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Research Progress on Traditional Chinese Medicine in the Intervention of Sarcopenia through Regulation of the mTOR Signaling Pathway and Satellite Cell Function

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Abstract: ***Sarcopenia is an age-related syndrome characterized by declines in skeletal muscle mass, muscle strength, and physical function. The mechanistic target of rapamycin (mTOR) signaling pathway plays a crucial role in skeletal muscle protein synthesis, energy metabolism, and the proliferation and differentiation of muscle satellite cells, and is considered one of the key mechanisms underlying the development and progression of sarcopenia. In recent years, traditional Chinese medicine (TCM) has demonstrated advantages in the prevention and treatment of sarcopenia through multi-target and multi-pathway synergistic regulation, and its effects are closely associated with the mTOR signaling pathway and satellite cell function. This review summarizes the roles of the mTOR signaling pathway and muscle satellite cells in sarcopenia, as well as recent advances in TCM-mediated regulation of the mTOR pathway to promote satellite cell activation, proliferation, and myogenic differentiation, thereby improving skeletal muscle mass and function. The aim is to provide a theoretical basis and therapeutic insights for the prevention and treatment of sarcopenia using TCM.***

Keywords: Sarcopenia, Traditional Chinese medicine, mTOR signaling pathway, Muscle satellite cells, Myogenic differentiation.

1. Introduction

Sarcopenia is a progressive, systemic skeletal muscle disorder characterized by the loss of skeletal muscle mass, reduced muscle strength, and impaired physical performance. It has been recognized as an independent disease entity in the 10th Revision of the International Classification of Diseases, Clinical Modification (ICD-10-CM), under code M62.84 [1]. With the accelerating global aging of the population, the disease burden associated with sarcopenia has become increasingly prominent. A systematic review and meta-analysis based on global data estimated the prevalence of sarcopenia to be approximately 10%–27%, although substantial variation exists according to diagnostic criteria, population characteristics, and geographic region [2]. A meta-analysis involving 7,584 community-dwelling older adults in China reported an estimated prevalence of approximately 6.4% among individuals aged ≥60 years, with higher rates observed in rural than urban areas and in women than in men [3]. Its clinical consequences have been confirmed by multiple prospective studies. Meta-analytic evidence indicates that sarcopenia is associated with an approximately 1.5- to 2.0-fold increased risk of falls and a 1.7-fold increased risk of fractures [4]. Furthermore, a meta-analysis of six prospective cohort studies involving 7,367 community-dwelling older adults demonstrated that individuals with sarcopenia had a significantly higher risk of all-cause mortality than those without sarcopenia (HR = 1.60, 95% CI: 1.24–2.06) [5]. In addition, sarcopenia is closely associated with cardiovascular events, cognitive decline, depression, prolonged hospital stays, and increased healthcare expenditures, and has consequently become a key target in the prevention and management of geriatric syndromes [6]. Therefore, the development of effective strategies for its early identification and intervention is of substantial public health importance.

2. Overview of the mTOR Signaling Pathway

The mammalian target of rapamycin (mTOR) is a highly evolutionarily conserved serine/threonine protein kinase that belongs to the phosphoinositide 3-kinase-related kinase (PIKK) superfamily and has a molecular weight of approximately 289 kDa [7]. Through association with distinct subunits, mTOR forms two functionally different complexes, namely mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2). mTORC1 is primarily composed of mTOR, Raptor, and mLST8 and can additionally associate with regulatory proteins such as PRAS40 and Deptor. As a scaffold for substrate recognition and presentation, Raptor facilitates the recruitment of substrates to the catalytic domain of mTORC1 by recognizing the TOR signaling (TOS) motifs in substrates such as S6K1 and 4E-BP1, thereby promoting their phosphorylation. PRAS40 mainly functions as an endogenous inhibitory regulator of mTORC1, whereas Deptor can inhibit both mTORC1 and mTORC2 and negatively regulate mTOR signaling [8]. mTORC2 consists of mTOR, Rictor, mSin1, mLST8, Protor1/2, and Deptor. In this complex, Rictor and mSin1 replace Raptor and confer unique substrate specificity. The pleckstrin homology (PH) domain of mSin1 can bind phosphatidylinositol 3,4,5-trisphosphate (PIP3), thereby contributing to membrane localization and mTORC2 activation; however, the precise underlying mechanism remains controversial [9]. Structurally, cryo-electron microscopy analysis at a resolution of 3.2 Å revealed that although both complexes adopt a rhomboid dimeric architecture, their subunit arrangements differ substantially. In mTORC2, the N-terminal regions of Rictor and mSin1

form an interwoven topology that extends along Rictor and subsequently connects to mLST8. In addition, the distance between the FAT domains of the two mTOR molecules is smaller in mTORC2 than in mTORC1. The C-terminal domain of Rictor directly occupies the surface of the FRB domain of mTOR, spatially overlapping with the binding site of the FKBP12–rapamycin complex. This structural feature explains, at least in part, the relative insensitivity of mTORC2 to rapamycin [10].

These differences in composition and conformation ultimately determine the functional division between the two complexes. mTORC1 primarily integrates nutritional and energy signals to promote protein synthesis and cell growth, whereas mTORC2 responds to growth factor signaling to regulate cellular metabolism and survival [11].

3. The Role of the mTOR Signaling Pathway and Satellite Cells in Sarcopenia

3.1 mTOR Regulates Protein Synthesis and Satellite Cell Activation and Differentiation

As a central intracellular integrator of nutritional and growth signals, mammalian target of rapamycin (mTOR) plays a pivotal role in skeletal muscle protein synthesis, cell proliferation and differentiation, and tissue regeneration [12]. Its activity is coordinately regulated by multiple signals, including nutrient availability, growth factors, and mechanical stimuli. Amino acids, particularly leucine, recruit mTOR complex 1 (mTORC1) to the lysosomal surface through Rag GTPase heterodimers, thereby facilitating its interaction with the active form of Rheb, Rheb-GTP. Insulin-like growth factor 1 (IGF-1), in contrast, enhances mTORC1 activity through the phosphoinositide 3-kinase/ protein kinase B (PI3K/Akt) pathway by phosphorylating tuberous sclerosis complex 2 (TSC2), thereby relieving the inhibitory effect of the TSC1/TSC2 complex on Rheb. In addition, mechanical loading can activate mTORC1 directly and independently of Akt through lipid mediators such as phosphatidic acid (PA). This mechanism is particularly important in resistance exercise-induced skeletal muscle hypertrophy [13].

Activated mTORC1 promotes skeletal muscle protein synthesis primarily through two downstream pathways involving S6K1 and 4E-BP1. First, mTORC1 phosphorylates S6K1 at Thr389, thereby activating ribosomal protein S6 (rpS6) and the translation initiation factor eIF4B, which enhances ribosome biogenesis and translational elongation [14]. Second, mTORC1 induces multisite phosphorylation of 4E-BP1, causing its dissociation from eIF4E and facilitating the formation of the eIF4F translation initiation complex, thereby enhancing cap-dependent translation initiation of mRNAs [15]. Together, these two signaling pathways coordinately regulate translation initiation and elongation, synergistically promoting the synthesis of myofibrillar proteins, including myosin heavy chain (MyHC) and actin, and thereby maintaining skeletal muscle mass and functional homeostasis [16].

The mTOR pathway also serves as a central regulator of satellite cell fate. Satellite cells are located between the sarcolemma and the basement membrane and, in the quiescent state, express high levels of Pax7 to maintain their stem cell characteristics and self-renewal capacity [17]. Following muscle injury or stimulation, mTORC1 activity is rapidly upregulated. Studies have shown that, during the early stage of satellite cell activation, mTORC1 maintains the proliferative potential of satellite cells by enhancing the cap-dependent translation of Pax7 mRNA, thereby ensuring the expansion of a sufficient pool of myogenic progenitor cells [18]. As satellite cells proliferate and differentiate, mTORC1 supports the expression of myogenic regulatory factors, such as MyoD, by promoting protein synthesis. During the early phase of activation, satellite cells can co-express Pax7 and MyoD. Subsequently, one subpopulation maintains Pax7 expression while downregulating MyoD and contributes to self-renewal, whereas another subpopulation downregulates Pax7, sustains MyoD expression, and enters the differentiation program. MyoD and myocyte enhancer factor 2 (MEF2) cooperatively induce the expression of myogenic genes, including Myogenin, thereby promoting terminal differentiation and cell-cycle exit. Subsequently, Myomaker and Myomerger/Myomixer mediate myoblast fusion to form newly generated myofibers, contributing to skeletal muscle repair and regeneration [19—21]. Thus, mTORC1 is involved throughout the entire satellite cell transition from quiescence to activation, proliferation, differentiation, and fusion, functioning as an indispensable signaling node for maintaining the regenerative capacity of skeletal muscle.

3.2 Dysregulation of the mTOR–Satellite Cell Axis in the Pathogenesis of Sarcopenia

Multilevel dysregulation of the mTOR–satellite cell axis constitutes a key pathological network underlying the onset and progression of sarcopenia. Anabolic resistance, satellite cell exhaustion resulting from impaired autophagy, and disruption of the inflammatory microenvironment are major pathological factors that drive dysregulation of the mTOR–satellite cell axis and promote sarcopenia progression.

Anabolic resistance is one of the core mechanisms underlying sarcopenia and is primarily characterized by an attenuated anabolic response of skeletal muscle to nutrient intake and exercise stimuli. Under normal conditions, insulin-like growth factor 1 (IGF-1) promotes protein synthesis by activating the PI3K/Akt/mTORC1 signaling pathway. However, during aging, the sensitivity of mTORC1 to upstream signals, including amino acids and IGF-1, progressively declines, resulting in reduced phosphorylation of its downstream effectors, S6K1 and eukaryotic translation initiation factor 4E-binding protein 1 (4E-BP1). This consequently impairs translation initiation and elongation. As the rate of protein synthesis declines while proteolytic processes persist, a net loss of muscle protein and subsequent muscle fiber atrophy ultimately occur [22]. Clinical studies have also demonstrated that aged skeletal muscle exhibits a blunted hypertrophic response to resistance exercise and nutritional supplementation, thereby further accelerating the decline in muscle mass and strength [23].

Moderate mTORC1 activity is essential for maintaining satellite cell homeostasis; however, its chronic

hyperactivation may impair autophagic function. Sustained mTORC1 activation has been shown to inhibit autophagy initiation through the phosphorylation of Unc-51-like kinase 1 (ULK1), thereby preventing the timely clearance of damaged proteins and dysfunctional mitochondria from cells [24]. As dysfunctional mitochondria accumulate and oxidative stress increases, satellite cells may activate the DNA damage response and upregulate p16^INK4a expression, consequently entering an irreversible senescent state and losing their capacity for self-renewal, proliferation, and differentiation. With the progressive depletion of the functional stem cell pool, the regenerative and reparative capacity of skeletal muscle following injury is markedly compromised, thereby accelerating the progression of sarcopenia [25].

Chronic low-grade inflammation, commonly referred to as "inflammaging," is considered an important factor affecting the homeostasis of the mTOR–satellite cell axis. With advancing age, the levels of proinflammatory cytokines, including tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), remain persistently elevated [26]. These inflammatory mediators may aberrantly regulate mTOR activity through signaling pathways such as nuclear factor-κB (NF-κB) and p38 mitogen-activated protein kinase (p38-MAPK), thereby disrupting normal mTOR signal transduction [27]. Meanwhile, chronic inflammation can remodel the satellite cell niche, suppress Pax7 expression, and promote aberrant differentiation toward fibrogenic and adipogenic lineages. As fibrosis and intramuscular adipose infiltration progressively increase, functional contractile muscle tissue is gradually replaced by noncontractile tissue, further exacerbating the loss of muscle mass and the impairment of muscle function [28].

4. Traditional Chinese Medicine Perspectives on Sarcopenia

Although sarcopenia, as defined in modern medicine, has no directly corresponding disease name in classical Chinese medical texts, its core clinical manifestations—including muscle atrophy, weakness of the limbs, and impaired physical function—have led most scholars to classify it within the traditional Chinese medicine (TCM) categories of "wei syndrome" (atrophy syndrome), "rou wei" (muscular atrophy), and "deficiency taxation" [29]. The *Huangdi Neijing: Suwen — Treatise on Wei Syndrome* states that "the Spleen governs the muscles of the body; when Spleen qi becomes overheated, the Stomach becomes dry and thirst develops, while the muscles become insensate, resulting in muscular atrophy." It further proposes the therapeutic principle of "treating wei syndrome by focusing exclusively on Yangming," thereby emphasizing the critical role of the Spleen and Stomach in muscle formation and in the development and progression of wei syndrome. The *Suwen—Treatise on the Taiyin and Yangming* states that "the four limbs receive their qi from the Stomach, but this qi can reach the channels only through the Spleen," elucidating the physiological role of the Spleen and Stomach in transforming and transporting the essence of food and cereals and nourishing the muscles of the limbs [30]. Later physicians further developed these concepts. In *Pi Wei Lun* (*Treatise on the Spleen and Stomach*), Li Dongyuan systematically described the pathological mechanisms by which Spleen–Stomach deficiency and dysfunction lead to muscle atrophy, thereby enriching the theoretical framework for treating wei syndrome from the perspective of the Spleen and Stomach.

Current evidence suggests that deficiency of the Spleen and Kidney constitutes the pathological basis of sarcopenia, whereas deficiency of qi and blood persists throughout the course of the disease. The Spleen is regarded as the foundation of postnatal life and governs the transformation and transportation of nutrients, thereby generating qi and blood. Spleen deficiency leads to insufficient production of essential nutrients, resulting in inadequate nourishment of the muscles and progressive muscle atrophy. The Kidney is considered the foundation of prenatal life; it stores essence, governs the bones, and generates marrow. Kidney deficiency consequently leads to depletion of essence and qi, with impairment of the tendons, bones, and muscles. From the perspective of the interaction between the prenatal and postnatal foundations, Jiang Fengyi et al. [31] proposed that prenatal Kidney essence depends on the nourishment provided by postnatal Spleen–Stomach transformation of dietary essence, whereas postnatal Spleen function requires the warming and activating effects of prenatal Kidney yang. As these two systems support and reinforce each other but gradually decline with aging, degenerative changes in skeletal muscle may eventually develop. Based on the TCM theory that "the Liver governs the tendons and stores blood," Shi Yiting et al. [32] suggested that Liver-blood deficiency results in inadequate nourishment of the tendons and channels, thereby impairing the functional integration of the muscles and bones. Accordingly, they advocated a therapeutic strategy that simultaneously regulates the Liver, Spleen, and Kidney while treating the bones, tendons, and muscles in an integrated manner.

In addition, advanced age, physical decline, or the prolonged consumption of bodily resources by chronic disease may lead to qi deficiency, blood stasis, and impaired Spleen transportation and transformation. These changes may subsequently result in the endogenous formation of phlegm-dampness and the obstruction of the channels by blood stasis. The mutual accumulation of phlegm and stasis can further obstruct the channels and impair the distribution and circulation of qi, blood, and body fluids. Consequently, the muscles and tendons become inadequately nourished, aggravating muscle atrophy and functional decline. Thus, sarcopenia is characterized by a complex pathogenesis involving deficiency of the Spleen and Kidney and insufficiency of qi and blood as the underlying condition, with obstruction of the channels by phlegm-dampness and blood stasis as the superficial manifestations. This pattern is commonly described as "deficiency at the root with excess at the branch" and as a mixture of deficiency and excess [33,34].

5. Research on Traditional Chinese Medicine Interventions for Sarcopenia via the mTOR Signaling Pathway and Muscle Satellite Cells

5.1 Polyphenols

Salidroside, a bioactive phenolic compound derived from the traditional Chinese medicinal herb *Rhodiola rosea*, possesses

multiple pharmacological activities, including antioxidant, anti-inflammatory, and anti-skeletal muscle atrophy effects. Huang Huizhi et al. [35] reported that salidroside dose-dependently increased PI3K protein expression and the phosphorylation levels of Akt and mTOR in the gastrocnemius muscle of rats with chronic obstructive pulmonary disease (COPD). It further enhanced the phosphorylation of the downstream effectors p70S6K and 4E-BP1, resulting in significant increases in muscle fiber cross-sectional area and muscle mass. These findings suggest that salidroside may alleviate COPD-associated skeletal muscle atrophy by activating the PI3K/Akt/mTOR signaling cascade and thereby promoting skeletal muscle protein synthesis. Resveratrol is a major bioactive constituent isolated from the traditional Chinese medicinal herb *Polygonum cuspidatum* and is representative of compounds that indirectly regulate mTOR signaling through upstream regulatory factors. Avital-Cohen et al. [36] demonstrated that resveratrol activated energy-sensing molecules, including SIRT1, AMPK, and PP2A, in C2C12 myoblast/myotube models, thereby remodeling the cellular metabolic regulatory network and modulating protein synthesis-related signaling nodes, including AKT, mTOR, p70S6K, and S6. Notably, the effects of resveratrol on the mTOR pathway are not characterized by simple linear activation or inhibition. Rather, resveratrol appears to dynamically regulate mTORC1 activity through AMPK-mediated energy-stress signaling and may also participate in protein translation and myogenesis through downstream molecules such as p70S6K. The study further showed that resveratrol regulated the expression and phase dynamics of circadian rhythm-related factors, including BMAL1, CLOCK, and CRY1, while upregulating the key myogenic transcription factor myogenin and promoting myotube formation and myogenic differentiation. Because satellite cell activation, proliferation, and differentiation are coordinately regulated by mTOR signaling, energy metabolism, and circadian rhythms, these findings suggest that resveratrol may improve the myogenic differentiation capacity of satellite cells and enhance muscle fiber regeneration and protein synthesis through an integrated regulatory network involving the SIRT1–AMPK–PP2A/Mtor –circadian rhythm axis. Curcumin is primarily derived from the rhizomes of *Curcuma longa* L. Asron Sani et al. [37] established a skeletal muscle atrophy model using dexamethasone-treated C2C12 myotubes to investigate the regulatory effects of curcumin and its derivatives on sarcopenia-related muscle atrophy. Their results showed that curcumin and its extracts significantly downregulated the expression of the muscle-specific E3 ubiquitin ligases Atrogin-1 and MuRF-1, thereby inhibiting muscle protein degradation. At the same time, curcumin increased Akt phosphorylation and activated the PI3K/Akt/mTOR signaling pathway, promoting protein synthesis. This process improved overall muscle quality through two complementary mechanisms: inhibition of the FOXO-mediated proteolytic pathway and enhancement of mTOR-dependent anabolic signaling. In a mouse model of disuse-induced muscle atrophy, Mañas-García et al. [38] found that resveratrol and curcumin significantly increased the numbers of α7-integrin^ +/CD34^+ muscle progenitor cells, Pax7^+/Myf5^− quiescent satellite cells, Pax7^+/Myf5^+ activated satellite cells, and total satellite cells in atrophied muscles. They also increased the overall population of muscle progenitor cells, suggesting that these two polyphenolic compounds can preserve the satellite cell reservoir and enhance muscle regenerative capacity during disuse. However, during the remobilization phase, neither compound further increased the expression of myogenic regulatory factors, including Pax7, MyoD, and myogenin, nor significantly altered satellite cell numbers. These findings indicate that their beneficial effects on muscle regeneration occur predominantly during the disuse phase. Saluber et al. [39] reviewed the potential mechanisms by which polyphenols regulate mTOR-related signaling pathways. Resveratrol was shown to regulate the activity of PGC-1α and FoxO through SIRT1-mediated deacetylation, thereby influencing the balance between AMPK and mTOR signaling. Epigallocatechin-3-gallate (EGCG) and curcumin may restore the transcriptional activity of MyoD and myogenin by inhibiting histone deacetylase (HDAC) activity and reversing aberrant methylation within the promoter regions of myogenic regulatory factors. In addition, polyphenols may regulate the expression of myogenic microRNAs, including miR-1, miR-133, and miR-206, which participate in the determination of satellite cell differentiation fate at the post-transcriptional level.

5.2 Polysaccharides

Polysaccharides, as naturally occurring bioactive compounds, are considered an important research direction for the intervention of sarcopenia using traditional Chinese medicine. Fan Gong et al. [40] reported that *Lycium barbarum* polysaccharide (LBP), extracted from the traditional Chinese medicinal herb Lycium barbarum, promoted muscle protein synthesis by activating the PI3K/Akt signaling pathway and its downstream mTOR/p70S6K axis. In addition, LBP reduced protein degradation by regulating the expression of Atrogin-1 and MuRF1 mediated by FoxO3a, thereby restoring protein metabolic homeostasis in obesity-associated muscle atrophy. Yang Li et al. [41] demonstrated that Polygonatum polysaccharide (PSP) significantly ameliorated skeletal muscle senescence and muscle atrophy by activating the PI3K/Akt/mTOR signaling pathway, while alleviating mitochondrial dysfunction and oxidative stress-induced damage. In both a D-galactose-induced cellular senescence model and a mouse model of sarcopenia, PSP reduced the expression of p16, p21, p53, and the muscle atrophy-related proteins MuRF1 and Atrogin-1. At the same time, it increased the levels of MyoD, myogenin, and myosin heavy chain (MyHC), thereby enhancing myotube differentiation and muscle regenerative capacity. Moreover, PSP increased mitochondrial membrane potential and reduced the production of reactive oxygen species (ROS) and MitoSOX, thus improving mitochondrial homeostasis. Mechanistic studies further demonstrated that LY294002, an inhibitor of the PI3K/Akt/mTOR signaling pathway, partially reversed the protective effects of PSP, suggesting that this pathway is a key target underlying its anti-sarcopenic activity. Zhihan Tian et al. [42] found that Astragalus polysaccharide (APS) alleviated muscle atrophy and improved muscle strength and morphology in a mouse model of cancer cachexia by inhibiting autophagy and mitophagy, preserving mitochondrial structural homeostasis, and modulating FOXO3-related signaling as well as the transcriptional activity of the mTOR/AMPK pathway.

5.3 Flavonoids

Jang et al. [43] demonstrated that apigenin, a naturally occurring flavonoid compound, upregulates the expression of protein arginine methyltransferase 7 (Prmt7), thereby activating the downstream p38 MAPK and Akt/mTOR signaling pathways. This promotes the differentiation of C2C12 cells and muscle satellite cells, as evidenced by increased expression of MyoD and myosin heavy chain (MHC), as well as an elevated myotube fusion index. In a mouse model, apigenin significantly increased skeletal muscle cross-sectional area and exercise capacity. These effects were reversed by Prmt7 knockdown using Prmt7-specific siRNA, suggesting that Prmt7 is a critical mediator through which apigenin activates mTOR signaling and promotes myogenic differentiation. Nirmala et al. [44] reported that linarin, a flavonoid glycoside derived from *Chrysanthemum zawadskii* (CZH), possesses potential exercise-mimetic activity. In primary myogenic cells from aged mice, namely primary myoblasts derived from muscle satellite cells, linarin increased the expression of Sestrin 1, activated the AMPK signaling axis, and modulated the phosphorylation levels of aging-related Akt/mTOR/S6K signaling components. These effects improved cellular energy metabolism and mitochondrial oxidative respiration while promoting myogenic differentiation. Further studies showed that siRNA-mediated knockdown of Sestrin 1 markedly attenuated linarin-induced AMPK activation, mitochondrial oxygen consumption rate, and myotube formation, indicating that Sestrin 1 is an important regulatory factor mediating the effects of CZH/linarin on the AMPK–mTOR-associated metabolic network and myogenesis. Regarding myotube hypertrophy, Lin et al. [45] confirmed in a C2C12 myotube model that *Epimedium* extract (EE), particularly its major bioactive component icariin (ICA), significantly promoted myotube hypertrophy and increased myosin heavy chain (MyHC) expression. This effect was closely associated with activation of the IGF-1 signaling pathway. Specifically, EE/ICA promoted the phosphorylation and activation of key signaling nodes, including IGF-1R, PI3K/Akt, mTOR, and p70S6K. The PI3K inhibitor LY294002 and the mTOR inhibitor rapamycin significantly reversed EE/ICA-induced myotube hypertrophy and MyHC upregulation, indicating that the hypertrophic effects of EE/ICA depend primarily on the canonical IGF-1/PI3K/Akt/mTOR protein synthesis pathway. In addition, EE/ICA increased the phosphorylation level of AMPK at Thr172 and modulated the expression of the slow-twitch myosin isoform MyHC-S. The AMPK inhibitor compound C partially attenuated EE-induced myotube hypertrophy and MyHC-S expression but exerted relatively limited effects on IGF-1-mediated responses. These findings suggest that AMPK may participate in the regulation of muscle fiber-type transitions, whereas its functional role is at least partially distinct from that of the IGF-1/mTOR pathway. Oh et al. [46] reported that kaempferol-3-O-glucoside, a flavonoid glycoside present in leek extract, promotes skeletal muscle cell proliferation and differentiation through the PI3K/Akt/mTOR pathway and upregulates MyoD expression. At the same time, this flavonoid glycoside inhibits the TGF-β/Smad pathway, thereby relieving negative regulation of myogenesis and exerting dual stimulatory effects on muscle satellite cell activation and skeletal muscle growth. Lee et al. [47] found that acacetin-7-O-β-D-rutinoside (AR), a major flavonoid constituent of the medicinal Asteraceae plant *Chrysanthemum zawadskii*, increased the expression of MyoD and myogenin in a dexamethasone-induced muscle atrophy model. These effects were accompanied by activation of the Akt/mTOR/S6K/4E-BP1 signaling pathway, which promoted protein synthesis and alleviated the muscle atrophy phenotype induced by dexamethasone.

5.4 Saponins

Regarding the regulation of the balance between protein synthesis and degradation, Li et al. [48] reported that ginsenoside Rg1 activated the PI3K/Akt/mTOR signaling pathway in a starvation-induced C2C12 myotube model, as evidenced by increased phosphorylation of Akt and mTOR. Rg1 also induced the phosphorylation of FoxO1 and FoxO3a and inhibited their nuclear translocation, thereby downregulating the expression of the muscle-specific E3 ubiquitin ligases MuRF1 and Atrogin-1 and attenuating protein degradation-related signaling. These effects were reversed by the PI3K inhibitor LY294002, suggesting that the regulatory effects of Rg1 on muscle protein homeostasis depend on the PI3K/Akt/mTOR/FoxO signaling axis.

Go et al. [49] further demonstrated that Rg1 promoted satellite cell differentiation and myotube growth by significantly upregulating myogenin expression and enhancing MyoD-associated expression and transcriptional activity during the myotube stage. Mechanistically, Rg1 promoted myoblast differentiation, fusion, and myotube hypertrophy through the coordinated activation of the Akt/mTOR and p38 MAPK signaling pathways. Similarly, black ginseng extract, which contains a variety of ginsenosides, enhanced myoblast differentiation and myotube growth by activating the Akt/mTOR/p70S6K pathway. This effect was abolished by LY294002 [50], suggesting that different ginsenoside monomers and compound preparations may promote muscle regeneration through a common Akt/mTOR signaling node.

In a glucocorticoid-induced muscle atrophy model, Kim et al. [51] found that ginsenoside Rg3 promoted protein synthesis by activating the Akt/mTOR pathway. In addition, Rg3 upregulated the expression of PGC-1α and its downstream targets NRF1 and Tfam, thereby improving mitochondrial dysfunction and counteracting dexamethasone-induced myotube atrophy through complementary anabolic and mitochondrial mechanisms. Notably, ginsenoside Rb3 increased TAZ levels in the skeletal muscle of dexamethasone-treated mice. As a transcriptional coactivator downstream of the Hippo pathway, TAZ can activate the Rheb/RhebL1-mediated mTOR/S6K1 signaling pathway. It also promotes skeletal muscle protein synthesis by suppressing the ubiquitin–proteasome degradation pathway mediated by Atrogin-1 and MuRF1, thereby alleviating dexamethasone-induced muscle atrophy [52]. These findings further underscore the critical role of mTOR signaling in maintaining skeletal muscle protein homeostasis.

At the in vivo level, Ma Leilei et al. [53] established a rat model of sarcopenia associated with type 2 diabetes mellitus through a combination of a high-sugar, high-fat diet and streptozotocin (STZ) injection. They demonstrated that total astragalosides promoted protein synthesis by activating the

PI3K/Akt/mTOR pathway and downregulated the expression of FoxO1 and MuRF1, thereby significantly improving skeletal muscle mass and strength in diabetic rats. These findings provide direct in vivo evidence that saponin compounds may be effective in alleviating metabolic sarcopenia.

5.5 Traditional Chinese Medicine Extracts

Lai Peng et al. [54] reported that *Morinda officinalis* extract ameliorated dexamethasone-induced sarcopenia in mice, potentially through regulation of the IGF-1/PI3K/Akt/mTOR signaling pathway. Specifically, the extract increased the expression of IRS-1, mTOR, MYOD, and MYOG, while reducing the expression of Atrogin-1, MuRF1, and MSTN, thereby improving muscle mass, exercise capacity, and mitochondrial structural damage. Fang Yajing et al. [55] demonstrated that *Cistanche deserticola* extract also alleviated dexamethasone-induced sarcopenia in mice, possibly by activating the IGF-1/PI3K/Akt/mTOR signaling pathway. This effect was characterized by increased expression of mTOR- and IGF-1-related genes and decreased expression of the muscle atrophy-associated genes Atrogin-1, MuRF1, and MSTN. Meanwhile, the expression levels of MYOD and MYOG were elevated, suggesting that the extract may contribute to the improvement of muscle structure and function by promoting the expression of myogenesis-related genes. In an obesity-induced muscle atrophy model, *Ophiopogon japonicus* root extract promoted anabolic protein metabolism by activating the PI3K/Akt/mTOR signaling axis and attenuated protein degradation by inhibiting the nuclear translocation of FoxO3a. In addition, it improved lipid metabolic disturbances in skeletal muscle, thereby preserving myocellular function through multiple mechanisms [56]. Furthermore, *Rosa chinensis* flower extract was shown to activate the Akt/mTOR/p70S6K pathway and suppress the expression of Atrogin-1 and MuRF1 in a disuse-induced muscle atrophy model [57]. These effects effectively counteracted immobilization-induced muscle fiber atrophy and the decline in muscle strength.

5.6 Acupuncture

In recent years, substantial progress has been made in the study of acupuncture-based interventions for sarcopenia. A systematic review and meta-analysis incorporating multiple randomized controlled trials demonstrated that acupuncture significantly improved handgrip strength, gait speed, and the skeletal muscle mass index in patients with sarcopenia. Moreover, acupuncture combined with rehabilitation training was more effective than conventional treatment alone and exhibited a favorable safety profile [58].

Several animal studies have elucidated the molecular basis underlying the anti-sarcopenic effects of acupuncture from the perspective of the mTOR signaling pathway. Using a dexamethasone-induced rat model of sarcopenia, Ji Dongfang et al. [59] found that electroacupuncture at Zusanli (ST36) upregulated mTOR signaling to promote protein synthesis, while simultaneously suppressing protein degradation by downregulating the MAFbx/MuRF1-mediated ubiquitin–proteasome pathway. These findings indicate that electroacupuncture exerts bidirectional regulatory effects on skeletal muscle protein metabolism. In a denervation-induced muscle atrophy model, electroacupuncture with a wide pulse width was shown to effectively delay skeletal muscle atrophy by activating the IGF-1/PI3K/mTOR signaling pathway. It also significantly increased PAX7 expression, thereby promoting the proliferation and expansion of the muscle satellite cell pool [60]. In addition to regulating protein metabolism, the ability of acupuncture to promote muscle satellite cell-mediated regeneration is closely associated with the mTOR pathway. Zhang Bo et al. [61] reported that acupuncture at the Shu–Mu points of the spleen meridian combined with treadmill training simultaneously increased the expression of the mTOR/p70S6K signaling pathway and the muscle satellite cell markers Pax7, MyoD, and myogenin, thereby promoting muscle fiber regeneration. The combined intervention was more effective than either treatment alone, suggesting that acupuncture may regulate both protein synthesis and stem cell-mediated muscle regeneration through the mTOR pathway. Furthermore, Li Xiaoyang et al. [62] demonstrated that fire acupuncture significantly increased the expression levels of phosphorylated PI3K, Akt, and mTOR in injured tissues, thereby promoting neural repair and functional recovery. These findings provide direct evidence at the mTOR signaling level that acupuncture may also indirectly protect skeletal muscle by improving neural innervation.

By activating mTOR-associated signaling pathways through multiple mechanisms, acupuncture exerts anti-sarcopenic effects by promoting protein synthesis, inhibiting protein degradation, activating muscle satellite cell-mediated regeneration, and improving neuromuscular axis function [63]. Collectively, these findings highlight the therapeutic characteristics of acupuncture as a multimodal intervention involving coordinated regulation of multiple targets.

5.7 Traditional Chinese Medicine Formulas

Recent studies have demonstrated that traditional Chinese medicine (TCM) compound formulations possess considerable clinical potential in the treatment of sarcopenia. Based on RNA sequencing (RNA-seq) transcriptomic analysis, Li Ning et al. [64]employed a collagen-induced arthritis (CIA) rat model to systematically investigate the potential mechanisms by which Huangqi Guizhi Wuwu Decoction—comprising raw *Astragalus membranaceus, Cinnamomum cassia* twig, *Paeonia lactiflora* root, *Ziziphus jujuba* fruit, and fresh *Zingiber officinale* rhizome—ameliorates sarcopenia associated with rheumatoid arthritis (RA) from the perspective of inflammation-related skeletal muscle atrophy. The results indicated that the PI3K/Akt/mTOR signaling pathway may represent an important regulatory axis underlying the skeletal muscle-protective effects of Huangqi Guizhi Wuwu Decoction. In addition, pathways related to calcium signaling, cyclic adenosine monophosphate (cAMP), cyclic guanosine monophosphate–protein kinase G (cGMP–PKG), and the ubiquitin–proteasome system were also involved in its effects. By suppressing inflammatory responses and skeletal muscle protein degradation while promoting protein synthesis, this formulation alleviated skeletal muscle atrophy in an inflammatory microenvironment. These findings provide high-throughput transcriptomic evidence supporting the

skeletal muscle-protective effects of this classical qi-tonifying and meridian-warming formula. Hao Linglun et al. [65] established an in vitro tumor-associated myotube atrophy model using a Transwell coculture system comprising C2C12 myoblasts and Lewis lung carcinoma cells. Their results showed that Liujunzi Decoction—which consists of *Panax ginseng*, *Poria cocos*, *Atractylodes macrocephala*, *Glycyrrhiza uralensis*, *Pinellia ternata*, and *Citri reticulatae* pericarpium—significantly increased the expression of MyoD, mTOR, PGC-1α, FTO, and TFAM, while decreasing FoxO1 protein levels. These findings suggest that Liujunzi Decoction may maintain mitochondrial function and promote myotube formation by regulating the PGC-1α/FoxO1 signaling pathway and modulating mTOR-related mechanisms. This study directly linked the therapeutic targets of a TCM compound formulation to the differentiation process of myoblasts, which are widely used as an in vitro model of satellite cells, and thus provides some of the most direct evidence that TCM compound formulations regulate satellite cell function. In a sex hormone-related muscle aging model, Yang Jiadi et al. [66] used a VCD-induced ovarian aging rat model to investigate the estrogen-like protective effects of Siwu Decoction—which consists of *Paeonia lactiflora* root, *Angelica sinensis* root, *Ligusticum chuanxiong* rhizome, and prepared *Rehmannia glutinosa* root—on skeletal muscle. The experimental results showed that Siwu Decoction increased the mRNA expression of IGF-1, PI3K, AKT, and mTOR. These findings suggest that Siwu Decoction may attenuate ovarian aging-associated muscle loss by regulating the IGF-1/PI3K/Akt/mTOR signaling pathway, thereby promoting skeletal muscle protein synthesis, improving skeletal muscle cell morphology, and reducing the formation of fibrous connective tissue.

6. Summary and Perspectives

The mTOR signaling pathway, as a central regulator of skeletal muscle protein synthesis, cell growth, and energy metabolism, plays a crucial role in the development and progression of sarcopenia. Meanwhile, muscle satellite cells represent a key cellular population responsible for maintaining skeletal muscle regeneration and repair capacity, and their activation, proliferation, differentiation, and fusion processes directly determine muscle mass and functional maintenance. Recent studies have demonstrated that traditional Chinese medicine (TCM) can delay the progression of sarcopenia to some extent by regulating mTOR-related signaling pathways, including PI3K/Akt/mTOR, AMPK/mTOR, and FoxO/mTOR pathways, thereby promoting protein synthesis, inhibiting excessive protein degradation and autophagy dysfunction, and alleviating pathological conditions such as inflammation, oxidative stress, and mitochondrial dysfunction. Furthermore, certain TCM-derived active compounds and herbal formulas can promote satellite cell activation and myogenic differentiation by upregulating the expression of myogenic regulatory factors, including Pax7, MyoD, and Myogenin, thereby exerting protective effects on skeletal muscle.

However, several limitations remain in the current application of TCM for sarcopenia treatment. First, most existing studies are still limited to animal models or in vitro cellular experiments, and high-quality, multicenter randomized controlled clinical trials are lacking. Second, the causal relationship between mTOR signaling and muscle satellite cell function has not yet been fully elucidated, particularly regarding the distinct roles and regulatory mechanisms of mTORC1 and mTORC2 under different pathological conditions. Third, current investigations predominantly focus on individual signaling pathways, while comprehensive studies addressing the interactions between mTOR signaling and broader regulatory networks, including inflammation, metabolism, mitochondrial function, and gut microbiota, remain insufficient. Fourth, the bioactive components of TCM are complex, and their effects on sarcopenia progression usually involve synergistic regulation of multiple pathways and targets, which increases the difficulty of elucidating precise mechanisms and achieving targeted clinical applications.

Future studies should integrate advanced approaches, including transcriptomics, proteomics, metabolomics, and single-cell sequencing, to systematically elucidate the molecular mechanisms underlying TCM-mediated regulation of mTOR signaling and muscle satellite cell function. Meanwhile, further investigations are needed to clarify the pharmacological basis, key active components, and synergistic mechanisms of TCM formulas in sarcopenia intervention. In addition, the establishment of sarcopenia animal models and clinical evaluation systems that better reflect TCM syndrome characteristics is warranted. Large-scale, high-quality clinical studies should also be conducted to validate the efficacy and safety of TCM in sarcopenia prevention and treatment, thereby facilitating its clinical translation into precision medicine and healthy aging management.

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