Plant-derived natural products alleviate dexamethasone-induced skeletal muscle atrophy by modulating FoxO (Review)

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Abstract. Muscle atrophy (MA) is a major global health issue, and systematic strategies for its prevention and treatment are lacking. Diverse factors contribute to MA, amongst which the exogenous over-supplementation and endogenous pathological elevation of glucocorticoids (GCs) are key causes. The present study summarizes MA induced by the GC dexamethasone (DEX) and its molecular mechanisms, including protein metabolism imbalance, mitochondrial dysfunction and abnormalities in epigenetic regulatory proteins, to explore potential therapeutic approaches for MA. FoxO transcription factor serves a central regulatory role in DEX-induced MA by modulating the ubiquitin-proteasome system, autophagy-lysosomal system and energy metabolism pathways. Therefore, FoxO may serve as a critical therapeutic target for DEX-induced MA. Plant-derived natural products are promising candidates for the development of clinical drugs for tumors, myocardial infarction and diabetic nephropathy. These products protect against MA by regulating FoxO activity through multiple signaling pathways, including Akt, AMPK, and SIRT. Plant monomer compounds, such as flavonoids, polyphenols and terpenes, exert therapeutic effects and may provide new strategies for the precise prevention and treatment of MA induced by elevated GC levels.

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Contents

1. Introduction

Skeletal muscle, which constitutes 30-40% of adult body mass and contains 50-75% of bodily proteins, is a dynamic and plastic tissue system crucial for human physiology (1). It governs locomotive functions, postural stability and systemic energy homeostasis while actively participating in glucose use and lipid metabolism regulation. Nevertheless, pathophysiological stressors, including senescence, immobilisation, nutritional deprivation and chronic comorbidity, can trigger the progressive degradation of muscle mass and functional capacity, culminating in muscle atrophy (MA) (2). MA, which clinically manifests as compromised mobility, metabolic dysregulation and elevated susceptibility to chronic disease, substantially impairs quality of life while imposing a heavy socioeconomic burden (3). The aforementioned factors underscore the need for developing mechanistically targeted interventions against this multifactorial disorder (4).

Synthetic glucocorticoids (GCs) are steroid hormones that are used in clinical settings for the treatment of inflammatory and autoimmune diseases due to their anti-inflammatory and immunosuppressive effects (5). However, their prolonged use can lead to adverse effects, one of which is MA (6). Patients typically exhibit a decline in muscle strength, reduced exercise endurance and difficulties in daily activities, such as climbing stairs and lifting heavy objects, that affect their quality of life (7). Notably, GC-induced MA is one of the most common drug-induced MA conditions, with muscle weakness occurring in ~60% of patients with Cushing's syndrome (8). Given the notable population of GC users and the non-negligible side effects of GCs, developing clinical interventions targeting GC-induced MA is imperative. GCs include ~20 common

synthetic drugs, amongst which dexamethasone (DEX) is widely used to construct MA models either through subcutaneous injection or *in vitro* treatment (9,10). In addition to the stability and reproducibility of models, DEX has a broad research base because of its greater pharmacological potency and longer half-life compared with other GCs (11,12). Several studies have identified the signalling molecules and pathways involved in DEX-induced MA, such as the Akt/mTOR pathway and mitophagy (13-15). DEX has a direct catabolic effect on muscle by suppressing the synthesis and enhancing the breakdown of muscle proteins. Consequently, DEX-induced MA is a crucial model for studying the mechanisms and potential interventions of drug-derived MA (15).

Forkhead box O (FoxO) is a key transcription factor in mammals. It belongs to the forkhead family, which is involved in the regulation of cell proliferation, differentiation, metabolism and apoptosis (16). In humans, four FoxO paralogues (FoxO1, FoxO3, FoxO4 and FoxO6) have been identified, of which FoxO1 and FoxO3 are the most abundant and functionally active isoforms in skeletal muscle (17). FoxO serves a key role in MA and influences muscle mass primarily by regulating two notable protein degradation pathways: The autophagy-lysosomal system (ALS) and the ubiquitin-proteasome system (UPS). A growing body of evidence indicates that DEX exacerbates MA by upregulating the activity of FoxO, which promotes the expression of genes associated with muscle protein breakdown (MPB) (18-20). Consequently, targeting FoxO may be a promising strategy for developing clinical drugs to counteract DEX-induced MA.

Natural products (NPs) are widely used in the design and development of medicine for tumors, myocardial infarction, and diabetic nephropathy) because of their diverse biological activities and low side effects in humans (21-23). Numerous plant-derived NPs (e.g., ginsenosides, resveratrol, astaxanthin) markedly attenuate proteolytic cascades in both animal and cellular models of DEX-induced MA by modulating FoxO transcription (24-26). The present review aimed to summarise the mechanism underlying DEX-induced MA and the key role of FoxO and potential of plant-derived NPs to alleviate MA by modulating FoxO activity. The present study aimed to provide a theoretical foundation for the development of novel, safe and effective therapeutic strategies against MA, as well as improved clinical solutions for patients undergoing long-term GC treatment.

2. DEX

Basic pharmacology of DEX. The molecular structure of DEX ($C_{22}H_{29}FO_5$) is based on the classical tetracyclic skeleton of cortisol, which consists of three six-membered rings (A, B and C rings) and one five-membered ring (D ring). DEX is produced by adding a double bond between C1 and C2 in the base structure of cortisol, introducing a fluorine atom at the C9 position of the A-ring and adding a methyl group at the C16 position of the D-ring (27). The anti-inflammatory activity of DEX is enhanced by the addition of fluorine and methyl groups. The C16 methyl group mitigates DEX-induced sodium retention. Following these modifications, DEX is up to 25 times more pharmacologically potent than natural cortisol and is the most potent member of the GC family (28,29).

The pharmacological actions of DEX are mediated through genomic and non-genomic mechanisms. In the canonical genomic pathway, cytosolic glucocorticoid receptors (GRs) undergo ligand-activated conformational changes following DEX binding, dissociating from heat shock protein complexes and translocating to the nucleus to modulate the transcriptional activity of target genes via direct DNA binding or coregulator interactions (30). In parallel, non-genomic effects are mediated by interaction with membrane proteins and alterations in the activities of intracellular ion channels or signalling molecules (31). These pathways confer DEX with multifaceted therapeutic properties, such as immunosuppression, cell metabolism regulation and oxidative stress mitigation (32). Since its initial synthesis in 1957 and subsequent approval by the US Food and Drug Administration for clinical use in 1958, DEX has become a key therapeutic agent for acute and chronic conditions (12), including cancer (33), rheumatism (34), eye disease (35) and asthma (36). Notably, its efficacy in reducing mortality amongst critically ill patients with coronavirus disease 2019 has expanded its therapeutic applications (37). However, the prolonged use of DEX is accompanied by numerous adverse effects, including hypertension, gastrointestinal ulcers, hyperglycaemia, insomnia and anxiety and MA (38). Therefore, it is important to elucidate the mechanisms underlying GC-induced MA and develop therapeutic strategies against this adverse effect.

DEX-induced MA. GC dysregulation is a well-established driver of skeletal MA, with clinical and experimental evidence (39-42). In 1932, Harvey Cushing documented that endogenous GC excess caused muscle weakness in several patients (39). Modern interventions, including adrenalectomy, GR antagonists and muscle-specific GR knockout models, have corroborated GC pro-catabolic role in muscle (40,43). Chronic exogenous GC administration induces steroid myopathy, which is clinically characterised by progressive proximal muscle wasting, weakness and pain (41). MA is a hallmark of cachexia syndromes triggered by elevated cortisol levels and a common side effect of treatment with synthetic GCs (39-41). A previous study demonstrated that the exogenous supplementation of DEX, a typical representative of synthetic GCs, rapidly induces MA in mice, as evidenced by weight loss after 3 days and muscle loss after 7 days (42). Research suggests that these phenomena may be driven by a combination of decreased muscle glycogen reserves (44) and increased muscle insulin resistance (45) and fat deposition (46). In addition, compared with slow-twitch fibres, type IIB/IIB fast-twitch muscles show greater atrophy, which is associated with their higher GR expression, decreased myophosphorylase activity and limited capacity to use alternative energy sources (47). DEX-induced MA is a complex pathological process accompanied by an imbalance in the regulation of multiple signalling molecules and pathways. DEX exacerbates the loss of muscle mass and function by disrupting protein synthesis and catabolism, impairing mitochondrial function and modulating the expression of epigenetic regulatory proteins (Fig. 1). Therefore, an in-depth understanding of these molecular mechanisms is essential for developing effective prevention and treatment strategies.

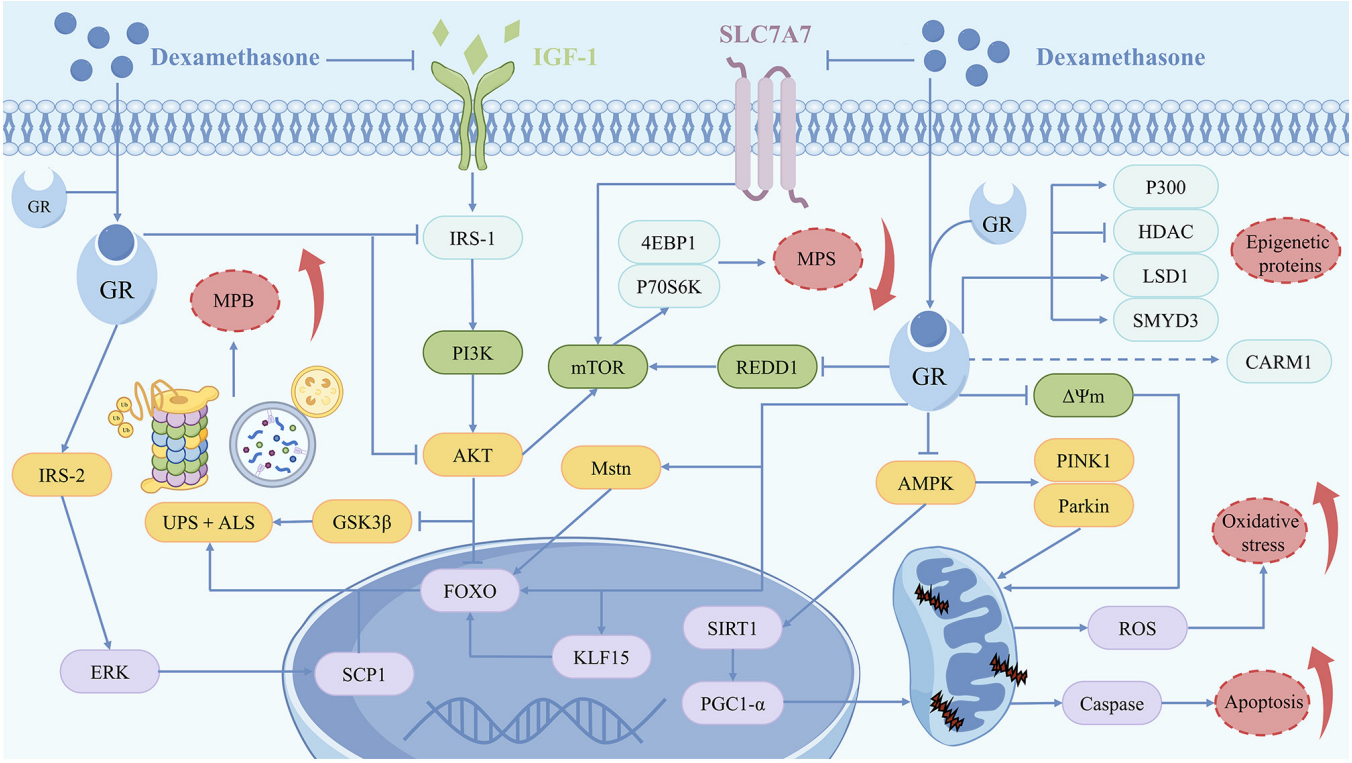

Figure 1. Molecular mechanisms of dexamethasone-induced muscle atrophy include protein metabolism imbalance, mitochondrial dysfunction and epigenetic regulation. GR, glucocorticoid receptor; IRS-2, insulin receptor substrate 2; MPB, muscle protein breakdown; UPS, ubiquitin-proteasome system; ALS, autophagy-lysosomal system; GSK3β, glycogen synthase kinase 3β; IGF-1, insulin-like growth factor 1; IRS-1, insulin receptor substrate 1; PI3K, phosphatidylinositol 3-kinase; FoxO, Forkhead Box O; Mstn, myostatin; KLF15, Krüppel-like factor 15; 4EBP1, eIF4E-binding protein 1; P70S6K, ribosomal protein 70 S6 kinase; SLC7A7, solute carrier family 7 member 7; MPS, muscle protein synthesis; REDD1, regulated in development and DNA damage responses 1; AMPK, AMP-activated protein kinase; HDAC, histone deacetylase; LSD1, lysine-specific demethylase 1; SMYD3, protein lysine methyltransferase SET and MYND domain-containing 3; CARM1, coactivator-associated arginine methyltransferase 1; ROS, reactive oxygen species; Δψm, mitochondrial membrane potential.

Protein metabolism imbalance. The regulation of skeletal muscle mass depends on the dynamic equilibrium between muscle protein synthesis (MPS) and MPB, with MA arising when MPB persistently exceeds MPS (48). Protein synthesis encompasses sequential steps, including amino acid transport, translation initiation and peptide chain elongation. DEX inhibits the expression of solute carrier family 7 member 7 transporter proteins; this disrupts amino acid transport and translation initiation, ultimately leading to the suppression of MPS (49). In mammals, PI3K/Akt is a major pathway regulating muscle metabolism and promoting MPS. DEX diminishes MPS by inhibiting Akt-mediated mTOR phosphorylation. This effect decreases the expression of the downstream effectors ribosomal protein 70 S6 kinase (P70S6K) and eIF4E-binding protein 1 (4EBP1) (15). Regulated in development and DNA damage responses 1, a direct transcriptional target of GR, regulates MPS by activating the mTOR signalling pathway, thereby participating in the regulation of MA (50). The P13K/Akt pathway not only activates the anabolic pathway but also effectively blocks the catabolic pathway by inhibiting FoxO, thereby resisting DEX-induced MA (51). Insulin-like growth factor 1 (IGF-1) is a key upstream regulator of the PI3K/Akt pathway, whereas DEX has a greater effect on the expression of IGF-1 and insulin receptor substrate 1 (IRS-1) compared with other GCs (52). DEX not only decreases IGF-1 synthesis in muscle cells but also impairs insulin signalling by accelerating the degradation of IRS-1 and lowering its tyrosine phosphorylation levels (53,54). These changes also partially explain the muscle insulin resistance that occurs during DEX use.

The increase in MPB is a key driver of DEX-induced MA and is primarily mediated by the activation of the UPS and ALS (20). Ubiquitin ligases mediate the specific degradation of target proteins by UPS through substrate selection, including myogenic differentiation (MyoD), myogenin (MyoG) and myosin heavy chain (MyHC), along with dynamic modulation of ubiquitin chain formation, which drives MPB (55). Thus far, several ubiquitin ligases mediating DEX-induced MA have been identified, including muscle RING-finger protein 1 (MuRF1), MA F-box protein 1 (atrogin-1), casitas B-lineage lymphoma proto-oncogene B (CBL-B), F-box and WD repeat domain-containing 7β and TNF receptor-associated factor 6 (56-58). MuRF1 and atrogin-1 are upregulated in MA models and are important in the study of MA mechanisms (13,59). In DEX-induced MA, the deletion of MuRF1 markedly protects muscle mass, whereas deletion of atrogin-1 does not show the same effect (60). FoxO is a key activator of both ubiquitin ligases, and studies have indicated that myostatin (Mstn) and Kruppel-like factor 15 regulate the expression of ubiquitin ligases by acting on FoxO, thereby participating in the regulation of MA (50,61,62). As a downstream target of the Akt signalling pathway, glycogen synthase kinase 3 (GSK3)β not only suppresses MPS by inhibiting the translation of eukaryotic transcription factor 2B but also mediates the DEX-induced

expression of atrogin-1 and MuRF1, as demonstrated by knockdown assays (63,64). Additionally, DEX activates the ERK signalling pathway by upregulating IRS-2 expression, which enhances the phosphorylation-dependent activity of the transcription factor specificity protein 1, directly upregulating ubiquitin gene expression and exacerbating MA (65). The ALS participates in MPB by recognising and promoting the degradation of ubiquitinated proteins in the lysosome (66). Notably, the regulatory effect of DEX on autophagy remains controversial (14,59,67,68). Troncoso *et al* (14) observed the conversion of the autophagy marker microtubule-associated protein light chain 3 (LC3)-I into LC3-II and a decrease in the expression of the autophagy substrate sequestosome 1 following addition of DEX to L6 and C2C12 cells; these changes are reversed by the addition of GR small interfering (si)RNA, suggesting that DEX increases autophagic flux through GR. *In vivo* and *ex vivo*, upregulation of autophagy induced by the inhibition of DEX effectively alleviates MA (67). This process is regulated by DEX-induced changes in the phosphorylation status of Akt and AMP-activated protein kinase (AMPK), which promote FoxO-mediated autophagy gene expression (14,67). However, other studies have reported that DEX administration inhibits muscle autophagic activity; enhancing autophagy to promote the clearance of degraded proteins contributes to the improvement of DEX-induced MA (59,68). Shen *et al* (59) suggested that DEX may exhibit a dose-associated bidirectional effect in regulating autophagy. Low doses of DEX promote autophagy through AMPK activation, whereas high doses of DEX cause AMPK inactivation and inhibit autophagy. However, concluding that DEX regulates autophagy in a dose-dependent bidirectional manner may be an oversimplification. Experimental results on autophagy changes under DEX treatment are not entirely consistent with the aforementioned conclusion (26,59,67-71). In *in vitro* studies, C2C12 cells treated with 10 μM DEX demonstrate autophagy inhibition and plant-derived compounds (myricanol, fucoxanthin) alleviate MA by activating autophagy (59,68,69). However, in *in vivo* studies, autophagy activation is observed following treatment with 5.0 or 0.8 mg/kg DEX (26,67). Notably, similar autophagy-related responses have been reported across studies using DEX doses that differ by more than tenfold, suggesting autophagy regulation by DEX may not only be dose-dependent but also affected by various factors, such as animal strains, the *in vitro* and external environment and the administration mode (26,67). To the best of our knowledge, few studies have examined autophagy-related indicators (26,59,67-71). Therefore, further studies using unified experimental models and standardized dosing regimens are needed to clarify autophagy changes under different DEX doses.

Mitochondrial dysfunction. Mitochondria serve as key subcellular targets for the action of DEX, with independently expressed GRs capable of sensing DEX and directly regulating mitochondrial DNA transcription. This regulation affects biological processes, including mitochondrial biogenesis, autophagy and respiratory chain activity (72). DEX impairs mitochondrial function through the regulation of AMPK activity, thereby promoting MA (73). Peroxisome proliferator-activated receptor γ coactivator 1-α (PGC-1α), a master regulator of mitochondrial biogenesis, demonstrates markedly decreased expression across multiple MA models (74,75). PGC-1α overexpression in adult muscle fibres suppresses FoxO-mediated atrogene transcription (74). DEX inhibits mitochondrial biogenesis and interferes with kinetic protein expression by inhibiting AMPK and its downstream sirtuin 1 (SIRT1) activity, impairing the PGC-1α deacetylation and its transcriptional activity and inducing MA (59,76). In addition, the upregulation of the AMPK-related mitochondrial autophagy factors PINK1 and parkin is an important regulator of DEX-induced MA (76). A flow cytometric assay demonstrated that DEX treatment notably decreases mitochondrial membrane potential ($\Delta\Psi$m) in myocytes, with $\Delta\Psi$m restoration showing therapeutic potential against MA (77). Concurrently, changes in $\Delta\Psi$m are accompanied by a marked increase in the BAX:Bcl-2 ratio and activation of caspase cascade proteins in muscle tissue, with these apoptotic signals exacerbating MA (77). Mitochondrial dysfunction typically induces reactive oxygen species (ROS) accumulation, triggering oxidative stress in DEX-treated muscle (78). Quantitative proteomics has revealed impairment of the glutathione redox system in DEX-treated muscle tissue, with mechanistic links to MAPK/haem oxygenase (HO)-1 pathway dysregulation (79,80).

Epigenetic regulation. Schakman *et al* (20) elucidated the key role of p300/histone deacetylase (HDAC)-mediated protein acetylation shifts in GC-induced MA and studies have further supported the importance of deacetylation reactions in DEX-induced MA (20,81). Lysine-specific demethylase 1 (LSD1), which modulates gene transcription via histone demethylation, is a key regulator of muscle differentiation and regeneration (82,83). Mechanistic investigations have demonstrated that LSD1 is recruited to GR binding sites, where it activates GR enhancers via H3K4 demethylation, thereby regulating the expression of GC target genes in myoblasts (84,85). Following the intraperitoneal injection of DEX, LSD1 knockout mice do not exhibit MA, unlike controls, indicating that LSD1 is required for DEX-induced alterations in both MPB- and MPS-associated pathways. Therefore, LSD1 represents a potential therapeutic target for mitigating the adverse muscle effects induced by DEX (85). These findings are in contrast to the conclusions of Araki *et al* (86), who reported that DEX-induced MA is exacerbated upon LSD1 deletion. This discrepancy stems mainly from differences in the LSD1 deletion technique and experimental design, with evidence favouring the former view (85). In addition, the upregulation of Mstn in DEX-induced MA is attributed to the fact that Mstn contains GC-responsive elements (GREs), and DEX binding induces an increase in Mstn promoter activity (87). Moreover, upregulation of Mstn is hypothesised to be epigenetically regulated by the histone methyltransferase protein lysine methyltransferase SET and MYND domain-containing 3 (SMYD3) (88). SMYD3 shows elevated expression in DEX-treated myoblasts, where it cooperates with bromodomain-containing protein 4 to enhance positive transcription elongation factor b chromatin recruitment and RNA polymerase (pol) II phosphorylation, thereby potentiating Mstn transcriptional activity and elongation (88). Moreover, coactivator-associated arginine methyltransferase 1 (CARM1) functions in DEX-induced MA by inducing autophagy and

regulating ubiquitin ligases (89). Although there are no changes in CARM1 expression following DEX treatment, CARM1 knockdown markedly attenuates the MA phenotype, and this phenomenon is associated with changes in FoxO methylation levels (89).

3. FoxO

FoxO activation is associated with MA, with Senf *et al* (90) demonstrating that the inhibition of FoxO expression improves MA by ≥40%. Under fasting conditions, FoxO is key for the normal induction of 29 out of 63 atrogenes, indicating that FoxO proteins serve a key role in MA by regulating the expression of multiple downstream genes (91). In DEX-induced MA, FoxO plays an important regulatory role in various biological processes, including the regulation of the ALS and UPS, muscle growth and differentiation and energy metabolism (17,92-94). *In vivo* and *ex vivo* analyses have confirmed that DEX enhances FoxO transcriptional activity (20,61,95). Integrated computational prediction, chromatin immunoprecipitation (ChIP) and luciferase reporter assays have identified functional GREs within the promoters of FoxO1 and FoxO3 (92,96). Collectively, these findings position FoxO as a promising therapeutic target for intervention in DEX-induced MA. In-depth investigation of FoxO molecular structure, functional properties and major upstream and downstream regulators is key for developing effective targeted therapeutic strategies.

FoxO structure and function. FoxO proteins are widely distributed in the cytoplasm and nuclei of human tissue and their four isoforms exhibit high structural similarity (97). The forkhead structural domain is the most distinctive feature of FoxO family members. It is named for its characteristic forked structure, which is formed by classical α-helices and β-sheets. This domain enables FoxO to bind DNA specifically, thereby regulating the expression of target genes (98). The transactivation domain (TAD), located in the C-terminus of FoxO proteins, not only facilitates the transcription of target genes via interactions with transcription factors or transcriptional regulators but also serves as a key region for FoxO to undergo various posttranslational modifications (PTMs) to regulate its activity, localisation and stability. Additionally, each FoxO isoform contains nuclear localisation signals (NLSs) and nuclear export signals, which regulate the transport of FoxO proteins between the nucleus and cytoplasm in response to intracellular and extracellular signals (99). The high degree of conservation of the forkhead structural domain is a key feature that allows FoxO proteins to perform essential functions across species. However, >70% of the FoxO region is predicted to be disordered. In particular, the TAD is located exclusively within intrinsically disordered regions (IDRs) (100). The IDR characteristic of TAD confers a high degree of binding flexibility to FoxO, thereby expanding its potential to interact with multiple coactivators and revealing the molecular basis for isoform-specific functional diversification (97).

In the physiological state, moderate FoxO activation is key for maintaining homeostasis. FoxO proteins are regulators of longevity, with their genetic association with human lifespan first demonstrated through a genome-wide association study of Japanese centenarians (101), which identified FoxO3 as the only gene amongst five longevity candidates showing a notable association with lifespan. The mechanism by which FoxO proteins promote longevity is hypothesised to be associated with activation of autophagy, resistance to oxidative stress and maintenance of stem cell homeostasis (16). FoxO serves a key regulatory role in several physiological processes, including glycolipid metabolism, DNA repair, angiogenesis, inflammation and immune regulation (102). Consequently, FoxO is a promising clinical therapeutic target for a range of human diseases, such as diabetes, cancer, cardiovascular disease and neurodegenerative disorder (103). Although the four FoxO isoforms originate from the same gene family, differences in their intrinsic structures and environment-dependent mechanisms allow them to exhibit functional differentiation in different biological processes (97). Gene-targeting studies have demonstrated that FoxO1 knockout impairs blood vessel formation, FoxO3 deletion causes infertility in female mice and FoxO6 deficiency disrupts memory consolidation (104,105). This functional differentiation is key for the development of targeted therapeutic strategies involving FoxO. For example, FoxO3 is implicated in slowing ageing, whereas FoxO1 is a key target for diabetes intervention (103). MA induced by GC overdose causes the pathologically aberrant activation of FoxOs, of which FoxO1 and FoxO3 are the most important regulators (92,106,107).

FoxO and MA

Targeting ALS and UPS. ALS and UPS serve key roles in DEX-induced skeletal muscle catabolism, with FoxO transcription factors serving as master regulators of both proteolytic pathways (108). DEX-induced FoxO activation promotes its nuclear translocation and leads to the upregulation of ubiquitin ligase expression, which is suppressed by FoxO knockdown (51). FoxO directly activates atrogin-1 and MuRF1 transcription by binding multiple FoxO response elements (FREs) in their promoter region rather than through indirect pathways, such as affecting their translational efficiency (19). The MuRF1 promoter contains FREs and adjacent GREs, and their interaction constitutes a key pathological mechanism underlying DEX-induced MA (93). Furthermore, atrogin-1 primarily targets regulatory proteins, such as MyoD, whereas MuRF1 is involved in the loss of MyHC induced by DEX (13,20). Notably, the FoxO regulatory network extends to other atrophy-associated ligases, including ubiquitination factor E4a (Ube4a) and muscle ubiquitin ligase of the SCF complex in atrophy-1 (MUSA1). Ube4a is a U-box-type E3 ubiquitin ligase that, in addition to catalysing substrate ubiquitination, serves as an E4 ubiquitin linker to extend the ubiquitin chain. Its expression increases in MA, whereas this increase is inhibited in the absence of FoxO (109). MUSA1, which is transcriptionally regulated by Smad and FoxO, is upregulated in various catabolic models, including MA models induced by DEX administration, denervation and fasting (91,110). Beyond canonical E3 ligases, Milan *et al* (91) detected a ubiquitin ligase in atrophied muscle, specific of muscle atrophy and regulated by transcription, and the expression of this enzyme exhibits FoxO dependence. Similarly, ZNF216, an A20 zinc finger-containing shuttle protein that directs ubiquitinated substrates to proteasomes, is upregulated in cells treated

with DEX and transfected with constitutively active FoxO *in vitro* (111). FoxO directly upregulates the expression of macroautophagy- and mitochondrial autophagy-associated proteins, upregulating the mRNA expression of LC3, autophagy-related 4b (Atg4b), GABA(A) receptor-associated protein like 1 (Gabarapl1), PINK1 and parkin (17,112). FoxO indirectly participates in the regulation of autophagy in skeletal muscle through its downstream transcription factors macroautophagy and youth optimizer (MYTHO) (113) and deformed epidermal autoregulatory factor-1 (DEAF1) (114). The knockdown of MYTHO, a FoxO-dependent gene in muscle, causes autophagy dysfunction, whereas the depletion of DEAF1 promotes autophagy hyperactivation. Both of these effects lead to MA (113,114). In addition, the lysosomal protein cathepsin L, regulated by FoxO, is a mediator of DEX-induced MPB (115).

Targeting muscle growth and differentiation. FoxO proteins indirectly regulate muscle growth factors, including Myod and Mstn (116,117), through the ALS and UPS, and directly affect their expression. FoxO exerts a dual effect on Myod regulation. Kitamura *et al* (118) suggested that the loss of function of FoxO1 removes the inhibitory effect on Notch signalling, resulting in the upregulation of MyoD expression. Hu *et al* (117) found through in vitro electrophoretic mobility shift assays and ChIP that FoxO3, but not FoxO1, binds two specific FREs in the Myod gene and activates Myod transcription by recruiting RNA pol II. Negative regulation by FoxO1 and direct activation by FoxO3 may reflect the regulation of MyoD expression by FoxO at different stages of differentiation or within specific microsignalling environments. Notably, in cachexia-induced MA , the blockade of FoxO expression concurrently elevates MyoD and decreases Mstn levels (94). The presence of five FoxO1-specific binding sites within Mstn mediates its transcriptional activation (116), and previous studies have revealed a mechanism by which Mstn drives MA by enhancing FoxO activity (119,120), suggesting that the a bidirectional positive feedback regulation process that amplifies muscle catabolic signalling. Furthermore, muscle satellite cells (MuSCs) serve a critical role in muscle injury, repair and regeneration by proliferating and differentiating into mature muscle cells to maintain muscle structure and function. FoxO1 and FoxO3 coordinate MuSC quiescence by upregulating $p27^{Kip1}$, a cell cycle inhibitor. Targeted FoxO attenuation restores MuSC proliferative capacity, thereby offering therapeutic potential for muscle regeneration and atrophy prevention (121,122).

Targeting energy metabolism. FoxO transcription factors serve as key regulators of skeletal muscle energy homeostasis by coordinating mitochondrial biogenesis and glycolipid metabolism (17). RNA sequencing shows that following the dual knockdown of muscle insulin and IGF-1 receptors, most of the altered genes, especially those associated with mitochondrial oxidative phosphorylation (OXPHOS) and tricarboxylic acid cycle, are dependent on the regulation of FoxO (123). Mechanistically, FoxO impairs mitochondrial respiratory chain activity via the selective suppression of complex I subunit expression (124). In ageing skeletal muscle and amyotrophic lateral sclerosis models, FoxO gene deletion restores OXPHOS capacity, thereby promoting ATP synthesis (109,125). In addition, FoxO promotes the conversion of muscle metabolic substrates from glucose to lipids by regulating pyruvate dehydrogenase kinase 4 (PDK4), lipoprotein lipase and fatty acid translocase CD36 in skeletal muscle (126,127). PDK4, the most abundantly expressed isoform of PDK in skeletal muscle, inhibits pyruvate dehydrogenase complex activity via phosphorylation in the mitochondrial matrix, thereby suppressing glucose oxidation. FoxO1 binds to the PDK4 promoter region to regulate energy under starvation conditions (128). Notably, PDK4 promotes the ubiquitinated degradation of atrogin-1 by enhancing MyoG phosphorylation, which promotes DEX-induced MA (129). FoxO1 impairs systemic glucose homeostasis and promotes muscle wasting through the down-regulation of glucose transporter type 4 expression in skeletal muscle (130,131) (Fig. 2).

Regulation of FoxO activity in MA. FoxO activity regulation involves a network of PTMs and protein-protein interactions, resulting in precise functional regulation at the levels of gene transcription and protein activity. The phosphorylation, acetylation and ubiquitination of FoxO are notable post-translational modifications involved in the regulation of MA , and methylation is also a regulatory mechanism associated with MA pathogenesis (132,133). Changes in the levels of multiple PTMs of FoxO are observed in mouse and human myotubular cells following DEX treatment, suggesting DEX-induced MA may be partially mediated by altering the modification pattern of FoxO (Table I) (134). Although previous reviews have addressed FoxO regulatory mechanisms (102,103), the present review specifically focuses on MA-associated pathways and proposes targeting upstream regulators of FoxO signalling as a complementary approach to direct FoxO modulation for MA intervention.

PTMs

Phosphorylation. Calissi *et al* (102) summarised >10 phosphokinases that regulate FoxO activity in organisms. Of these, only Akt, AMPK and mammalian sterile 20-like kinase 1 (MST1) have been specifically implicated in MA (134-137). Akt is the most important negative regulator of FoxO activity, binding FoxO to 14-3-3 proteins through phosphorylation, causing the nuclear exclusion of FoxO and inhibiting its transcriptional activity (138). This altered nuclear repulsive capacity may be associated with the charge neutralisation effect induced by Akt phosphorylation, which impairs the functionality of FoxO NLS (102). By contrast, AMPK enhances FoxO transcriptional activity through site-specific phosphorylation and interferes with the binding of FoxO to 14-3-3, thereby enhancing FoxO intranuclear stability (139). The direct substrate association between AMPK and FoxO was first established by Greer *et al* (140), who identified three distinct phosphorylation sites on FoxO3 following AMPK activation in mammalian cells. Each FoxO isoform contains multiple unique phosphorylation sites for Akt and AMPK, a molecular characteristic that has driven extensive investigation into the Akt/FoxO and AMPK/FoxO signalling pathways in MA (73,141). DEX suppresses Akt activity while activating AMPK in muscle; these effects promote FoxO transcription and induce MA (134). MST1 is widely expressed in muscle and important for the differentiation of C2C12 cells and its activation depends on caspase 3-mediated cleavage (142). In denervation-induced MA, MST1 enhances fast-twitch atrophy

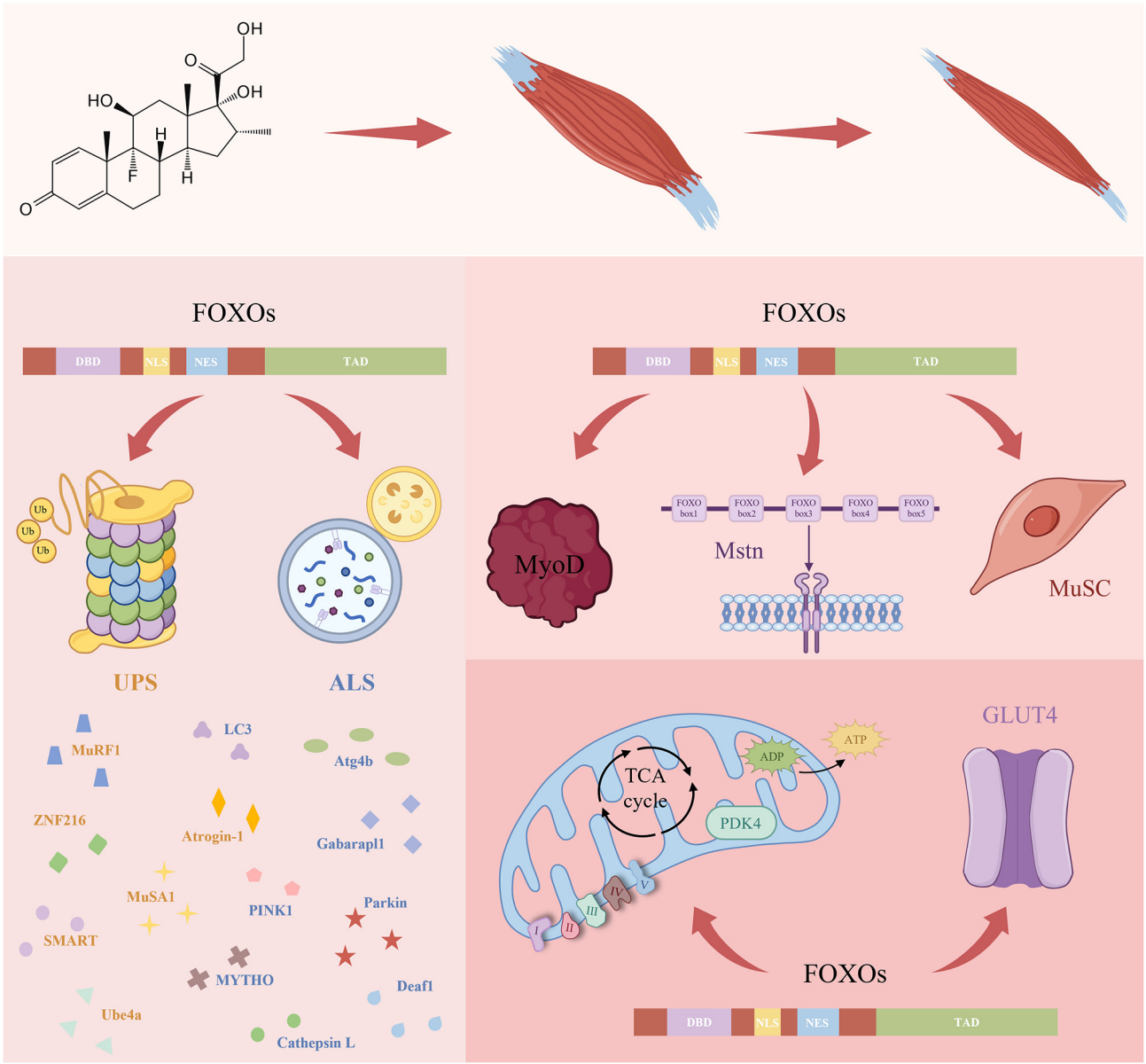

Figure 2. FoxO promotes DEX-induced MA by affecting ALS, UPS, muscle growth and differentiation, and energy metabolism. FoxO, forkhead Box O; DBD, DNA-binding domain; NLS, nuclear localization signal; NES, nuclear export signal; TAD, transactivation domain; ALS, autophagy-lysosomal system; UPS, ubiquitin-proteasome system; MuRF1, muscle RING-finger protein 1; atrogin-1, muscle atrophy F-box protein 1; MyoD, myogenic differentiation; Mstn, myostatin; MuSC, muscle satellite cell; PDK4, pyruvate dehydrogenase kinase 4; GLUT4, glucose transporter type 4; TCA, tricarboxylic acid.

by promoting FoxO phosphorylation at Ser207, whereas MST1 knockdown attenuates this effect (137). The different functions observed under physiological and pathogenic conditions require further exploration.

Acetylation. In DEX-treated muscle, MA-related transcription factors (FoxO and NF-κB) are acetylated (143). The acetylation site of FoxO is primarily located in the forkhead structural domain, regulating its transcriptional activity by affecting the affinity of FoxO for DNA. FoxO acetylation exerts precise and complex effects on transcriptional activity, with activation or suppression dictated by cell type and microenvironment (144). The acetyltransferase P300 was identified as a FoxO regulator in skeletal muscle by Senf *et al* (145); transfection of a P300-deficient plasmid into rat skeletal muscle leads to a 4.6-fold increase in overall FoxO activity, with a 16-fold increase in FoxO3-specific activity. In a DEX-induced MA model, P300 overexpression inhibits the transcriptional activity of FoxO and differentially regulates the expression of its downstream target genes, providing a potential strategy for the treatment of MA (146). Mutants of FoxO3 have been used to verify that P300-mediated Lys262 acetylation is key for regulating FoxO3 subcellular localisation and transcriptional activity (146). HDAC1 is also a key factor regulating FoxO activity in muscle. HDAC1 overexpression (via plasmid delivery) or HDAC1 suppression (by trichostatin A) demonstrate that the deacetylation function of HDAC1 increases the activity of FoxO, its nuclear localisation, and the transcription of atrophy-related target genes. IP experiments with anti-acetylated lysine antibodies further demonstrate that FoxO is a direct target of HDAC1 deacetylation activity in muscle (147). SIRT1 is a class III HDAC and can dually regulate FoxO through deacetylation. During MA, SIRT1 directly inhibits

Table I. PTMs of FoxO in MA models. ('/' indicates that the specific modification site was not reported or is not applicable to the corresponding entry.)

Enzyme	PTM	Action site	Effect on FoxO activity	FoxO isoform	MA model	(Refs.)
Akt	Phosphorylation	Thr24 (FoxO1) Thr32 and Ser253 (FoxO3)	Inhibition	FoxO1/FoxO3/ FoxO4	DEX-treated C2C12 and human muscle stem cells	(134)
AMPK	Phosphorylation	Ser588	Activation	FoxO3	High CO_2 exposure in C57 mice	(135)
AMPK	Phosphorylation	Ser413 and Ser588	Activation	FoxO3	AMPK agonist-treated C2C12 cells	(136)
MST1	Phosphorylation	Ser207	Activation	FoxO3	Denervated mice	(137)
SIRT1	Deacetylation	/	Inhibition	FoxO1/FoxO3	Denervated and fasting CD1 mice	(148)
HDAC1	Deacetylation	/	Activation	FoxO1/FoxO3	Immobilized SD rats, nutrient-deprived C57 mice and C2C12 cells	(147)
P300	Acetylation	/	Inhibition	FoxO1/FoxO3/ FoxO4	Plaster-fixed rats, nutrient deprivation and DEX treatment of C2C12 cells	(145)
P300	Acetylation	Lys262	Inhibition	FoxO3	Denervated C57 mice	(146)
PRMT6	Methylation	Arg188 and Arg249	Activation	FoxO3	Muscle-specific PRMT1 knockout mice and PRMT1 knockdown C2C12 cells	(133)
Mdm2	Ubiquitination	/	Inhibition	FoxO3	Denervated C57 mice	(146)

PTM, post-translational modification; MA, muscle atrophy; DEX, dexamethasone; AMPK, AMP-activated protein kinase; C57, C57BL/6; MST1, mammalian sterile 20-like kinase 1; SIRT1, sirtuin 1; HDAC1, histone deacetylase 1; SD, Sprague-Dawley; PRMT, protein arginine methyltransferase; Mdm2, murine double minute 2.

FoxO transcriptional activity through deacetylation, a finding confirmed by luciferase reporter gene assay and ChIP (148).

Ubiquitination. Among ubiquitylated ligases reported to use FoxO as a substrate (144), only murine double minute 2 (Mdm2) has been reported in MA. In denervation-induced MA, Mdm2 expression is significantly upregulated, and its inhibition via RNA interference markedly restores FoxO3 expression (146). Mdm2 and FoxO3 form a complex, resulting in a substantial reduction in total FoxO3 protein levels (146). In addition, p300 enhances the interaction between Mdm2 and FoxO3, further promoting FoxO3 degradation (146). However, the specific sites of Mdm2 action and the contribution of this ubiquitination to MA remain to be explored.

Methylation. Protein arginine methyltransferases (PRMTs) serve a key role in MuSC function and phenotypical adaptive remodelling (149). In mice, the muscle-specific depletion of PRMT1 results in decreased muscle mass and muscle weakness, accompanied by elevated levels of FoxO3 protein (133). While PRMT1 does not directly methylate FoxO3, its depletion triggers the compensatory upregulation of PRMT6 (133). PRMT6 catalyses asymmetric dimethylation at FoxO3 Arg188/Arg249 residues, inducing transcriptional hyperactivation that exacerbates autophagy and proteolysis, revealing the molecular mechanism by which PRMT1 deletion triggers MA (133).

Protein-protein interactions. FoxO activity is dynamically regulated by direct interaction with various proteins; such regulation influences muscle cell adaptability to atrophy-inducing stimuli. PGC-1α promotes the conversion of myofibrils into an oxidative state in skeletal muscle by regulating mitochondrial function and oxidative metabolism, thereby affecting muscle size and resistance to atrophy (74). The transfection of persistently activated FoxO3 mutants into mouse tibialis anterior muscle results in a marked decrease in muscle fibre cross-sectional area (CSA) and PGC-1α co-expression abolishes this atrophy (74). PGC-1α-mediated protection occurs via the suppression of FoxO3-driven ubiquitin ligase induction, independent of FoxO3 expression or phosphorylation changes (74,150). By contrast, Smad not only enhances the binding of FoxO3 to the MuRF1 promoter region, thereby promoting the transcriptional activity of MuRF1, but also dose-dependently increases FoxO3 protein levels by binding to specific DNA sequences in MuRF1 (151). Therefore, the combined action of Smad with FoxO may be

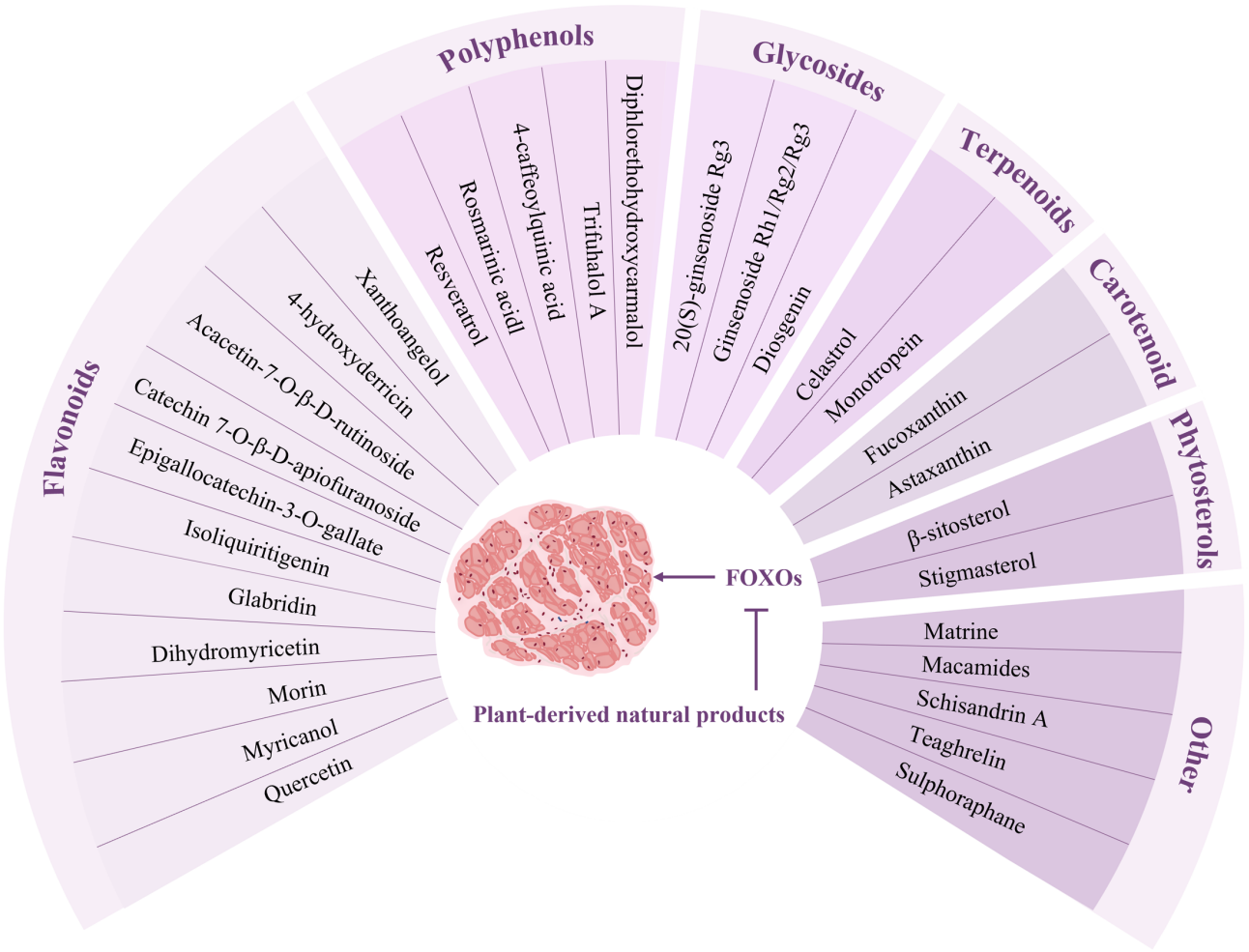

Figure 3. Plant-derived monomer compounds ameliorating dexamethasone-induced muscle atrophy by modulating FoxO transcription factors.

required for the optimal activation of ubiquitin ligases. However, FoxO and Smad act independently in the regulation of Mstn expression and myoblast differentiation (116).

4. Plant-derived NPs target FoxO to ameliorate DEX-induced MA

FoxO activation drives MA through multiple signalling pathways. DEX not only directly activates FoxO but also regulates FoxO activity by affecting FoxO PTMs and protein interactions. Notably, plant-derived NPs have garnered attention because of their biological activities, particularly in terms of anti-inflammatory, antioxidant, antiviral and immunomodulatory aspects (21-23). At the same time, their safety profile and low cost make them valuable for long-term treatment. Numerous plant-derived NPs alleviate DEX-induced MA, with these beneficial effects associated with FoxO activity modulation (24-26) (Fig. 3; Table II).

Flavonoids

Quercetin. Quercetin is a naturally occurring flavonoid found in plants and is widely distributed in many vegetables and fruits, such as onions, apples and asparagus. It accounts for >50% of dietary flavonoid intake (152). Quercetin is a 3,3',4',5,7-pentahydroxyflavone featuring five phenolic hydroxyl groups and a conjugated double bond in its molecular structure, both of which confer powerful antioxidant activity (153). In addition, its anti-inflammatory, antiviral, anticancer and antimicrobial properties have led to a wide range of applications in dietary supplements and pharmaceutical research (154). Quercetin ameliorates DEX-induced C2C12 cell damage by scavenging ROS and restoring $\Delta\psi m$, highlighting its potential against MA (77). Glycosylated derivatives are the primary form of quercetin in plants, with rutin (quercetin 3-O-β-glucuronide) being the most abundant (155). In mice, rutin restores the DEX-induced weight loss of the gastrocnemius, tibialis anterior and extensor digitorum longus muscles by decreasing FoxO3 expression, thereby suppressing atrogin-1 and MuRF1-mediated protein degradation (106). In an *ex vivo* model, the ethanolic extract of *Ricinus communis* leaves alleviates DEX-induced MA by reducing oxidative stress and enhancing FoxO3 phosphorylation, which inhibits UPS-mediated MPB (156). Liquid chromatography-tandem mass spectrometry reveals that the main active component of the extract is rutin (156). In addition, the primary active ingredient of the aqueous extract of lotus leaf is a quercetin derivative, quercetin 3-O-β-glucosiduronic acid, which inhibits the expression of FoxO3 and its downstream atrophy-related genes by affecting the phosphorylation levels of AMPK and Akt, thereby increasing muscle mass in DEX-induced MA mice (157). In mice, an isoquercetin

Table II. Dosing regimen, molecular mechanism and targeting of monomeric compounds that alleviate DEX-induced MA by modulating FoxO transcription factor.

A, Flavinoids

Monomeric compound	DEX dosing regimen	NP dosing regimen	Mechanism	Target	(Refs.)
Quercetin	C57 mice: Intraperitoneal injection, 20 mg/kg/day, 2 weeks; C2C12 cells 1 μM, 48 h	C57 mice: Oral administration, 60.0 mg/kg/day, 3 weeks; C2C12 cells: 100.0 μM, 48 h	Inhibits FoxO3 activity and downstream atrogin-1 and MuRF1 expression	FoxO3	(157)
Myricanol	C57 mice: Intraperitoneal injection, 25 mg/kg/day, 10 days C2C12 cells: 10 μM, 24 h	C57 mice: Intraperitoneal injection, 5.0 or 50.0 mg/kg/day, 10 days C2C12 cell: 2.5, 5.0 or 10.0 μM, 24 h	Decreases MPB, enhances autophagy and promotes mitochondrial biogenesis and function via the SIRT1/ PGC-1α/FoxO3 and SIRT1/ Akt/FoxO3 pathways	FoxO3	(59)
Morin	C2C12 cells: 10 μM, 24 h	C2C12 cells: 10.0 μM, 1 h	Inhibits ROS accumulation and FoxO3 expression, decreases upregulation of multiple atrogenes	FoxO3	(78)
Dihydro-myricetin	SD rats: Intraperitoneal injection, 500 μg/kg/ day, 10 days; L6 cells: 10 μM, 24 h	SD rats: Gavage, 50.0, 100.0 or 200.0 mg/kg/ day, 24 days; L6 cells: 2.0 μM, 24 h	Reverses mitochondrial dysfunction via PGC-1α/ TFAM and PGC-1α/mfn2 pathways, inhibition of FoxO3 activity and activation of Akt/mTOR	FoxO3	(174)
Glabridin	C57 mice: Intraperitoneal injection, 5 mg/kg/day, 1 week; C2C12 cells: 1 μM, 24 h	C57 mice: Oral administration, 40.0 mg/kg/day, 2 weeks; C2C12 cells: 0.1, 1.0 or 10.0 μM, 30 min	Inhibits GR nuclear translocation and FoxO3 expression	FoxO3	(58)
Isoliquiri-tigenin	C57 mice: Intraperitoneal injection, 10 mg/kg/day, 2 weeks; C2C12 cells: 50 μM, 24 h	C57 mice: oral administration, 10.0 or 20.0 mg/kg/ day, 3 weeks; C2C12 cells: 1.0 or 5.0 μM, 24 h	Activates Akt/mTOR signaling; increases phosphorylation of FoxO1 and FoxO3a	FoxO1 and FoxO3	(187)
(-)-epigal-locatechin-3-O-gallate	C2C12 cells: 1 μM, 24 h	C2C12 cells: 5.0 μM, 24 h	Inhibits FoxO3 and MuRF1 expression by 67-kDa laminin receptor	FoxO3	(195)
Catechin 7-O-β-D-apiofuranoside	C2C12 cells: 5 μM, 24 h	C2C12 cells: 10.0, 50.0 or 100.0 μg/ml, 24 h	Activates the Akt/mTOR pathway, increases FoxO1 and FoxO3 phosphorylation, inhibits atrogin-1 and MuRF1 expression	FoxO1 and FoxO3	(200)
Acacetin-7-O-β-D-rutinoside	C57 mice: Intraperitoneal injection, 25 mg/kg/day for 1 week and 5 mg/kg/day for 2 weeks; C2C12 cells: 5 μM, 24 h	C57 mice: Diet containing 0.1% extract, 8 weeks; C2C12 cells: 100.0 or 250.0 nM, 24 h	Inhibits GR translocation, improves proteostasis via Akt/mTOR and FoxO3 and prevents decreased mitochondrial respiration	FoxO3	(205)

Table II. Continued.

Monomeric compound	DEX dosing regimen	NP dosing regimen	Mechanism	Target	(Refs.)
A, Flavinoids					
4-hydroxy-derricin and xanthoangelol	C57 mice: Intraperitoneal injection, 5 mg/kg/day, 1 or 2 weeks; C2C12 cells: 1 μM, 24 h	C57 mice: Oral administration, 37.5, 75.0 or 150.0 mg/kg/day, 1 week or 2 weeks; C2C12 cells: 3.0, 10.0 or 30.0 μM, 30 min	Inhibits GR nuclear translocation and FoxO3 expression	FoxO3	(211)
B, Polyphenols					
Resveratrol	C57 mice: Intraperitoneal injection, 5 mg/kg/day, 18 days; L6 cells: 1 μM, 24 h; C2C12 cells: 1 μM, 24 h	C57 mice: Intraperitoneal injection, 5.0 or 50.0 mg/kg/day, 21 days; L6 cells: 100.0 μM, 24 h; C2C12 cells: 10.0 μM, 24 h	Inhibits ubiquitin ligase expression via the SIRT1/FoxO1 pathway, inhibits mitochondrial dysfunction and atrogene expression via the AMPK/FoxO3 pathway	FoxO and FoxO3	(25, 73)
Rosmarinic acid	C2C12 cells: 10 μM, 24 h	C2C12 cells: 1.0 or 5.0 μM, 24 h	Activates Akt, decreases FoxO3 and downstream ubiquitin ligase expression, inhibits ROS production and apoptosis and restores autophagy, SOD activity and mitochondrial content	FoxO3	(69)
4-Caffeoyl-quinic acid	C2C12 cells: 5 μM, 5 h	C2C12 cells: 0.1 or 0.5 μM, 5 h	Inhibits nuclear translocation of GR and FoxO3a, downregulates atrogenes, activates mTOR to promote MPS	FoxO3	(230)
Trifuhalol A	Zebrafish: 0.01% DEX solution, 1 h/day for 7 days; C2C12 cells: 10 μM, 6 days	Zebrafish: 0.3, 1.0 and 3.0% TFA in feed, 10 days; C2C12 cells: 2.5, 5.0, 10.0 μg/ml, 6 days	Activates Akt/mTOR signaling; upregulates MyoD, myogenin, MyHC; inhibits FoxO3a, MuRF1, atrogin-1	FoxO3	(235)
Diphlorethohydroxycarmalol	ICR mice: Hypodermic injection, 1 mg/kg/day, 10 days	ICR mice: Oral administration, 2.4 mg/kg/day, 38 days	Regulates expression of molecules such as TGF-β, SIRT1, Akt, FoxO3 and Mstn, exerting anti inflammatory and antioxidant effects	FoxO3	(240)
C, Glycosides					
20(S)-ginsenoside Rg3	C2C12 cells: 200 μM, 24 h	C2C12 cells: 20.0, 200.0 or 2000.0 nM, 24 h	Restores mitochondrial function, promotes myoblast differentiation and decreases ubiquitin ligase expression by regulating the AMPK/FoxO3 and Akt/FoxO3 pathways	FoxO3	

Table II. Continued.

C, Glycosides					
Monomeric compound	DEX dosing regimen	NP dosing regimen	Mechanism	Target	(Refs.)
Ginsenoside Rh1, Rg2 and Rg3	C2C12 cells: 200 μM, 24 h	C2C12 cells: 0.5, 1.0 or 2.0 μM, 24 h	Downregulates FoxO3 protein expression and promotes mitochondrial biogenesis via activation of SIRT1/PGC-1α and IGF-1/Akt/mTOR signaling pathways	FoxO3	(249)
Diosgenin	C2C12 cells: 1 μM, 24 h	C2C12 cells: 0.1, 1.0 or 10.0 μM, 30 min	Inhibits GR nuclear translocation, regulates Akt and FoxO3 phosphorylation to downregulate MuRF1 and CBL-B	FoxO3	(255)
D, Terpenoids					
Celastrol	C2C12 cells: 150 μM, 24 h	C2C12 cells: 1.5 μM, 24 h	Activates the heat shock response, Akt1 and ERK1/2 pathways, inhibits FoxO3-mediated proteasome activity and upregulates MuRF1 expression	FoxO3	(261)
Monotropein	C57 mice: Intraperitoneal injection, 10 mg/kg/day, 10 days; C2C12 cells: 100 μM, 24 h	C57 mice: Intraperitoneal injection, 40.0 or 80.0 mg/kg/day, 10 days; C2C12 cells: 25.0, 50.0, 100.0 μM, 24 h	Regulation of muscle catabolic status via the Akt/mTOR/FoxO3 pathway	FoxO3	(267)
E, Carotenoids					
Fucoxanthin	ICR mice: Oral aqueous solution, 1 mg/l, 13 days; C2C12 cells: 10 μM, 24 h	ICR mice: Diet containing 0.2% fucoxanthin, 27 days; C2C12 cells: 1.0, 5.0, 10.0 or 100.0 μM, 24 h	Activates the SIRT1/Akt/FoxO3a pathway, inhibits oxidative stress, apoptosis and ubiquitin ligase expression levels, promotes autophagy and improves mitochondrial content and function	FoxO3	(68, 70)
Astaxanthin	C57mice: Intraperitoneal injection, 5 mg/kg/day, 4 weeks	C57 mice: gavage, 30.0, 60.0 or 120.0 mg/kg/day, 4 weeks	Decreased FoxO3 and increased PGC1α expression ameliorate mitochondrial autophagy, ubiquitination degradation and disorders of glucolipid metabolism	FoxO3	(26)

Table II. Continued.

Monomeric compound	DEX dosing regimen	NP dosing regimen	Mechanism	Target	(Refs.)
F, Phytoesterols					
β-sitosterol	C57 mice: Intraperitoneal injection, 20 mg/kg/day, 2 weeks; C2C12 cells: 1 μM, 48 h	C57 mice: Oral administration, 200.0 mg/kg/day, 3 weeks; C2C12 cells: 0.5 mM, 48 h	Decreased creatine kinase, inhibition of FoxO1 and downstream atrogin-1 and MuRF1 expression	FoxO1	(107)
Stigmasterol	C57 mice: Intraperitoneal injection, 20 mg/kg/day, 21 days; C2C12 cells: 50 μM, 24 h	C57 mice: oral 3.0 mg/kg/day, 21 days ; C2C12 cells: 10.0 μM, 24 h	Inhibits FoxO3 nuclear translocation; downregulates MuRF1/MAFbx; activates mTORC1/p70S6K/4E-BP1	FoxO3	(290)
G, Other					
Matrine	C2C12 cells: 100 μM, 48 h	C2C12 cells: 0.1-0.8 mM, 48 h	Activates Akt/mTOR/FoxO3 to inhibit ubiquitin ligase expression and promote myoblast differentiation	FoxO3	
Macamides	C2C12 cells: 50 μM, 48 h	C2C12 cells: 20.0 or 40.0 μg/ml, 48 h	Activates Akt to enhance muscle differentiation, inhibits nuclear translocation of FoxO3	FoxO3	(299)
Schisandrin A	C57 mice: Intraperitoneal injection, 20 mg/kg/day, 8 days; C2C12 cells: 1 μM, 12 h	C57 mice: Oral administration, 20.0 mg/kg/day, 10 days; C2C12 cells: 10.0 μM, 12 h	Regulation of Akt/FoxO and Akt/P70S6K pathways decreases atrogene expression and increases MPS	FoxO1	(303)
Teaghrelin	SD rats: Intraperitoneal injection, 800 μg/kg/day, 5 days; C2C12 cells: 1 μM, 24 h	SD rats: Oral administration, 10.0, 20.0 or 40.0 mg/kg/day, 10 days; C2C12 cells: 250.0, 25.0 or 2.5 mM, 24 h	Inhibits UPS and autophagy activation via the Akt/FoxO1 pathway and activates Akt/mTOR to promote MPS	FoxO1	(67, 71)
Sulphoraphane	C2C12 cells: 5 μM, 24 h	C2C12 cells: 5.0 μM, 24 h	Activates Akt/FoxO1 pathway and inhibits Mstn and atrogin upregulation	FoxO1	(313)

MA, muscle atrophy; GC, glucocorticoid; DEX, dexamethasone; NP, natural product; FoxO, forkhead Box O; atrogin-1, muscle atrophy F-box protein 1; MuRF1, muscle RING-finger protein 1; MPB, muscle protein breakdown; SIRT1, sirtuin 1; PGC-1α, peroxisome proliferator-activated receptor γ coactivator 1-α; ROS, reactive oxygen species; TFAM, mitochondrial transcription factor A; Mfn2, mitofusin 2; GR, glucocorticoid receptor; TGF, transforming growth factor; Mstn, myostatin; SOD, superoxide dismutase; AMPK, AMP-activated protein kinase; CBL-B, casitas B-lineage lymphoma proto-oncogene B; IGF-1, insulin-like growth factor 1; MPS, muscle protein synthesis; UPS, ubiquitin-proteasome system; P70S6K, ribosomal protein 70 S6 kinase.

glycoside prepared from quercetin glycoside and bittersweet ameliorates the DEX-induced decrease in the gastrocnemius muscle wet weight-to-body weight ratio, as well as increasing Akt phosphorylation levels and decreasing FoxO1 content on the third day of administration (158).

Myricanol. Myricanol, a diarylheptanoid derived from parts of Myrica species (such as Myrica rubra bark), is a plant secondary metabolite. Although research on myricanol is limited, studies have observed multiple biological effects, including anti-inflammatory, antioxidant, apoptosis-inducing,

ferroptosis-inhibiting and neuroprotective activity, in models of diseases, such as lung cancer, Alzheimer's disease and renal fibrosis (159-161). Myricetin is an AMPK activator. In zebrafish fed a high-fat diet, it effectively inhibits lipid accumulation by binding to the AMPK γ subunit (162). Shen *et al* (59) identified myricanol as a SIRT1 activator that directly inhibits downstream FoxO3 transcription by enhancing SIRT1 deacetylase activity, thereby alleviating DEX-induced MA and weakness. SIRT1 activation also improves autophagy and apoptosis imbalance and restores mitochondrial content/function in myotubes via the PGC-1α/FoxO3 and Akt/FoxO3 pathways (59). Given that AMPK and SIRT1 are central regulators of energy metabolism (163), myricanol is hypothesised to play a critical role in mitigating muscle metabolic dysfunction. Metabolomics analysis reveals that myricanol notably rectifies DEX-induced disturbances in glucose, lipid and protein metabolism, consequently reversing muscle mass loss and strength decline in mice (164). This effect may involve irisin secretion from myotubes, which enhances metabolic homeostasis and myogenesis (165). Recent evidence indicates that myricanol ameliorates ageing-related sarcopenia by decreasing oxidative stress (166), solidifying its status as a clinically promising candidate for regulating muscle metabolism and combating MA.

Morin. Morin, a natural pigment extracted from mulberry plants and traditional Chinese herbs, is particularly abundant in mulberry leaves. It has notable efficacy in the prevention and treatment of organ damage, neurodegenerative disease, cancer, diabetes and arthritis, primarily because of its potent antioxidant and anti-inflammatory properties (167). Morin effectively counteracts DEX-induced MA *in vitro*, as evidenced by increases in myotube thickness and diameter and MyHC expression (78). Moreover, it exerts antioxidant effects by inhibiting the DEX-induced upregulation of p66Shc (a redox protein) and enhancing the expression of antioxidant enzymes, such as SOD1 and catalase (78). It decreases the expression of downstream atrogenes by elevating the levels of PGC-1α and phosphorylated FoxO3 within myotubes, thereby mitigating MPB (78).

Dihydromyricetin. *Ampelopsis grossedentata*, a botanical species used in traditional Chinese medicine, is primarily employed to alleviate inflammation-related symptoms, detoxify the body, promote blood circulation and decrease phlegm. Dihydromyricetin, its predominant bioactive constituent, accounts for 30-40% of its extract (168). The bioactivities of dihydromyricetin, including its antioxidant, antimicrobial, antiviral, anti-inflammatory and antiapoptotic properties, underscore its broad therapeutic potential in disease prevention and treatment (169). Preliminary clinical validation has demonstrated its efficacy in managing metabolic-associated fatty liver disease (MAFLD) (170) and type 2 diabetes mellitus (171). Dihydromyricetin exhibits therapeutic effects in mouse models of MA induced by cisplatin and high-fat diet (172,173). In DEX-induced MA, dihydromyricetin targets PGC-1α, counteracting MA by improving $\Delta\psi m$, regulating mitochondrial fission-fusion dynamics and enhancing the activity of respiratory chain complexes (174). FoxO3 siRNA transfection *in vitro* demonstrates that dihydromyricetin suppresses atrogin-1 and MuRF1 expression via FoxO3 inactivation while restoring MyHC content via Akt/mTOR pathway activation (174).

Glabridin. Liquorice is one of the most widely used herbal medicines globally and is employed in traditional Chinese medicine to relieve pain, improve digestive function and alleviate cough. Glabridin, a natural isoflavonoid isolated from liquorice root extract, constitutes 0.08-0.35% of its dry weight (175). Glabridin has garnered notable attention in the cosmetics industry, accounting for 70% of patents in this field (176,177). As a potent tyrosinase inhibitor, glabridin suppresses melanogenesis, thereby exhibiting depigmentation efficacy (178). Furthermore, its antioxidant, anti-inflammatory, anticancer and antimicrobial activities have been extensively reported, providing avenues for developing drugs for treating obesity, diabetes and malignancy (179,180). Notably, glabridin serves as a phyto-oestrogen with structural and lipophilic properties analogous to those of oestradiol, suggesting its key regulatory role in bone health (181). Glabridin notably decreases MPB-related MuRF1 and CBL-B expression in C2C12 cells and mouse tibialis anterior muscle by inhibiting DEX binding to GR, blocking GR nuclear translocation and suppressing FoxO3 phosphorylation (58). Moreover, while changes in p38 phosphorylation are observed, siRNA interference reveals that p38 is not involved in the regulation of DEX-related MA (58).

Isoliquiritigenin. Isoliquiritigenin is a natural chalcone flavonoid primarily isolated from liquorice root. This compound exhibits notable anti-inflammatory and antioxidant properties (182,183). By modulating multiple signalling pathways, including the Nrf2/HO-1, MAPK and SIRT1 pathways, it exerts notable protective effects in disease models, such as myocardial ischaemic injury, diabetic cardiomyopathy, acute kidney injury and Parkinson's disease (182,184). Isoliquiritigenin has been shown to activate the transcription factors FoxO and Nrf2, which are key regulators of cell antioxidant responses (185,186). In skeletal muscle, isoliquiritigenin has also been shown to ameliorate MA by targeting FoxO. In DEX-treated C2C12 cells and mice, isoliquiritigenin supplementation alleviates atrophic changes; specifically, it improves grip strength and exercise endurance in mice and reduces the expression of atrophy-related genes in both models (187). Isoliquiritigenin activates the Akt/mTOR signalling pathway, enhances FoxO1 and FoxO3 phosphorylation and thereby inhibits MPB and promotes MPS (187).

(-)-Epigallocatechin-3-O-gallate (EGCG). EGCG is the most potent catechin derivative in green tea extract, where it accounts for 50-80% of the bioactive components (188). Its 21 hydroxyl groups and stereochemical structure confer potent antioxidant activity, which manifests as chelation of metal ions and neutralisation of free radicals in redox reactions (189). Compared with other catechins, EGCG demonstrates superior biological activity, including anti-inflammatory, antiviral, antimicrobial and anticancer properties, positioning it as a promising therapeutic agent for chronic diseases, such as obesity, diabetes and cardiovascular disease (190,191). Its antitumor efficacy has progressed to clinical trials across multiple cancer types, including breast and lung cancers (192,193), with the 67 kDa laminin receptor identified as the primary mediator of its anticancer activity (194). Notably, in C2C12 cells, EGCG counteracts the DEX-induced upregulation of FoxO3 and MuRF1 via the aforementioned receptor, as evidenced by the unaltered expression observed following

siRNA-mediated receptor silencing (195). High concentrations of EGCG promote the phosphorylation of FoxO3 via the activation of the PI3K/Akt signalling pathway, thereby inhibiting FoxO activation and decreasing MPB (196). Although EGCG exerts regulatory effects on multiple forms of MA through the modulation of the NF-κB, MAPK and PI3K/Akt signalling pathways (197), the molecular mechanisms underlying its protective effects against DEX-induced MA remain largely unexplored.

Catechin 7-O-β-D-apiofuranoside (C7A). C7A is a flavonoid-derived catechin isolated from *Ulmus macrocarpa* (UM). UM, a deciduous tree predominantly distributed in China, South Korea and Japan, is traditionally utilised for treating allergic dermatoses through its root extract, while its bark exhibits therapeutic properties in skeletal health maintenance, as well as diuretic and anti-oedematous effects (198,199). UM extracts and purified C7A protect against DEX-induced MA in vitro (200). Both inhibit MPB and promote MPS by activating the Akt/mTOR signalling pathway and increasing the phosphorylation levels of FoxO1 and FoxO3 in a dose-dependent manner. Moreover, UM and C7A exhibit robust antiapoptotic properties under H_2O_2-induced muscle oxidative stress (200). Subsequent *in vivo* study using C57BL/6 mice confirmed the protective efficacy of UM extract (though not specifically C7A) against MA, highlighting its therapeutic potential (201).

Acacetin-7-O-β-D-rutinoside (AR). AR, also known as linarin, is a flavonoid glycoside abundantly found in plants of the Asteraceae, Lamiaceae and Scrophulariaceae families. To the best of our knowledge, research on AR remains limited, with its anti-inflammatory, antioxidant, sedative and anti-osteoporotic activities preliminarily characterised in animal models or *in vitro* studies, with none having advanced to clinical investigation (202,203). Notably, molecular docking simulation has revealed that the hydroxyl groups of AR forms robust hydrogen bonding interactions with multiple residues of acetylcholinesterase (AChE), suggesting its potential as an AChE inhibitor and therapeutic candidate for Alzheimer's disease (204). The traditional herb *Chrysanthemum zawadskii* Herbich (CZH) exerts protective effects against DEX-induced MA by suppressing GR nuclear translocation, modulating the Akt/mTOR and FoxO3 pathways and downregulating atrogenes (205). As the most abundant bioactive constituent in CZH, AR partially mediates the aforementioned antiatrophic effects through upregulating MyoD, MyoG and MyHC expression, coupled with enhancing mitochondrial respiration in myocytes (205).

4-Hydroxyderricin (HD) and xanthoangelol (XAG). 4-HD and XAG are the two primary chalcone-derived bioactive compounds isolated from Angelica keiskei (AK). Chalcones are α,β-unsaturated carbonyl compounds and serve as a biological precursor of plant flavonoids (206). Studies have characterised their anti-inflammatory properties and regulatory effects on glucose-lipid metabolism, highlighting their therapeutic potential in diabetes and obesity management (207-209). A 12-week randomised double-blind trial in obese populations demonstrated that 4-HD and XAG supplementation decrease visceral fat area and waist circumference in overweight individuals (210). Yoshioka *et al* (211) revealed that prolonged and acute treatment with 4-HD/XAG attenuates DEX-induced MA by inhibiting GR nuclear translocation, suppressing FoxO3 activity and downregulating ubiquitin ligase expression. Changes in the phosphorylation of p38 following 4-HD and XAG intervention are not involved in the regulation of MA (211). However, in C2C12 cells, treatment with 4-HD alone enhances myogenesis by activating the p38 signalling pathway (212). Additionally, the ethanolic extract of AK partially ameliorates DEX-induced muscle strength loss and CSA decreases, with improved effects when combined with Morus alba L. extract (141). These findings collectively suggest that the antiatrophic properties of AK are associated with its primary bioactive constituents 4-HD and XAG (Fig. 4).

Polyphenols

Resveratrol. Resveratrol, one of the most widely studied polyphenols, is produced by a range of plants in response to pathogen attack and participates in plant self-defence responses as an antitoxin (213,214). It is extracted from >70 plant species and is found at particularly high concentrations in grape skin and wine products (215). Evidence from human clinical trials has demonstrated resveratrol therapeutic potential across pathologies, such as Alzheimer's disease, knee osteoarthritis, and diabetic kidney disease, attributable to its pleiotropic biological activity, including antioxidant, anti-inflammatory, antitumor, antiproliferative and antiviral properties (216,217). Howitz (218) found that resveratrol mimics the effects of caloric restriction by activating SIRT1, thereby decelerating ageing. This promoted resveratrol in ageing research and facilitated its commercialisation in nutraceutical formulations (219,220). Although conclusive evidence regarding its ability to extend human lifespan remains elusive, its role as a potent SIRT1 agonist has been widely validated (216,218). It has demonstrated notable efficacy in MA treatment through SIRT1 targeting (221-224). Resveratrol alleviates MA induced by chronic kidney disease (221), ageing (222), cancer (223) and MAFLD (224) by modulating the SIRT1/FoxO1 and AMPK/SIRT1 pathways. Experimental evidence from DEX-treated L6 myotubes reveals that resveratrol suppresses FoxO1 acetylation via SIRT1 activation, consequently downregulating atrogenes, including atrogin-1 and MuRF1, at the transcriptional level (25). The introduction of SIRT1 siRNA further demonstrated that the inhibitory effect of resveratrol on DEX-induced atrogene expression in myotubes is SIRT1-dependent (25). Liu *et al* (73) demonstrated that the resveratrol targeting of AMPK/FoxO3 signalling not only restores DEX-impaired mitochondrial respiration but also suppresses ubiquitin ligase expression, ultimately reversing skeletal muscle mass reduction in mice. Furthermore, resveratrol exhibits notable myoprotective effects through the suppression of inflammatory cascades, oxidative insult and insulin resistance (225), making it a commonly used herb in MA treatment.

Rosmarinic acid (RA). RA is a water-soluble phenolic acid compound found in culinary herbs, such as rosemary, perilla, mint, sage and other labiate plants (226). It exhibits pharmacological effects similar to those of other plant-derived NPs. These effects encompass anti-inflammatory, antioxidant, antibacterial, anticancer and immunomodulatory properties and confer potential for RA application in the pharmaceutical, food and cosmetic industries (227). Clinical evidence highlights its beneficial effects in ameliorating arthritis, cognitive impairment, allergic

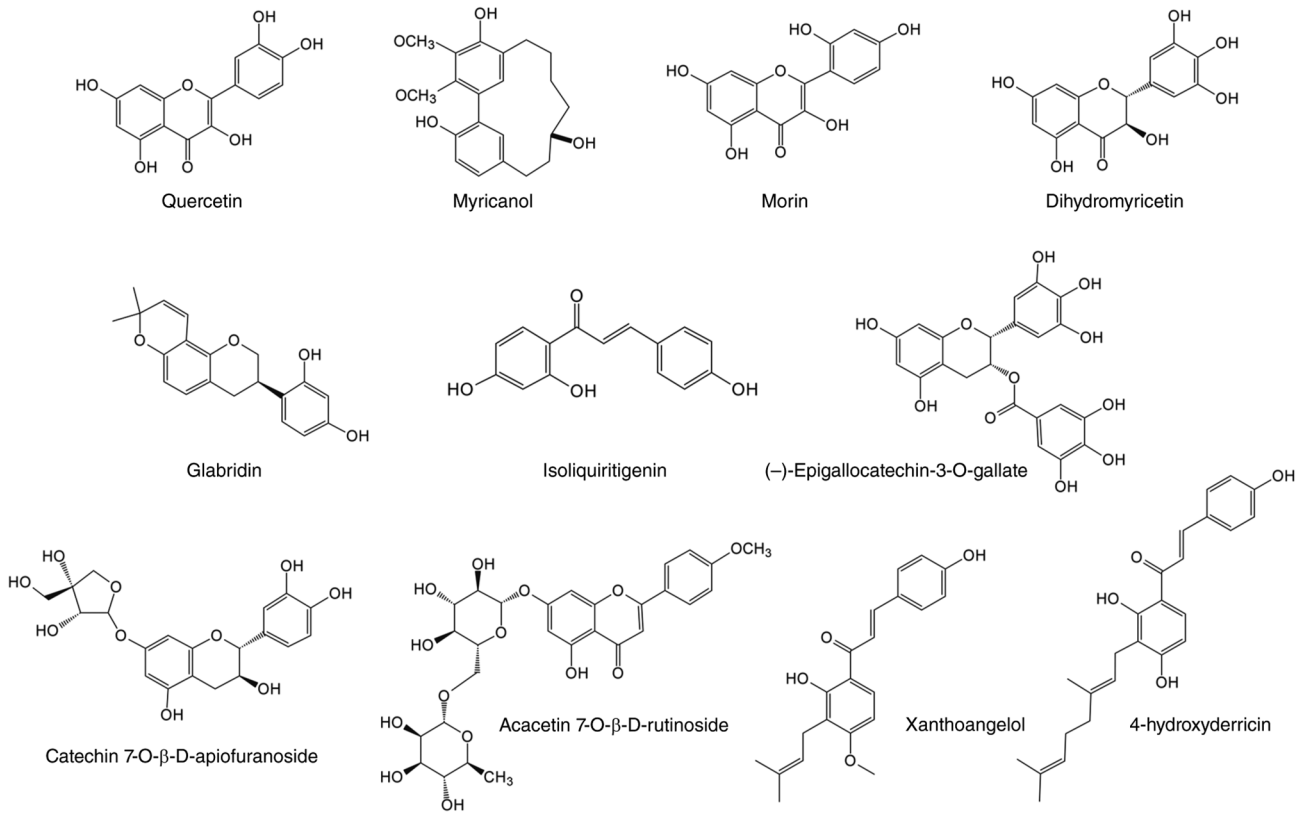

Figure 4. Chemical structural formula of flavonoids.

disorder, dermatological conditions and metabolic syndrome manifestations (228). Ethanolic extract of the traditional herb *Salvia plebeia* R. Br. is effective in reversing DEX-induced cell viability loss and atrogene upregulation, thereby attenuating MA progression. Centrifugal partition chromatography and high-performance liquid chromatography analyses have identified RA as a major active component in this extract (69). The coadministration of DEX with RA mitigates myotube cytotoxicity and atrophy (69). This effect is mechanistically attributed to the RA-mediated activation of the Akt/mTOR/p70S6K signalling pathway, suppression of ROS generation and apoptotic pathways, inhibition of FoxO3-mediated ubiquitin ligase expression, enhancement of autophagic flux and restoration of mitochondrial content and functionality (69).

4-Caffeoylquinic acid (CQA). 4-CQA, a naturally occurring phenolic acid derivative, is synthesised by esterification between caffeic acid and the C4 hydroxyl group of quinic acid. This compound is abundantly distributed in *Asteraceae* and *Lamiaceae* species, where it exerts anti-inflammatory and antioxidant effects in conjunction with other quinic acid derivatives (229). 4-CQA is the predominant bioactive constituent in *Peucedanum japonicum* Thunb., demonstrating notable therapeutic potential against DEX-induced MA (230). In C2C12 myoblasts, 4-CQA regulates muscle protein metabolism by inhibiting the nuclear translocation of GR and FoxO3 while simultaneously activating the mTOR pathway, thereby promoting an increase in myotube diameter (230).

Trifuhalol A. Trifuhalol A is a phloroglucinol compound primarily derived from the ethyl acetate extract of the edible brown alga *Agarum cribrosum*. By contrast with polyphenols from terrestrial plants, those from brown algae are polymers of phloroglucinol (1,3,5-trihydroxybenzene) monomers, endowing them with unique chemical structures and diverse biological activities (231). As a representative monomer, trifuhalol A has a low molecular weight and a simple structure but notable pharmacological activity, including anti-inflammatory, antiadipogenic and antidiabetic effects (232-234). Yang *et al* (235) reported the protective role of trifuhalol A in MA. In C2C12 cells and a zebrafish model, trifuhalol A notably improves myotube diameter and fusion index and increases muscle fibre CSA while also upregulating the locomotor capacity of zebrafish. Mechanistically, trifuhalol A inhibits protein degradation by suppressing the transcriptional activity of FoxO3, thereby downregulating the expression of its downstream targets MuRF1 and atrogin-1 (235). Concurrently, it activates the Akt/mTOR pathway and upregulates the expression of molecules such as MyoD, promoting MPS (235).

Diphlorethohydroxycarmalol (DPHC). DPHC is a polyphenolic compound derived from the edible brown alga *Ishige okamurae*. Previous investigations have primarily focused on its therapeutic properties in inflammation suppression (236), oxidative stress mitigation (237), lipogenesis inhibition (238) and cutaneous protection (239). Compared with DEX, DPHC administration effectively prevents reductions in lean body weight, CSA and gastrocnemius muscle thickness in mice (240). These protective effects are mediated through the coordinated modulation of key signalling pathways, including the TGF-β, SIRT1, Akt, FoxO3 and Mstn pathways, which collectively decrease MPB while promoting anabolic processes (240). DPHC protects muscle tissue from

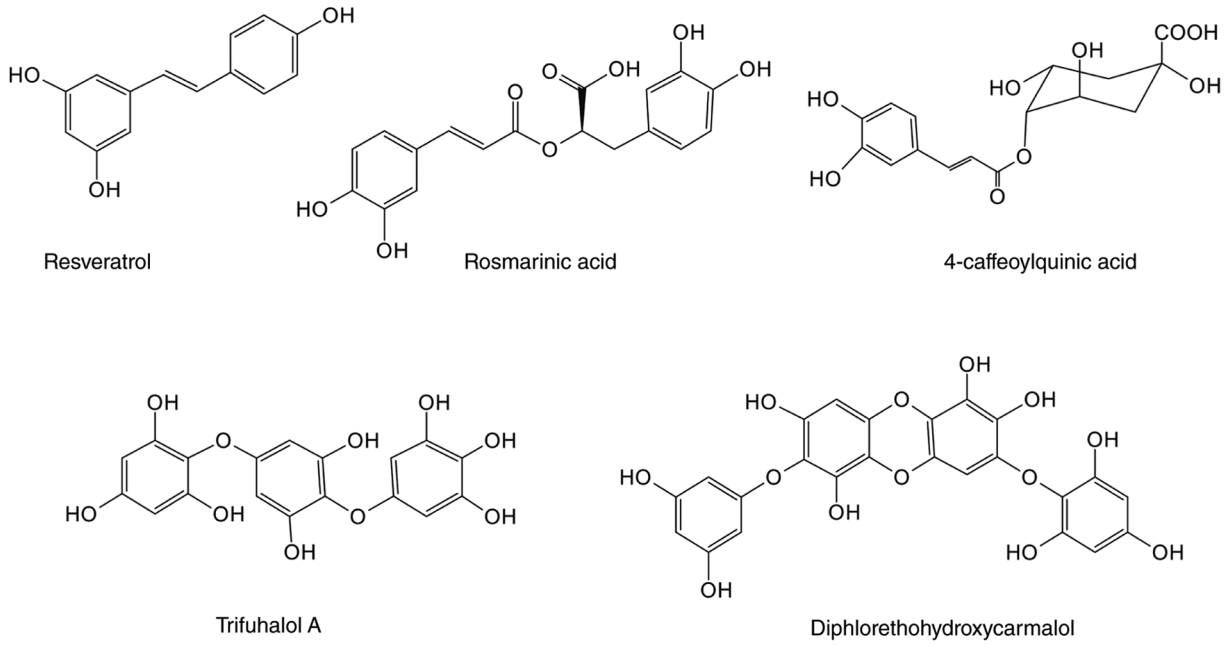

Figure 5. Chemical structural formulae of polyphenols.

DEX-induced damage by reversing the expression of the inflammatory factors IL-1β and inducible nitric oxide synthase and the antioxidant gene glutathione peroxidase 4 (240) (Fig. 5).

Glycosides

Ginsenosides. As members of the triterpenoid saponin family, ginsenosides are predominantly derived from plants of the genus *Panax*, which is used in traditional medicinal. To date, ~300 distinct ginsenosides have been isolated (241). They are classified into two primary categories on the basis of their aglycone carbon skeletons: Tetracyclic dammarane and pentacyclic oleanane types, with the former including common ginsenosides, such as Rb, Rg and Re. Ginsenosides have received extensive attention in pharmacology, as exemplified by Rg3, which achieved regulatory approval by National Medical Products Administration (NPMA) in 2000 as the first monomeric antitumor drug derived from traditional Chinese medicine (242,243). They demonstrate multifaceted therapeutic properties through the modulation of key biological processes, including cellular proliferation, apoptosis, oxidative stress, inflammation and immune regulation, thereby exhibiting clinical relevance in neurodegenerative disorder (244), cardiovascular diseases (245), ageing (246) and metabolic syndrome (247). Zha *et al* (248) reported that ginsenosides possess therapeutic potential for the treatment of sarcopenia by promoting muscle repair and growth: Rh1, Rg1, Rg2, Rg3 and Rg5 improve DEX-induced MA (24,249-252). Mechanistic studies have revealed that 20(S)-ginsenoside Rg3 (S-Rg3) substantially attenuates mitochondrial structural abnormality and respiratory dysfunction in a DEX-treated C2C12 *in vitro* atrophy model via the modulation of the AMPK/FoxO3 signalling pathway, concurrently suppressing atrogene and apoptotic protein expression (251). S-Rg3 enhances C2C12 myoblast differentiation by regulating the Akt/mTOR/FoxO3 pathway (251). This has been validated by the use of the Akt inhibitor GDC-0068 and is consistent with the findings of Men *et al* (24,249). Men *et al* (249) further demonstrated that compared with DEX, Rh1, Rg2 and Rg3 administration notably improves mitochondrial biogenesis through SIRT1/PGC-1α pathway activation.

Diosgenin. Diosgenin, a phytosteroidal saponin, is predominantly found in fenugreek seeds and wild yam rhizomes. Its medicinal value is derived from its hypoglycaemic, hypolipidaemic, anti-inflammatory, antioxidant and immunomodulatory activity, which show notable therapeutic potential in cancer, metabolic and inflammatory disease (253). Serving as a precursor for steroid hormone synthesis, diosgenin is used in the production of hormone drugs via chemical conversion into corticosteroids, oestrogens and androgens (254). As a steroid analogue molecule, diosgenin competitively inhibits DEX and GR binding, thereby effectively mitigating DEX-induced MA (255). The antiatrophic mechanisms of diosgenin involve the upregulation of MyHC expression and suppression of ubiquitin-proteasome activity and are mediated by intracellular signalling alterations associated with GR nuclear translocation inhibition, including the modulation of Akt activation, FoxO3 Ser253 phosphorylation and P70S6K phosphorylation levels (255) (Fig. 6).

Terpenoids

Celastrol. Celastrol, a pentacyclic triterpenoid predominantly isolated from the root extract of *Tripterygium wilfordii*, demonstrates pharmacological activities that are intrinsically linked to its functional groups, notably its C-20 carboxyl, quinone methide and C-3 hydroxyl groups. These structural features directly mediate its antimicrobial, antiproliferative, antineoplastic and cytotoxic properties (256). Celastrol exhibits broad-spectrum protective effects in *in vitro* and *in vivo* models of inflammatory disorder, obesity, diabetes mellitus and neurodegenerative diseases, establishing its status as a promising therapeutic candidate (257,258). Research has

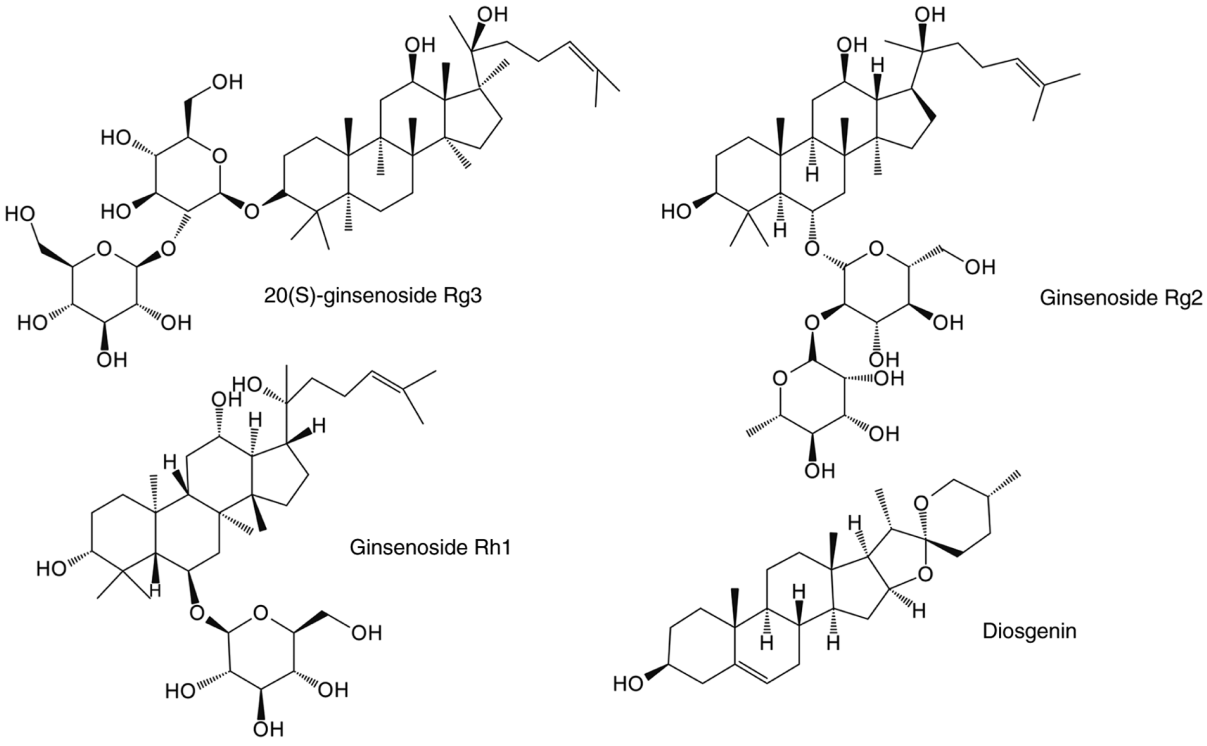

Figure 6. Chemical structural formulas of glycosides.

indicated that celastrol inhibits GR activity and promotes GR degradation by enhancing the interaction between GR and Ube3a (259,260). This molecular mechanism underpins its efficacy in alleviating DEX-induced MA in C2C12 myotubes. Celastrol modulates the DEX-induced downregulation of FoxO3 phosphorylation via HSP70 activation, concurrently suppressing MuRF1 expression and 26S proteasome overactivation (261). Pharmacological inhibition using tanespimycin (an HSP90 inhibitor) and U0126 (an ERK1/2 inhibitor) have revealed that the Akt/mTOR and ERK1/2 signalling pathways mediate celastrol anti-MA effects through the regulation of FoxO3 phosphorylation status (261). Celastrol exerts protective effects in an *in vitro* model of MA induced by doxorubicin (262).

Monotropein. Monotropein is a natural iridoid glycoside that is abundantly found in the root, stems and leaves of *Morinda officinalis* How (263). NF-κB is the most extensively studied downstream target of monotropein (264,265). Molecular docking studies have revealed that monotropein binds NF-κB, thereby inhibiting its DNA-binding activity and decreasing the expression of inflammatory factors (264,265). This anti-inflammatory action, combined with antioxidant effects, suggests monotropein may have therapeutic efficacy in osteoporosis, acute organ injury, asthma and renal cancer (266). Its antiosteoporotic effects involve oxidative stress suppression through the activation of the Akt/mTOR pathway, which contributes to MA mitigation (267,268). By modifying FoxO3 phosphorylation, monotropein-activated Akt/mTOR signalling suppresses atrogene upregulation and enhances MyHC expression in DEX-treated cells and animal (267). Therefore, focusing on the Akt/mTOR pathway may provide a molecular basis for expanding the pharmacological activity of monotropein and its potential clinical application (Fig. 7).

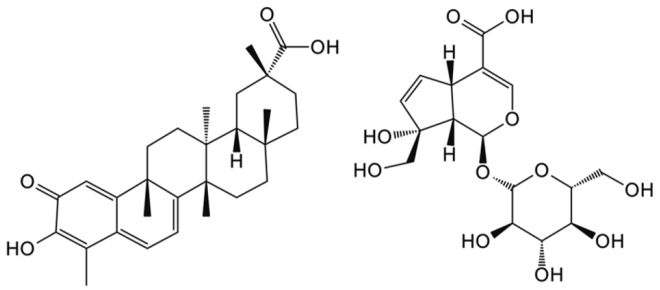

Figure 7. Chemical structural formulae of terpenoids.

Carotenoids

Fucoxanthin. Fucoxanthin is abundantly distributed in algal species, particularly brown algae, accounting for ~10% of all naturally occurring carotenoids (269). As the primary photosynthetic pigment in these organisms, fucoxanthin serves as a key component of light-harvesting complexes, facilitating photon capture and energy transfer (270). Fucoxanthin is the first naturally isolated carotenoid containing an allenic bond, a structure that is hypothesised to be the basis for its multiple pharmacological effects, including anticancer, anti-obesity, antibacterial and intestinal flora regulation effects (271). The epoxy and conjugated carbonyl groups in fucoxanthin confer potent antioxidant capacity, predominantly via singlet oxygen quenching and free radical scavenging mechanisms (272). Yoshikawa *et al* (70) demonstrated that this antioxidative property of fucoxanthin exerts protective effects in DEX-induced MA. Compared with DEX treatment, fucoxanthin ameliorates mitochondrial dysfunction by suppressing AMPK pathway activation and markedly decreases muscular malondialdehyde

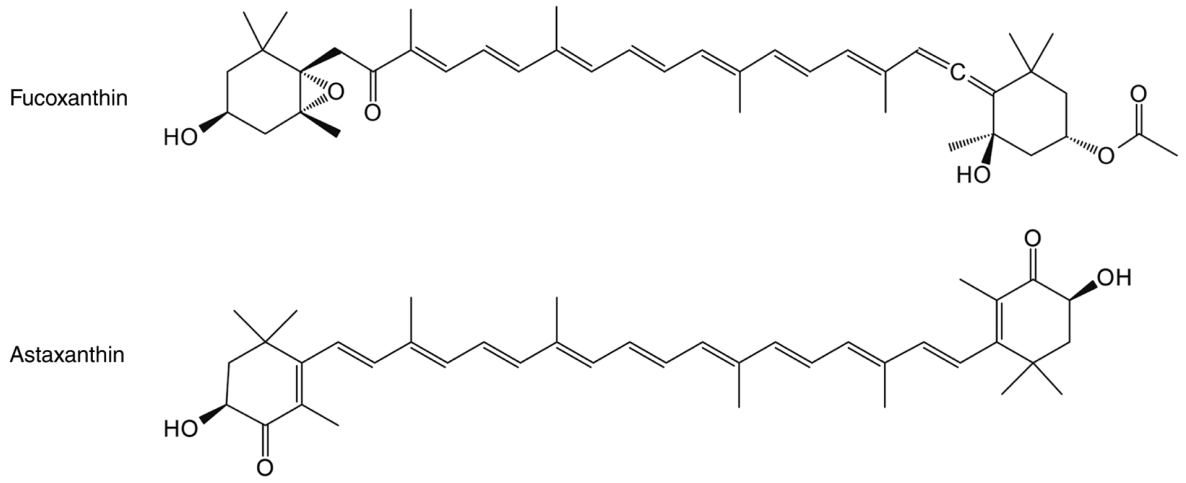

Figure 8. Chemical structural formulae of carotenoids.

and ROS. In an *in vitro* mechanistic study, DEX notably increased the acetylation of FoxO3 and decreased its phosphorylation in C2C12 cells (68). These effects are accompanied by a notable imbalance in ubiquitin ligase autophagy and apoptosis (68). These pathological alterations are reversed by fucoxanthin supplementation via SIRT1 pathway activation; these protective effects are attenuated by cotreatment with a SIRT1 inhibitor (68).

Astaxanthin. Astaxanthin is primarily derived from *Haematococcus pluvialis*, a microalgal species whose astaxanthin content accounts for 5-7% of its dry biomass, making it a key industrial source of this compound (273). Astaxanthin has better antioxidant efficacy than other carotenoids because of its oxygen-containing molecular structure (hydroxyl and ketone groups) and superior membrane permeability (274). Clinical studies have demonstrated that astaxanthin exerts beneficial effects, including neurological, cardiovascular, ocular, dermatological and immune functions, without notable adverse effects (275,276). Astaxanthin is utilised in health supplements, nutraceuticals, dermatological care and aquaculture (277,278). Additionally, astaxanthin serves as an effective sports nutrition supplement, enhancing skeletal muscle performance during exercise and mitigating adverse effects associated with muscle disuse (279). Yue *et al* (26) revealed that astaxanthin ameliorates DEX-induced MA. In mice, astaxanthin alleviates ubiquitination degradation, mitochondrial autophagy and glycolipid metabolism disorder and medium and high doses of astaxanthin effectively inhibit FoxO3 expression (26) (Fig. 8).

Phytosterols

β-sitosterol. Extensive clinical trials have established that phytosterols are natural bioactive compounds capable of effectively decreasing serum cholesterol levels (280,281). A daily intake of 2.0-2.5 g lowers the risk of cardiovascular disease (280). β-sitosterol, a structural analogue of cholesterol, is one of the most abundant phytosterols and is predominantly found in plant-derived foods, such as nuts, seeds, leafy greens and vegetable oils (282). β-sitosterol is commonly incorporated into dietary supplements, particularly those targeting cardiovascular health and prostate function (283,284). Its cancer-preventive properties, attributed to its anti-inflammatory, antioxidant, proapoptotic and immunomodulatory activity, have been validated in cell assays, animal models and clinical studies (285,286). β-sitosterol has demonstrated beneficial effects on skeletal muscle mitochondrial function, biogenesis and glucolipid metabolism in multiple biological systems, including mice, C2C12 myotubes, chicken skeletal muscle (287,288). Hah *et al* (107) used C57BL/6 mouse and C2C12 cell models of DEX intervention to investigate the effects of β-sitosterol on skeletal muscle catabolism. Treatment with β-sitosterol ameliorates DEX-induced MA by increasing muscle mass, enhancing physical performance and suppressing MPB (107). Mechanistically, FoxO1 is a pivotal mediator of β-sitosterol catabolic inhibition, with its activation associated with the decreased expression of atrogin-1, MuRF1 and creatine kinase (107).

Stigmasterol. Stigmasterol is a common phytosterol whose chemical structure is similar to that of β-sitosterol, differing only by an additional double bond in its side chain (289). It is widely distributed in plant cell membranes, such as those of soybeans and nuts, and has analgesic, cholesterol-lowering and memory-improving properties (289). Hah *et al* (290) demonstrated the anti-MA effect of stigmasterol. *In vivo*, oral administration of stigmasterol notably reverses DEX-induced decreases in muscle mass, myofibre CSA and bone mineral density. *In vitro*, 10 μM stigmasterol markedly increases the diameter and fusion index of C2C12 cells, effectively ameliorating DEX-induced MA. From a molecular mechanism perspective, stigmasterol alters the subcellular distribution of FoxO3 in C2C12 cells (290). This manifests as notable inhibition of the DEX-induced nuclear accumulation of FoxO3 (290). Furthermore, stigmasterol concurrently restores mTORC1 activity, elevates the phosphorylation levels of its downstream targets p70S6K and 4EBP1 and promotes MPS in skeletal muscle (290) (Fig. 9).

Others compounds

Matrine. Matrine, an isoquinoline alkaloid compound derived from the traditional Chinese medicinal herb ku shen, has agricultural and pharmaceutical applications (291). In agriculture, matrine is used as a low-toxicity and broad-spectrum

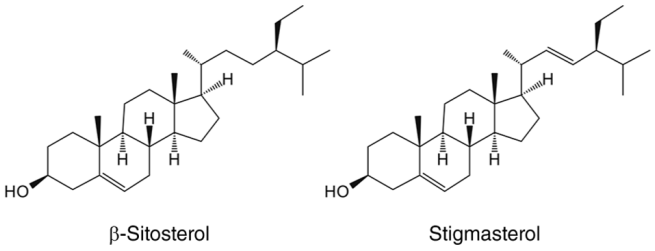

Figure 9. Chemical structural formulae of phytosterols.

insecticide with a good preventive effect against crop pests, such as beetles and aphids (292). In clinical practice, matrine injection has been approved by the NMPA as an adjuvant therapy to enhance chemotherapeutic outcomes in various types of cancer, including pancreatic, lung, and breast cancer (293). Mechanistically, matrine exerts its anticancer effects by inhibiting tumour cell proliferation and metastasis, inducing apoptosis and mitigating drug resistance and systemic toxicity associated with chemotherapeutic agents (294). Furthermore, its anti-inflammatory, antibacterial, antiviral, cardioprotective, neuroprotective and hepatorenal protective properties in *in vitro* and *in vivo* models have been comprehensively reviewed (293,295). The dual immunofluorescence staining of MyHC and MyoD demonstrates that matrine considerably ameliorates DEX- and TNF-α-induced MA by promoting myoblast differentiation in a dose-dependent manner (296). Treatment with 0.1-0.4 mM matrine, either alone or in combination with DEX, enhances myotube differentiation, whereas treatment with 0.4-0.8 mM matrine induces atypical myotube fusion and decreases MyoD expression (296). Mechanistically, treatment with 0.1 mM matrine for 48 h reverses the alteration of Akt/mTOR/FoxO3 pathway phosphorylation by DEX, thereby restoring the balance between protein synthesis and degradation to mitigate MA (296).

Macamide. Macamides are secondary metabolites unique to maca root, with all 26 identified macamides belonging to the N-benzylamide group (297). Maca is known for its pharmacological effects on enhancing sexual function and fertility, and macamides are the primary bioactive compound mediating these benefits (298). Maca root comes in various colours, with the extract from red maca root showing the most potent muscle homeostatic modulation in promoting muscle differentiation and inhibiting MPB. An *in vitro* intervention experiment showed that N-(3-methoxybenzyl) linoleamide, a macamide from *Lepidium meyenii*, inhibits the nuclear translocation of GR and FoxO3 and downregulates MURF1 and atrogin-1 expression in a concentration-dependent manner, thereby attenuating DEX-induced MA. Molecular docking and dynamics simulation have identified multiple binding sites between MAC (18:3) and Akt1, providing mechanistic insight into its ability to enhance Akt phosphorylation during DEX challenge (299).

Schisandrin A (SA). SA, a natural lignan extracted from the traditional herb *Schisandrae fructus* (SF), features a characteristic flavonoid-like core structure with four methoxy substituents (300). SA possesses diverse pharmacological properties, including anti-inflammatory, antioxidant, antineoplastic, hepatoprotective and neuroprotective activity, mediated through the modulation of multiple critical signalling pathways, such as NF-κB, Nrf2, MAPK and NLRP3 (301). SF extracts and SA exhibit therapeutic potential against DEX-induced MA. SF extract inhibits MA progression by enhancing protein synthesis in human MuSCs via the upregulation of phosphorylated (p-)4EBP1 and p-P70S6K levels (302). An *in vivo* experiment has revealed that SA administration reverses DEX-induced MA phenotypes in mice, as evidenced by the restoration of muscle mass, grip strength and myofibre diameter (303). SA exerts anti-MA effects by upregulating Akt, FoxO1 and P70S6K phosphorylation while suppressing atrogenes (303).

Teaghrelin. Teaghrelin, an acylated flavonoid tetraglycoside derived from oolong tea, regulates appetite and gastrointestinal function while promoting growth hormone secretion (304). Its pharmacological activity is associated with neuroprotection (305) and MA improvement (67,71). Hsieh *et al* (71) and Jhuo *et al* (67,71) demonstrated teaghrelin therapeutic efficacy against DEX-induced MA *in vitro* and *in vivo*. In C2C12 myotubes, teaghrelin mitigates DEX-induced MA by decreasing E3 ubiquitin ligase expression, maintaining MyHC levels and activating the Akt/mTOR signalling pathway (71). Teaghrelin regulates ubiquitin ligase and autophagy marker expression associated with MPB in a Sprague-Dawley rat model via Akt/FoxO1 pathway activation (67).

Sulphoraphane. Sulphoraphane, an isothiocyanate abundant in Brassicaceae vegetables, including broccoli, primarily exists in plants in the form of its glucosinolate precursor glucoraphanin (306). Its clinical development as an Nrf2 activator stems from its covalent modification of Keap1 cysteine sensors, which liberates Nrf2 for activation (307). Through Nrf2/NF-κB regulation and epigenetic modification (308), sulphoraphane exhibits pharmacological activities, such as antioxidant, anti-inflammatory, antitumor and neuroprotective activity (309), and is used to treat diabetes (310). As a natural phytochemical that promotes muscle health, sulphoraphane exerts a skeletal muscle protective effect in models of muscle disease and sports injury (311,312). Sulphoraphane monotherapy at subtoxic concentrations enhances MyHCIb and MyHCIIx isoform expression levels in C2C12 myotubes without cytotoxicity (313). When DEX is co-administered with sulphoraphane, sulphoraphane promotes FoxO1 inactivation through Akt activation, leading to the effective inhibition of the DEX-induced upregulation of Mstn and atrogin-1 expression, showing a potential protective effect against MA (313) (Fig. 10).

5. Discussion

Plant-derived NPs primarily exert anti-MA effects by modulating FoxO activity, with their regulatory mechanisms exhibiting common molecular characteristics (Table II). Most compounds promote the phosphorylation inactivation of FoxO1/FoxO3 or inhibit their transcriptional activity via SIRT1-mediated deacetylation, thereby preventing their nuclear translocation and downregulating the expression of atrophy-associated genes. Concurrently, certain compounds (myricanol, dihydromyricetin, fucoxanthin) indirectly inhibit the abnormal activation of FoxO by improving mitochondrial function, decreasing oxidative stress or restoring autophagy

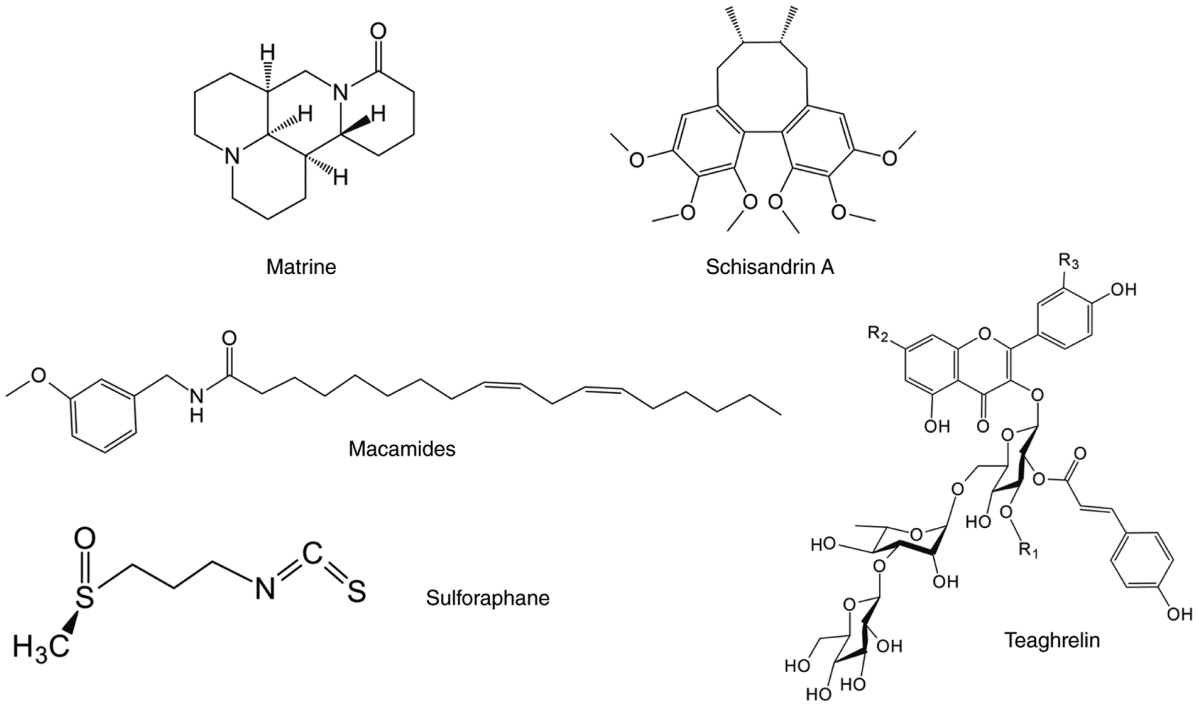

Figure 10. Chemical structural formulae of other monomeric compounds.

homeostasis (59,68,70,174). In addition, GR is a direct target of certain compounds (such as glabridin, AR and diosgenin) that inhibit DEX-mediated FoxO activation by blocking GR nuclear translocation, thereby exerting anti-MA effects (58,205,255).

In DEX-induced MA, existing studies have primarily focused on indirectly affecting FoxO activity by regulating upstream signalling pathways, such as PI3K/Akt, SIRT and GR (58,59,187). To the best of our knowledge, plant-derived compounds directly targeting FoxO have not yet been reported. However, a limited number of studies in other disease areas have begun to explore the direct effects of NPs on FoxO (314-316). Kim *et al* (314) reported that syringaresinol directly binds to the forkhead DNA-binding domain of FoxO3 and enhances its transcriptional activity by stabilising the FoxO-DNA complex. Through molecular docking, Gupta *et al* (315) identified NPs, such as fraxin, as potential direct inhibitors of FoxO1. Guan *et al* (316) demonstrated that quercetin and catechin directly act on different sites of FoxO3 and inhibit its transcriptional activity, thereby ameliorating acute alcoholic liver injury. From a structural perspective, although these compounds are derived from diverse sources, they are often rich in aromatic rings and phenolic hydroxyl groups, exhibiting certain conjugation and molecular rigidity. They may bind the surfaces of FoxO proteins via hydrogen bonds and π-π interactions, thereby modulating their conformation or DNA-binding state (314-316). Nevertheless, to the best of our knowledge, no systematic comparison has been performed to support an association between the structure of plant-derived compounds and FoxO-targeting activity.

The regulatory strategies for FoxO remain predominantly indirect. For example, Orea-Soufi *et al* (103) summarised clinical drug-targeting strategies for FoxO across different disease contexts and indicated that the majority of FoxO-targeting drug strategies rely on indirect regulation through various signalling pathways, with molecules directly acting on FoxO being limited. This may be associated with structural characteristics of FoxO proteins, namely, their lack of a classic small-molecule binding pocket and their high proportion of IDRs, which make formation of a stable drug-binding interface difficult (317). Targeted protein degradation technologies offer new possibilities to overcome this limitation (318,319). Among these technologies, transcription factor-proteolysis-targeting chimera (PROTAC) has garnered considerable attention (320,321). By contrast with traditional PROTAC, which requires small-molecule ligands, transcription factor-PROTAC directly uses the inherent DNA-binding capacity of transcription factors. A transcription factor is selectively degraded by conjugating the DNA-binding sequence of the target gene with an E3 ubiquitin ligase ligand (320). This approach may be feasible in the context of DEX-induced MA, as it does not require a small-molecule ligand for FoxO. To the best of our knowledge, however, none of the plant-derived compounds included in the present review have been shown to bind FoxO directly. Therefore, lead structures for the development of traditional PROTAC ligands are lacking. FoxO proteins specifically recognise DNA sequences through their forkhead domain, providing a directly usable recognition element for the design of transcription factor-PROTACs. Furthermore, certain NPs (syringaresinol, fraxin, quercetin) possess direct affinity for FoxO (314-316), offering potential structural templates for the development of FoxO degraders derived from NPs. Therefore, developing highly efficient FoxO-targeting degraders by integrating transcription factor-PROTAC with the structural features of NPs may provide novel intervention strategies for DEX-induced MA.

Notably, all studies included in the present review were conducted on animal or *ex vivo* models and lack direct human

or clinical research data. Although these models hold value for mechanistic studies, they possess certain limitations for clinical translation. Firstly, differences exist between rodents and humans in their response to GC-induced MA. Langendorf *et al* (95) compared the response of human primary myotubes and murine C2C12 cells to DEX and found that while human cells exhibit upregulation of atrophy-associated factors, they do not show the typical myosin degradation observed in mice. Secondly, DEX-induced MA primarily affects type II fibres, an effect that is associated with their high GR expression (47). Systematic differences exist between mice and humans in terms of skeletal muscle structure and molecular composition. Overall, mouse muscles overall exhibit a fast-twitch fibre-biased phenotype and have higher collagen content than human muscle. These differences may lead to variations in sensitivity to GC intervention. Furthermore, animal experiments typically employ short-term, high-dose DEX interventions, whereas clinical patients typically present with complex exposure patterns involving long-term, low-dose use or the presence of other underlying comorbidities (such as diabetes and hypertension) (322). Nakao *et al* (323) found that the dosing regimen can influence the extent of DEX-induced MA. In consideration of the limitations of animal models, clinical studies are crucial for validating the anti-atrophy potential of various plant-derived NPs. Given the ethical and safety constraints associated with human studies on GC-induced MA, future research should perform retrospective analyses using existing patient cohorts, prospectively monitor the muscle status of patients requiring long-term GC use, develop targeted gene therapy and exosome-based intervention strategies to overcome the limitations of animal models and use patient-derived skeletal muscle stem cells to construct 3D organoids or myotube models.

Although the transcriptional activity of FoxO is regulated by PTMs, such as phosphorylation, acetylation and methylation, the existing research on plant-derived NPs is primarily restricted to the dynamic regulation of phosphorylation modifications (134-136). Phosphorylation detection techniques are mature and widely applied (134-136). By contrast, acetylation and methylation detection relies on complex technical approaches, such as co-IP, mass spectrometry and site-specific antibodies (133), with experimental complexity limiting research. Moreover, current investigations have predominantly focused on classical signalling pathways, such as the PI3K/Akt and AMPK pathways, and their phosphorylation sites have been extensively reported (134-136). The association between phosphorylation and FoxO nuclear translocation, as well as transcriptional activity, is established, making it readily applicable for mechanistic interpretation (324). These factors collectively render phosphorylation the most direct and commonly used indicator. Nevertheless, with technological advancements, future research may investigate the regulation of multiple PTMs of FoxO, thereby enabling study into the mechanisms underlying the regulatory effects of plant-derived NPs on FoxO.

6. Conclusion

As a potent synthetic GC, DEX is used to induce skeletal MA, . DEX mediates the pathological process of skeletal MA through multiple pathways, with the key mechanism being the dynamic imbalance of muscle protein metabolism, which manifests as the bidirectional dysregulation of anabolic inhibition and catabolic activation. FoxO is associated with the MPB pathway, activating the ALS and UPS to degrade key proteins involved in muscle growth and differentiation while disrupting the homeostasis of muscle energy metabolism. DEX intervention alters FoxO transcriptional activity in myocytes, particularly FoxO1 and FoxO3. Therefore, the FoxO family may serve as the central molecular hub in DEX-induced MA, integrating catabolic signalling with energy metabolism networks to promote the progressive loss of muscle mass and function. FoxO is evolutionarily highly conserved and stable, with gene mutations and deletions being rare. Therefore, the pharmacological modulation of its inhibition or activation represents a promising therapeutic strategy for various diseases, such as cancer, diabetes and MA. NPs exhibit the advantages of low toxicity, multitarget effects and broad-spectrum pharmacological activity, with herbal compounds having been proven to be effective (21-23). The present review focused on drug-induced MA caused by DEX, summarising the roles of plant-derived monomeric compounds in ameliorating this type of MA. Plant-derived NPs have potential in alleviating DEX-induced MA by modulating FoxO. The present review not only expands the application prospects of NPs in drug-induced MA but also provides insights into the pathological mechanisms and intervention strategies associated with drug-induced MA.

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Availability of data and materials

Not applicable

Authors' contributions

WD conceived the study and wrote the manuscript. JW conceived the study and edited the manuscript. XM, LK, MW and HG edited the manuscript. WW and WX supervised the study and edited the manuscript. Data authentication is not applicable. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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