine, also decrease muscle protein breakdown and activate mTOR signalling.^[35] Inhibiting proteolytic pathways, especially the ubiquitin-proteasome system (UPS), is another important strategy. The goal of experimental approaches targeting muscle-specific E3 ubiquitin ligases, such as Atrogin-1 and MuRF-1, is to reduce excessive myofibrillar protein degradation.^[36] Despite the existence of direct proteasome inhibitors, their systemic toxicity restricts their therapeutic use in treating muscle atrophy. Autophagy modulation is also crucial; therapeutic interventions aim to preserve basal cellular quality control while preventing excessive autophagic breakdown.^[37] By suppressing Akt signalling and promoting Smad2/3 activation, myostatin impairs muscle development. The goal of follistatin-based treatments, activin receptor blockers, and monoclonal antibodies against myostatin is to alleviate this inhibitory impact and encourage muscle growth.^[38]

Anti-inflammatory treatments such as TNF- α inhibitors and IL-6 pathway blockers may reduce NF- κ B- and JAK/STAT-mediated catabolic signalling, as inflammation plays a major role in muscle atrophy. It is also possible to lessen steroid-induced myopathy by limiting glucocorticoid exposure.^[39] N-acetylcysteine and coenzyme Q10 are examples of antioxidants that may limit activation of proteolytic signalling pathways by reducing reactive oxygen species and maintaining mitochondrial integrity.^[40] Emerging strategies such as targeted molecular inhibitors, stem cell-based therapies, and gene therapy seek to modify atrophy-related genes or enhance regenerative capacity. However, these approaches remain largely experimental.

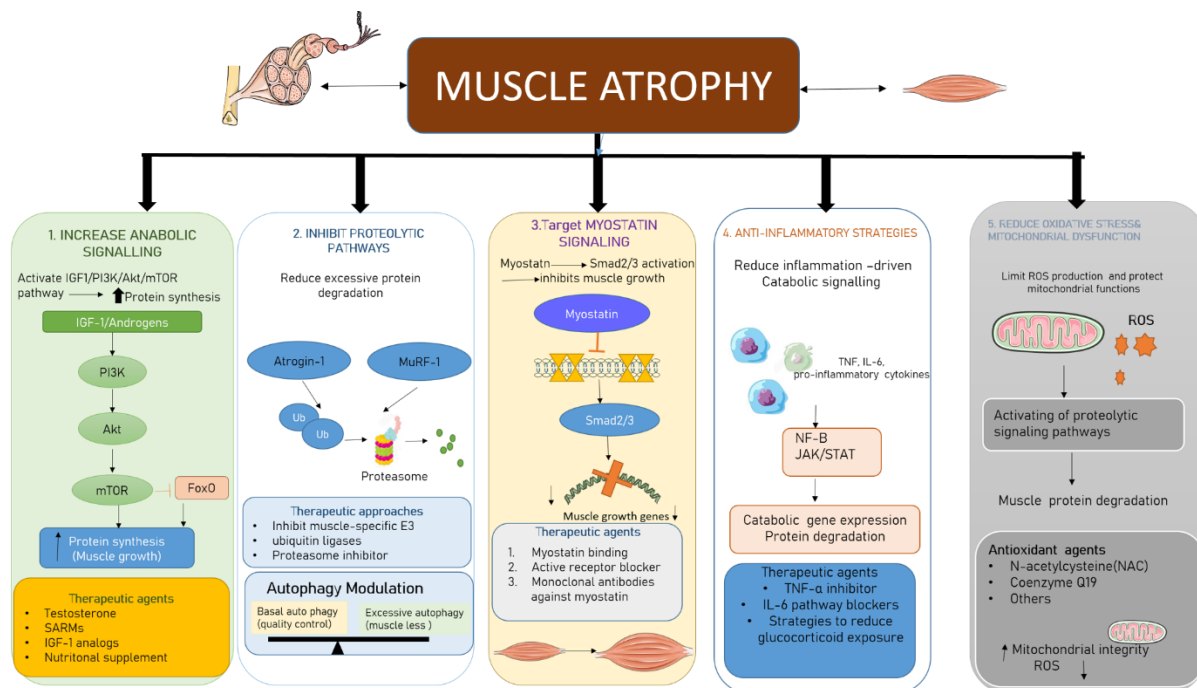


Fig 4: Schematic overview of the major molecular mechanisms underlying skeletal muscle atrophy and key pharmacological intervention strategies.

4. Ostivone Potential for Therapy

4.1 Antioxidant Properties

Pharmacological management of muscle atrophy requires a comprehensive approach that integrates resistance training and adequate nutrition. Future therapeutic strategies are expected to emphasise combination approaches that enhance anabolic processes, inhibit proteolysis, reduce inflammation, and protect mitochondrial function to achieve sustained improvements in muscle mass and strength. Reactive oxygen species (ROS) play a significant role in skeletal muscle atrophy by damaging myofibrillar proteins and activating proteolytic pathways, including NF-κB and FoxO. Elevated ROS levels also initiate apoptotic signaling, decrease ATP synthesis, and impair mitochondrial function.^[41] By scavenging free radicals and boosting natural antioxidant defenses, including superoxide dismutase, catalase, and the glutathione system, ostivone may have protective effects.^[42] Lowering ROS levels reduces protein degradation, inhibits the activation of muscle-specific E3 ubiquitin ligases (MuRF-1 and Atrogin-1), and protects mitochondrial integrity.^[43] Therefore, under atrophic conditions, ostivone's antioxidant effects help preserve muscle protein stability and overall muscle function. Additionally, maintaining Akt phosphorylation enhances mTORC1 activity, which increases protein synthesis through 4E-BP1 and p70S6K, thereby promoting translational efficiency and ribosomal biogenesis.^[44] Concurrently, Akt activation inhibits the nuclear translocation of FoxO transcription factors, reducing the expression of muscle-specific E3 ubiquitin ligases, including Atrogin-1 and MuRF-1. This dual mechanism

supports the maintenance of muscle mass and fiber cross-sectional area by promoting protein synthesis and suppressing catabolic gene expression during atrophic conditions.^[45]

4.2 Anabolic Signaling Modification

By stimulating the IGF-1/PI3K/Akt/mTOR pathway, estrogen may enhance skeletal muscle anabolism. Maintaining Akt phosphorylation increases mTORC1 activity, which, in turn, boosts protein synthesis via 4E-BP1 and p70S6K, thereby promoting translational efficiency and ribosomal biogenesis.^[46] At the same time, Akt activation suppresses the nuclear translocation of FoxO transcription factors, thereby reducing the expression of muscle-specific E3 ubiquitin ligases, namely Atrogin-1 and MuRF-1.^[47] During atrophic conditions, this dual action helps maintain muscle mass and fiber cross-sectional area by increasing protein synthesis and suppressing catabolic gene expression.^[48]

4.3 Proteolytic Pathway Inhibition

Ostivone may limit excessive muscle protein breakdown by modulating autophagy and suppressing the ubiquitin-proteasome system. By inhibiting FoxO- and NF-κB-mediated transcription, it reduces the production of Atrogin-1 and MuRF-1, thereby decreasing polyubiquitination and proteasomal degradation of myofibrillar proteins.^[49] Ostivone may also restore autophagic balance, maintaining essential cellular quality control while preventing excessive breakdown of organelles and cytoplasmic components. Together, these effects reduce proteolysis and help preserve the structural integrity and function of skeletal muscle fibers.^[50]

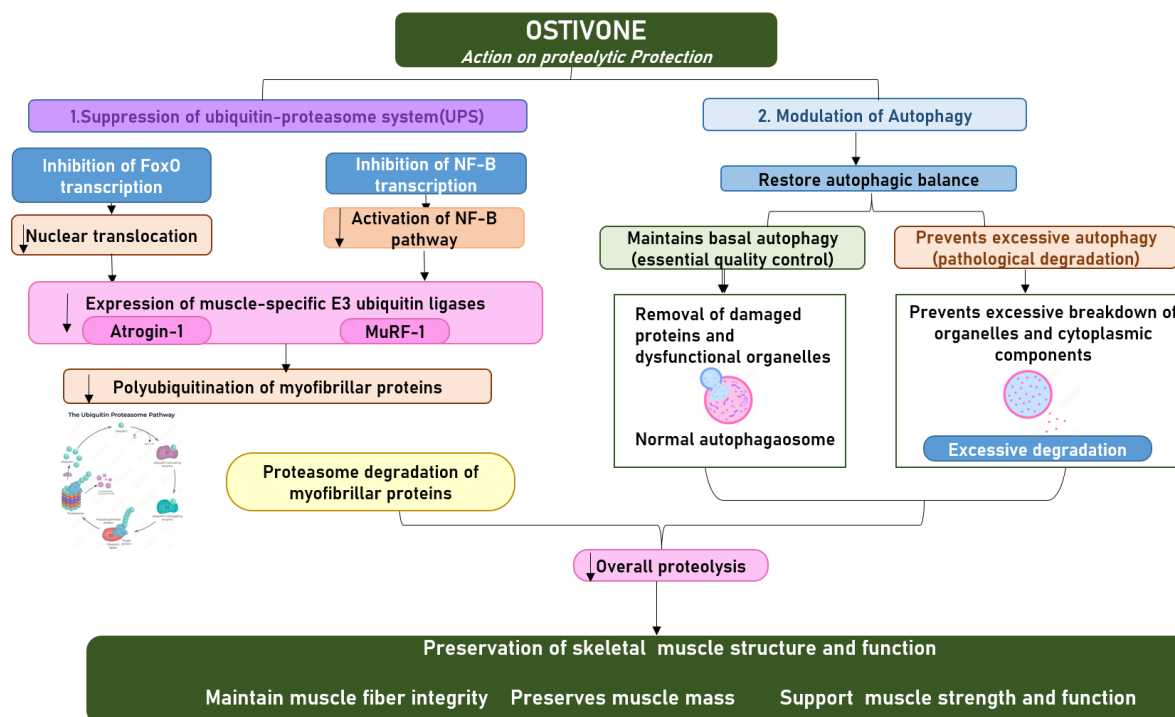


Fig.5: Flowchart illustrating the anti-proteolytic effects of ostivone in skeletal muscle.

4.4 Reduction of Inflammation

Chronic inflammation contributes significantly to skeletal muscle atrophy by activating the NF- κ B and JAK/STAT3 pathways, thereby increasing catabolic gene expression and impairing regeneration.^[51] Ostivone may reduce this inflammatory response by lowering pro-inflammatory cytokines such as TNF- α , IL-6, and IL-1 β .^[52] Suppressing these pathways supports muscle repair, reduces oxidative stress, and limits proteolysis. In cases of persistent inflammation, ostivone's anti-inflammatory effects help maintain muscle mass, fiber integrity, and function.^[53]

4.5 Protection of Mitochondria

Mitochondrial dysfunction is a major contributor to muscle atrophy, leading to reduced ATP synthesis, increased ROS, and activation of AMPK and apoptotic pathways.^[54] Ostivone may protect mitochondrial integrity by lowering ROS production, improving electron transport chain efficiency, and stabilizing membrane potential. Maintaining energy production and reducing oxidative stress helps preserve muscle fibers by supporting protein synthesis and preventing activation of proteolytic pathways.^[55]

5. Evidence from Preclinical Research

Animal studies on aging-related sarcopenia, glucocorticoid-induced muscle atrophy, and disuse atrophy demonstrate that ostivone preserves muscle fiber size, reduces atrophy-associated gene expression, improves endurance and grip strength, and lowers oxidative stress markers.^[56] As a multi-target agent, ostivone shows promise for conditions such as glucocorticoid-induced myopathy, cancer cachexia,

sarcopenia, chronic inflammatory disorders, and disuse atrophy.^[57] By enhancing anabolic signaling, inhibiting proteolytic pathways, reducing oxidative stress, protecting mitochondrial function, and mitigating inflammation, ostivone addresses the multifactorial nature of muscle atrophy more effectively than single-pathway therapies.^[58] When combined with resistance training and nutrition, Ostivone may further improve muscle mass, strength, and recovery. However, comprehensive clinical trials are required to determine its safety, optimal dosage, pharmacokinetics, and long-term efficacy.^[59] Future research should prioritize combination strategies, biomarker-guided therapy, and targeted delivery to maximize therapeutic benefits and minimize risks. Additional clinical and translational studies are necessary to establish ostivone as an effective treatment for muscle atrophy.^[60] Skeletal muscle atrophy is a highly complex degenerative process. A central aspect of its progression is the activation of catabolic regulators, such as FoxO transcription factors, which upregulate muscle-specific E3 ubiquitin ligases (MuRF-1 and Atrogin-1), alongside repression of the IGF-1/PI3K/Akt/mTOR anabolic pathway.^[61] This leads to excessive activity of the ubiquitin-proteasome system and selective degradation of myofibrillar proteins. Simultaneously, mitochondrial dysfunction reduces ATP synthesis and increases reactive oxygen species (ROS) production, while dysregulated autophagy accelerates the breakdown of organelles and cytoplasmic components.^[62] Through the NF- κ B, JAK/STAT, and stress kinase pathways, oxidative stress and chronic inflammation further amplify proteolytic signaling, creating a self-perpetuating cycle of muscle protein loss, impaired regeneration, and progressive functional

decline.^[63] Given the multifaceted nature of muscle atrophy, therapeutic strategies targeting a single pathway are often insufficient. Ostivone represents a promising multidimensional therapeutic option capable of modulating several convergent pathways simultaneously. By enhancing anabolic signaling through preservation of Akt/mTOR activity, suppressing FoxO-mediated transcription of MuRF-1 and Atrogin-1, regulating autophagic processes, reducing oxidative stress, maintaining mitochondrial integrity, and attenuating inflammatory cytokine signaling.^[64] Ostivone offers a comprehensive approach to restoring muscle homeostasis. Its capacity to influence interconnected molecular pathways suggests potential benefits in complex conditions such as sarcopenia, cachexia, chronic inflammatory disorders, and disuse-induced atrophy.^[65] While preclinical data show improvements in mitochondrial activity, fiber size, muscle mass, and function, clinical application requires further evaluation.^[66] Future studies should focus on determining optimal dosing, long-term safety, pharmacokinetics, and efficacy across diverse patient populations. Combination strategies involving resistance training, nutrition, and pharmaceutical therapy may further enhance clinical outcomes.

6. CONCLUSION

Skeletal muscle atrophy is a multifactorial and highly complex degenerative condition characterized by a persistent imbalance between protein synthesis and degradation. A central feature of its progression is the activation of catabolic regulators, particularly FoxO transcription factors, which drive the upregulation of muscle-specific E3 ubiquitin ligases such as MuRF-1 and Atrogin-1, alongside suppression of the IGF-1/PI3K/Akt/mTOR anabolic signaling pathway. This shift enhances the activity of the ubiquitin–proteasome system, resulting in selective degradation of myofibrillar proteins. Simultaneously, mitochondrial dysfunction reduces ATP production while increasing reactive oxygen species (ROS) generation, and dysregulated autophagy contributes to excessive breakdown of organelles and cytoplasmic components. Oxidative stress and chronic inflammation further exacerbate this process through activation of NF- κ B, JAK/STAT, and stress kinase pathways, creating a self-perpetuating cycle of proteolysis, impaired regeneration, and progressive functional decline. Given the multifaceted nature of muscle atrophy, therapeutic strategies targeting a single pathway often yield limited efficacy. Ostivone represents a promising multi-target therapeutic approach capable of modulating several converging mechanisms simultaneously. It enhances anabolic signaling by preserving Akt/mTOR activity, suppresses FoxO-driven expression of MuRF-1 and Atrogin-1, and helps maintain autophagic balance. In addition, it mitigates oxidative stress, preserves mitochondrial integrity, and attenuates inflammatory cytokine signaling. Through these integrated actions, Ostivone contributes to the restoration of muscle homeostasis and may offer therapeutic benefit

in complex conditions such as sarcopenia, cachexia, chronic inflammatory disorders, and disuse-induced atrophy. Preclinical studies suggest that Ostivone improves mitochondrial function, increases muscle fiber cross-sectional area, preserves muscle mass, and enhances functional performance. However, translation into clinical practice requires comprehensive evaluation. Future investigations should focus on optimizing dosing regimens, establishing long-term safety profiles, and assessing pharmacokinetics and therapeutic efficacy across diverse patient populations. Furthermore, combining such pharmacological interventions with resistance exercise and targeted nutritional strategies may yield synergistic benefits and improve clinical outcomes.

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