Ursolic Acid Attenuates Glucocorticoid-Induced Sarcopenia: Molecular Mechanisms and Therapeutic Potential

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Abstract

Sarcopenia is an age-associated disorder characterized by the progressive loss of skeletal muscle mass, strength, and functional capacity, leading to increased frailty, falls, and reduced quality of life in older adults. While aging is the main cause of primary sarcopenia, chronic glucocorticoid therapy significantly contributes to secondary sarcopenia. Muscle atrophy induced by glucocorticoids occurs through activation of catabolic pathways and suppression of anabolic processes. Glucocorticoids inhibit insulin-like growth factor-1 (IGF-1)/Akt signalling, suppress mammalian target of rapamycin (mTOR), activate forkhead box O (FOXO) transcription factors, upregulate E3 ubiquitin ligases atrogin-1 and MuRF1, enhance ubiquitin–proteasome degradation, induce myostatin expression, stimulate NF-κB–mediated inflammatory signalling, and promote oxidative stress and mitochondrial dysfunction. These changes shift the anabolic–catabolic balance toward protein degradation and functional decline. Ursolic acid (UA), a pentacyclic triterpenoid found in apple peels, Ocimum sanctum, and rosemary, has emerged as a promising compound capable of modulating these dysregulated pathways. UA activates Akt/mTOR signalling, inhibits FOXO-mediated proteolysis, suppresses atrogin-1 and MuRF1 expression, attenuates NF-κB activation, reduces reactive oxygen species production, enhances mitochondrial biogenesis via PGC-1α, and downregulates myostatin signalling. Preclinical models show preservation of muscle mass and strength following UA administration. Despite strong mechanistic evidence, development is limited by poor solubility, low bioavailability, and lack of clinical trials. This review examines the mechanisms of glucocorticoid-induced sarcopenia and evaluates ursolic acid as a pharmacological modulator.

Keywords: Sarcopenia; Glucocorticoid; Muscle atrophy; Ursolic acid; Preclinical models; Pharmacological modulator.

How to cite this article: Arshad MZ, Mishra AP, Rajpoot A, Prajapati A. Ursolic Acid Attenuates Glucocorticoid-Induced Sarcopenia: Molecular Mechanisms and Therapeutic Potential. Int J Drug Deliv Technol. 2026;16(22s): 551-568. DOI: 10.25258/ijddt.16.22s.67

Graphical Abstract

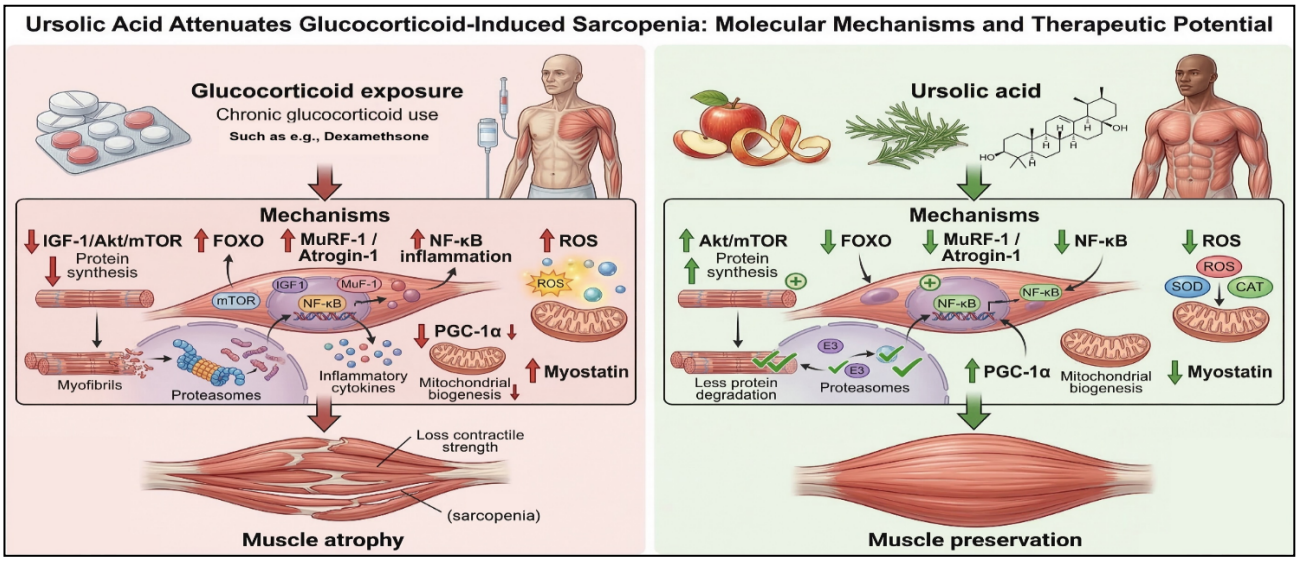

Figure 1: *Ursolic acid mitigates glucocorticoid-induced sarcopenia by enhancing Akt/mTOR signalling, inhibiting FOXO-mediated proteolysis, and reducing oxidative stress and inflammation, thereby preserving muscle mass.*

Introduction

Sarcopenia is a condition that progressively affects skeletal muscles, reducing muscle mass, strength, and functional ability (Carmeli, 2020; Cruz-Jentoft & Sayer, 2019). This disorder has become a significant public health issue in aging populations globally (Tu et al., 2025). Sarcopenia contributes to frailty, disability, falls, and diminished quality of life in older adults (Zhou et al., 2023, p. 2). It also places economic strain on healthcare systems through increased hospital admissions and long-term care needs (Beaudart et al., 2025). The European Working Group on Sarcopenia in Older People (EWGSOP) defines sarcopenia as a syndrome of low muscle strength, reduced muscle quantity or quality, and impaired physical performance. Epidemiological research shows sarcopenia affects 5% to 13% of those aged 60 to 70 years, reaching over 50% in individuals above 80 years (He et al., 2021). While primarily associated with aging, sarcopenia can be accelerated by chronic illnesses like diabetes, cancer, kidney disease, and chronic obstructive pulmonary disease, along with nutritional deficiencies, physical inactivity, and extended medication use. (Luis et al., 2024).

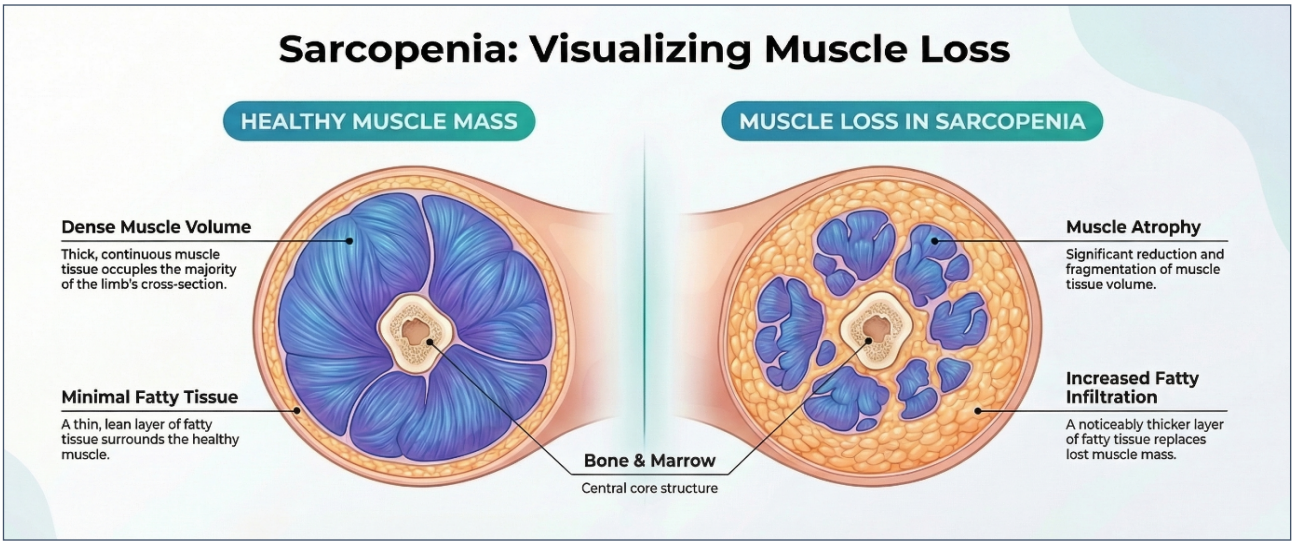

Figure 2: *Comparison of healthy and sarcopenic muscle showing reduced muscle mass, fibre atrophy, and increased fatty infiltration in sarcopenia.*

Chronic glucocorticoid therapy is identified as a significant factor in skeletal muscle wasting among pharmacological causes (Hasselgren et al., 2010). Glucocorticoids are prescribed to treat inflammatory, autoimmune, and cancerous conditions due to their immunosuppressive and anti-inflammatory effects (Reichardt et al., 2021). However, prolonged use of glucocorticoids like dexamethasone and prednisone can cause side effects including osteoporosis, metabolic syndrome, and muscle atrophy (Hardy et al., 2020).

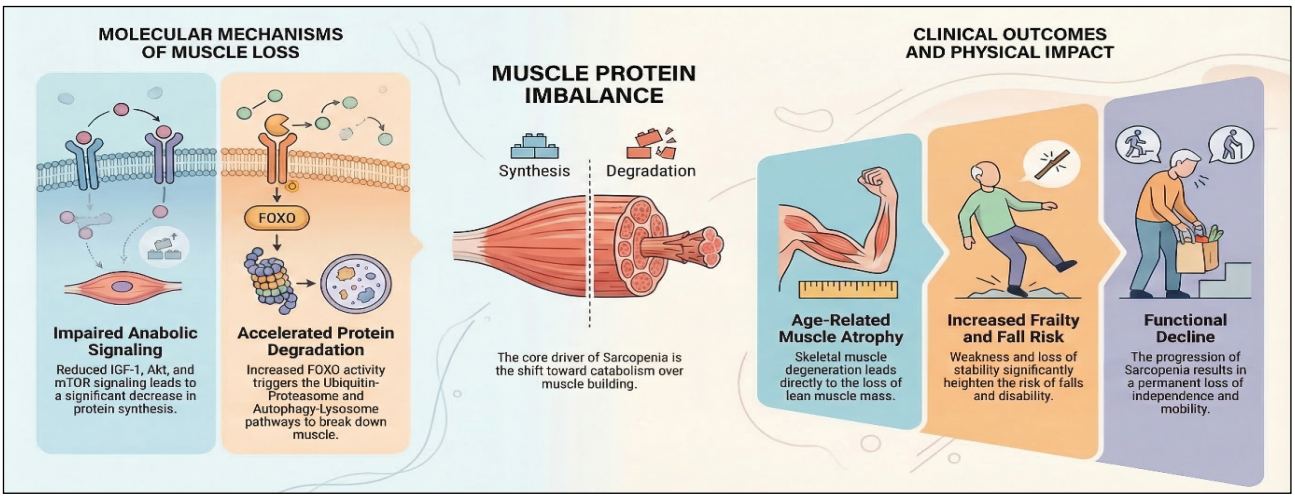

Figure 3: *Molecular pathways driving sarcopenia and their clinical outcomes, highlighting impaired anabolic signalling, enhanced proteolysis, and resultant functional decline.*

Glucocorticoid-induced sarcopenia arises from an imbalance in anabolic and catabolic signalling pathways controlling muscle protein turnover (Schakman et al., 2013). Skeletal muscle mass is maintained by a balance between protein synthesis and degradation (Paulussen et al., 2021). Anabolic pathways like IGF-1/Akt/mTOR promote protein synthesis, while catabolic pathways, including the ubiquitin–proteasome system (UPS) and autophagy, facilitate protein breakdown. Glucocorticoids disrupt this balance by inhibiting anabolic signalling and triggering catabolic activities (Hardy et al., 2020).

Through suppression of the IGF-1/Akt pathway, reduced Akt activation leads to diminished mTOR signalling, impairing protein synthesis and muscle regeneration (Wang et al., 2016). Glucocorticoids stimulate forkhead box O (FOXO) transcription factors, increasing expression of muscle-specific E3 ubiquitin ligases, atrogin-1 (MAFbx) and muscle RING finger-1 (MuRF-1), which mark myofibrillar proteins for degradation via the ubiquitin–proteasome system (Pang et al., 2023). Oxidative stress contributes to muscle atrophy through reactive oxygen species (ROS) damaging mitochondrial membranes and activating proteolytic pathways (Braun & Marks, 2015). Prolonged glucocorticoid exposure triggers inflammatory signalling pathways like nuclear factor-κB (NF-κB), increasing catabolic gene expression and hindering muscle regeneration. Due to sarcopenia's complexity, single-pathway treatments have shown limited effectiveness (Yoon & Kwon, 2021). There is growing interest in multi-target therapeutic strategies that influence several pathological pathways (Yu et al., 2017).

Natural bioactive compounds from plants have attracted attention as potential treatments for muscle wasting disorders (Nikawa et al., 2021). Phytochemicals like flavonoids, polyphenols, and triterpenoids offer antioxidant, anti-inflammatory, and metabolic effects that may protect skeletal muscle from degeneration (Kim & Hwang, 2020).

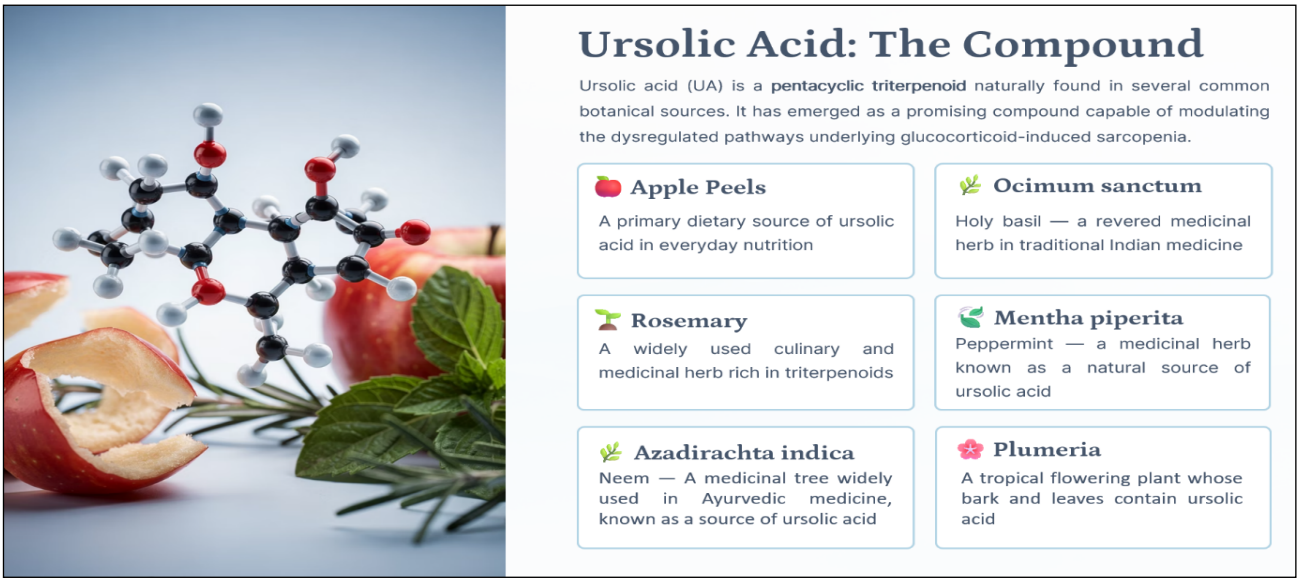

Figure 4: *Natural sources and chemical representation of ursolic acid.*

Ursolic acid is a potential option for preventing and treating sarcopenia, according to Al-kuraishy et al. (2022). This pentacyclic triterpenoid is found in medicinal plants and foods, such as apple peels, rosemary, basil, and thyme (Shaikh et al., 2021). Research shows that ursolic acid has anti-inflammatory, antioxidant, anti-cancer, and metabolic regulatory effects (Liu et al., 2023). Studies indicate that ursolic acid influences signalling pathways in skeletal muscle metabolism (Yadav & Dabur, 2023). It activates the IGF-1/Akt signalling pathway, inhibits FOXO-mediated proteolysis, decreases oxidative stress, and promotes mitochondrial biogenesis (Yadav & Dabur, 2023, p. 13). These effects suggest ursolic acid could serve as a multi-target therapeutic agent for glucocorticoid-induced sarcopenia (Kwak & Kwon, 2019; Liu et al., 2024).

This review aims to deliver a thorough examination of the molecular processes that contribute to glucocorticoid-induced sarcopenia and to assess the potential of ursolic acid as a pharmacological treatment for muscle wasting conditions.

Molecular Mechanisms of Sarcopenia and Glucocorticoid-Induced Muscle Atrophy

The regulation of skeletal muscle homeostasis involves signalling pathways that control protein synthesis, breakdown, mitochondrial activity, and inflammation (Hindi et al., 2018).

In normal states, muscle mass is maintained through balance between anabolic pathways promoting protein synthesis and catabolic pathways facilitating degradation (Deane et al., 2024). Disruption of this equilibrium leads to declining muscle mass and function, characteristic of sarcopenia (Kim et al., 2020).

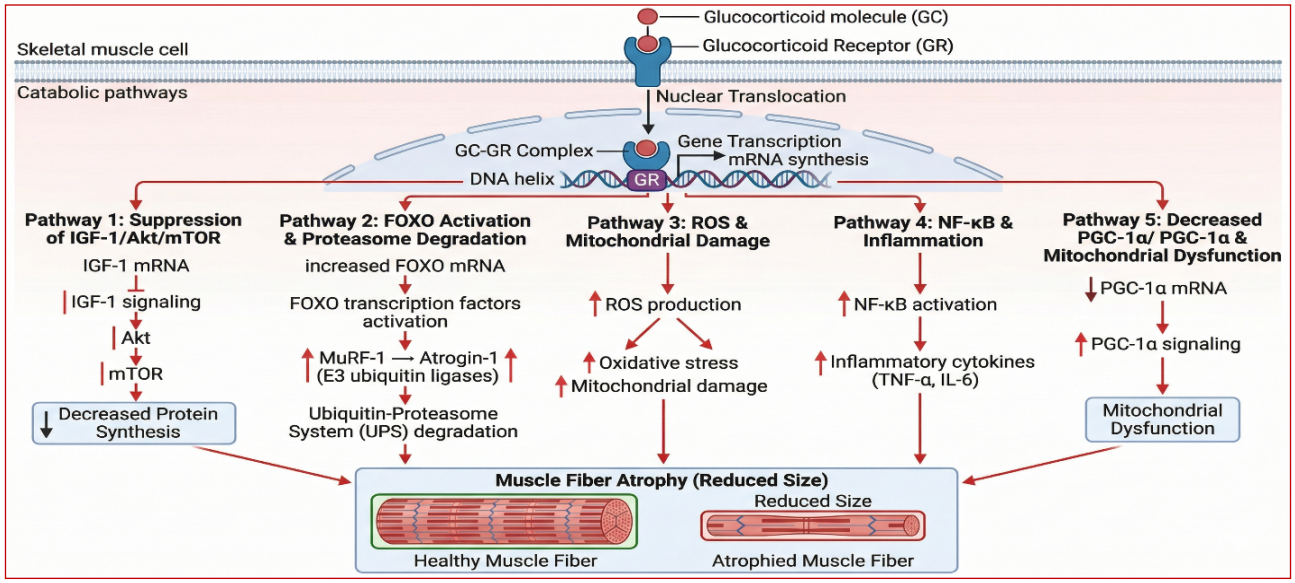

Figure 5: *Glucocorticoid-induced molecular pathways leading to skeletal muscle atrophy, including impaired anabolic signalling, enhanced proteolysis, oxidative stress, inflammation, and mitochondrial dysfunction.*

Glucocorticoids are powerful pharmacological agents that induce muscle wasting (Hasselgren et al., 2010). These hormones activate the glucocorticoid-receptor (GR), a ligand-activated transcription factor regulating gene expression in skeletal muscle cells. When glucocorticoids bind to the receptor, it enters the nucleus and interacts with glucocorticoid response elements, influencing transcriptional activity. This leads to changes in metabolic, inflammatory, and proteolytic pathways, facilitating muscle catabolism (Braun & Marks, 2015). Glucocorticoid-induced muscle atrophy occurs through interconnected molecular mechanisms, including anabolic signalling inhibition, proteolytic pathway activation, oxidative stress, mitochondrial dysfunction, inflammatory signalling, and myostatin-mediated muscle growth suppression (Permpoon et al., 2025; Schakman et al., 2013).

Table 1: *Molecular Pathways involved in Glucocorticoid-Induced Sarcopenia*

S.N.	Pathway (Mechanism)	Mechanism of Action	Molecular Changes	Physiological Outcome	References
1.	Suppression of anabolic signalling (IGF-1/Akt/mTOR)	Glucocorticoids reduce IGF-1 expression and inhibit Akt phosphorylation, leading to decreased mTOR activity and reduced protein synthesis; FOXO activation is enhanced	↓ IGF-1, ↓ Akt, ↓ mTOR	Reduced protein synthesis	Yoshida & Delafontaine, 2020; Schiaffino & Mammucari, 2011
2.	Activation of ubiquitin–proteasome system (FOXO-mediated)	Suppressed Akt signalling allows FOXO nuclear translocation, increasing expression of E3 ubiquitin ligases that tag proteins for degradation	↑ MuRF-1, ↑ Atrogin-1	Accelerated muscle protein degradation	Webb & Brunet, 2014; Baumann et al., 2016
3.	Oxidative stress and ROS accumulation	Glucocorticoids increase ROS production, activating NF-κB and FOXO pathways, damaging cellular components and impairing mitochondrial function	↑ ROS	Mitochondrial damage	Checa & JM, 2020; Zhang et al., 2023

S.N.	Pathway (Mechanism)	Mechanism of Action	Molecular Changes	Physiological Outcome	References
4.	Mitochondrial dysfunction	Reduced PGC-1α expression decreases mitochondrial biogenesis and oxidative metabolism, leading to impaired ATP production	↓ PGC-1α	Impaired ATP production	Fernandez-Marcos & Auwerx, 2011; Rahnert et al., 2016
5.	NF-κB-mediated inflammatory signalling	Activation of NF-κB increases inflammatory cytokines and proteolytic enzymes, while inhibiting muscle regeneration	↑ NF-κB, ↑ TNF-α	Catabolic muscle environment	Li et al., 2008; Webster et al., 2020
6.	Myostatin signalling	Elevated myostatin inhibits Akt signalling and activates SMAD transcription factors, suppressing muscle growth and promoting degradation	↑ Myostatin	Inhibition of muscle growth	Sartori et al., 2021; Abati et al., 2022

Current Therapeutic Strategies and Limitations

Pharmacological and non-pharmacological strategies have been explored for managing sarcopenia. Pharmacological interventions include anabolic steroids, testosterone therapy, selective androgen receptor modulators (SARMs), and growth hormone therapy. While these treatments enhance muscle protein synthesis (McCullough et al., 2020), their prolonged use causes adverse effects like cardiovascular complications (McCullough et al., 2020), endocrine disturbances (Wen-bo & Zhang, 2023), and hepatotoxicity (Ayubi et al., 2022), limiting their clinical application. Nutritional interventions, including high-protein diets, amino acid supplementation, creatine, and vitamin D, show modest benefits in muscle metabolism (Rondanelli et al., 2016; Xie et al., 2025), but prove insufficient against glucocorticoid-induced catabolic signalling (Ferreira & Duarte, 2023; Revel et al., 2017). Exercise interventions, particularly resistance training, remain the most effective non-pharmacological approach for preserving muscle mass (Giallauria et al., 2016, p. 1), though their efficacy reduces in patients on chronic glucocorticoid therapy (Kupr et al., 2017; Macedo et al., 2023). As current therapies target single pathological pathways, there is growing interest in multi-target interventions that modulate oxidative stress, inflammation, mitochondrial dysfunction, and proteolytic signalling.

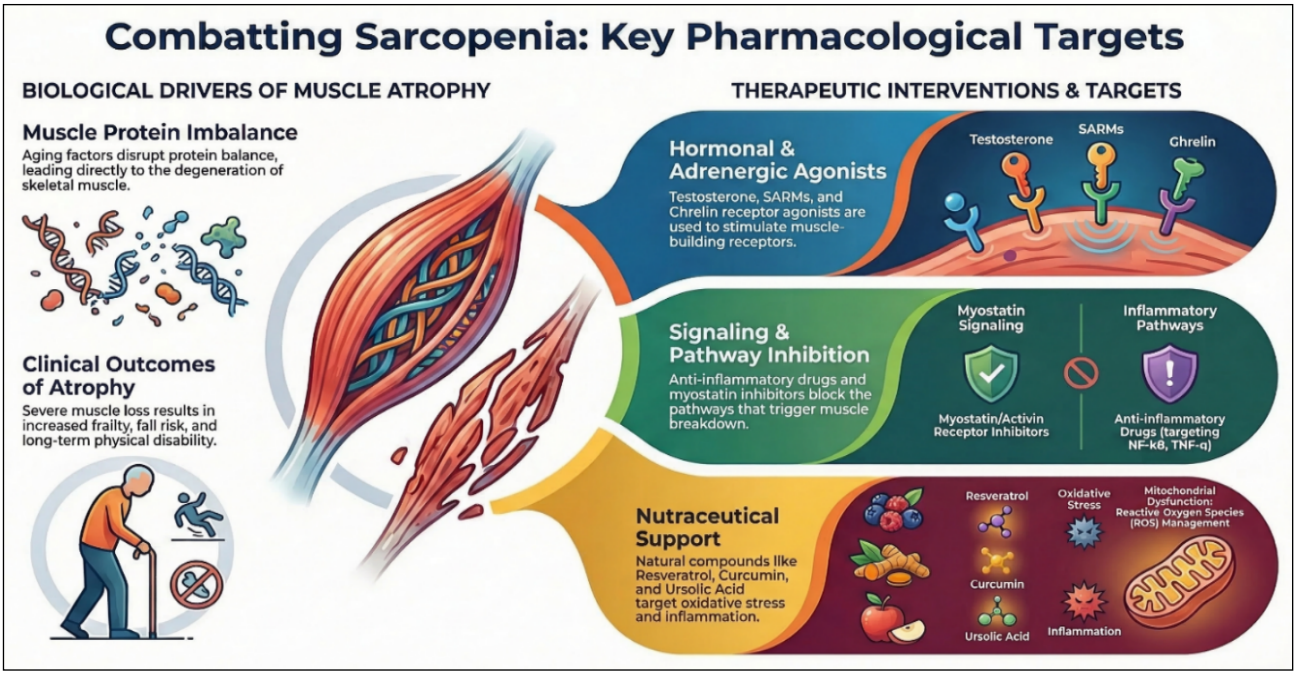

Figure 6: *Overview of biological drivers of sarcopenia and multi-target therapeutic strategies, including hormonal modulation, pathway inhibition, and nutraceutical interventions.*

Pharmacological Properties of Ursolic Acid

Ursolic acid is a pentacyclic triterpenoid found in various medicinal plants and dietary sources, particularly concentrated in apple peels, rosemary (Rosmarinus officinalis), basil (Ocimum basilicum), thyme (Thymus vulgaris), and medicinal herbs. Its structural characteristics and lipophilic nature enable interaction with cellular membranes and intracellular signalling molecules, influencing multiple biological pathways. Interest in ursolic acid has increased due to its diverse pharmacological activities, including antioxidant, anti-inflammatory, anti-tumor, hepatoprotective, anti-diabetic, and cardioprotective properties (Al-kuraishy et al., 2022; Bakry et al., 2025).

These effects suggest ursolic acid modulates complex disease processes through multiple molecular targets. In skeletal muscle physiology, ursolic acid regulates signalling pathways involved in muscle growth, protein turnover, and metabolic homeostasis (Kunkel et al., 2012; Makanae et al., 2019; Ogasawara et al., 2013). Studies show that ursolic acid promotes anabolic signalling, inhibits proteolytic mechanisms, and enhances mitochondrial function (Kunkel et al., 2012; Makanae et al., 2019; Yadav & Dabur, 2023), contributing to skeletal muscle mass preservation in various experimental models (Kang et al., 2019; Kunkel et al., 2012)

Table 2: *Key Molecular Mechanisms of Ursolic Acid in Skeletal Muscle Protection*

S.N.	Mechanistic Pathway	Mechanism of Action	Molecular Changes	Physiological Outcome	References
1	Activation of anabolic signalling (IGF-1/Akt/mTOR)	Ursolic acid activates Akt phosphorylation, which stimulates mTOR signalling and downstream translational machinery, enhancing protein synthesis	↑ IGF-1, ↑ Akt, ↑ mTOR	Increased muscle mass, strength, and hypertrophy	Kunkel et al., 2012
2	Inhibition of proteolytic pathways (FOXO-mediated)	Prevents FOXO nuclear translocation and suppresses expression of ubiquitin ligases, reducing proteasomal degradation	↓ FOXO, ↓ MuRF-1, ↓ Atrogin-1	Reduced muscle protein breakdown and preservation of muscle integrity	Kang et al., 2019; Webb & Brunet, 2014; Liu et al., 2024
3	Antioxidant and cytoprotective effects	Decreases ROS production and enhances endogenous antioxidant enzyme activity, protecting mitochondrial and cellular integrity	↓ ROS, ↑ SOD, ↑ Catalase	Reduced oxidative damage, improved muscle metabolism and endurance	Zhang et al., 2023; Pordanjani et al., 2022
4	Anti-inflammatory activity	Inhibits NF-κB signalling, reducing pro-inflammatory cytokine production and inflammatory damage	↓ NF-κB, ↓ TNF-α, ↓ IL-6	Reduced muscle inflammation and enhanced regeneration	Al-kuraishy et al., 2022; Antuna et al., 2022
5	Mitochondrial biogenesis	Activates PGC-1α, promoting mitochondrial DNA replication and expression of mitochondrial genes	↑ PGC-1α	Improved ATP production, oxidative metabolism, and muscle endurance	Koo et al., 2017; Zhu et al., 2023

S.N.	Mechanistic Pathway	Mechanism of Action	Molecular Changes	Physiological Outcome	References
6	Modulation of myostatin signalling	Reduces myostatin expression and relieves inhibition of Akt signalling, promoting anabolic pathways	↓ Myostatin, ↓ SMAD	Enhanced muscle growth and hypertrophy	Grade et al., 2019; Kunkel et al., 2012

Preclinical Evidence Supporting the Anti-Sarcopenic Effects of Ursolic Acid

Evidence suggests ursolic acid protects against muscle atrophy via multiple pathways. Preclinical studies with cell cultures, rodents, and metabolic disease models show its influence on muscle metabolism.

Kunkel et al. (2012) found dietary ursolic acid increased muscle mass in mice by enhancing Akt phosphorylation and mTOR signalling, boosting protein synthesis and muscle hypertrophy. It reduced atrogin-1 and MuRF-1 expression, indicating inhibition of the ubiquitin–proteasome pathway.

Table 3: *Experimental Studies investigating Ursolic Acid in Skeletal Muscle Atrophy*

S.N.	Study	Model	Dose	Key findings
1.	Kunkel et al., 2011	Murine model	200 mg/kg	Increased skeletal muscle mass
2.	Kunkel et al., 2012	Mouse model	0.14%	Activation of Akt/mTOR signalling
3.	Ogasawara et al., 2013	C2C12 myotubes	5 μM	Enhanced protein synthesis
4.	Bang et al., 2014	Rodent model	100 mg/kg	Reduced muscle atrophy markers
5.	Ma et al., 2014	Mouse model	50 mg/kg	Reduced oxidative stress
6.	Jeong et al., 2015	Mouse model	Varying	Increased skeletal muscle mass
7.	Chen et al., 2017	C2C12 myotubes	100 mg/kg	Improved mitochondrial metabolism
8.	Katashima et al., 2017	Animal model	150 mg/kg	Improved mitochondrial function
9.	Ebert et al., 2024	Animal model	2 mg/kg	Improved skeletal muscle expression
10.	Suo et al., 2025	T2DM mice model	40 mg/kg	Reducing neuroinflammation

Experimental investigations have validated these findings and clarified ursolic acid's muscle preservation mechanisms. Studies using C2C12 myotubes revealed that ursolic acid activates the PI3K/Akt/mTOR signalling pathway, increasing protein synthesis and myotube diameter. These effects suppressed FOXO transcription factors and decreased muscle-specific ubiquitin ligases expression, showing both anabolic and anti-catabolic actions. Animal studies demonstrated ursolic acid's benefits on skeletal muscle metabolism. In mice with high-fat diet-induced obesity, ursolic acid supplementation improved muscle insulin sensitivity, enhanced mitochondrial oxidative capacity, and increased muscle mass, linked to AMPK activation and elevated PGC-1α expression.

Beyond its anabolic properties, ursolic acid shields skeletal muscle from oxidative stress damage, a significant factor in muscle degeneration associated with sarcopenia and glucocorticoid-induced atrophy. Ursolic acid reduces reactive oxygen species (ROS) buildup and increases endogenous antioxidant enzyme activity, including superoxide dismutase (SOD), catalase, and glutathione peroxidase, helping maintain mitochondrial integrity. Additionally, ursolic acid's anti-inflammatory effects protect skeletal muscle by inhibiting NF-κB activation and reducing inflammatory cytokines like TNF-α and IL-6.

By curbing inflammatory signalling, ursolic acid preserves muscle homeostasis and prevents expression of catabolic genes linked to muscle degradation.

Recent research has investigated how ursolic acid influences myostatin signalling, which inhibits skeletal muscle growth. Myostatin prevents muscle enlargement by blocking Akt signalling and triggering SMAD transcription factors that promote muscle breakdown.

Studies show that ursolic acid reduces myostatin levels and promotes muscle growth. Additionally, ursolic acid affects mitochondrial function. Mitochondrial dysfunction contributes to sarcopenia in aging and chronic diseases (Marzetti et al., 2013). Ursolic acid enhances mitochondrial biogenesis by activating PGC-1α and nuclear respiratory factors (NRF-1 and NRF-2), increasing oxidative metabolism and muscle endurance (Schlagowski, 2014).

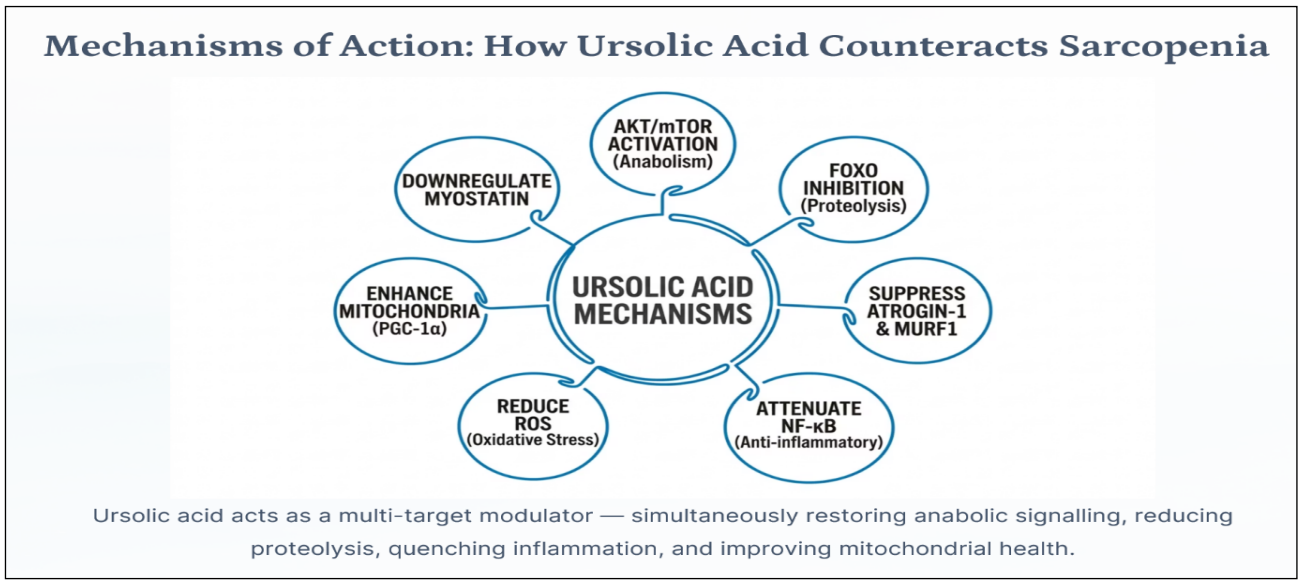

Figure 7: *Multi-target mechanisms of ursolic acid, including activation of anabolic pathways, inhibition of proteolysis, and reduction of oxidative stress and inflammation.*

These findings indicate that ursolic acid safeguards skeletal muscle by activating anabolic pathways (Kunkel et al., 2012), suppressing proteolysis (Kang et al., 2019), reducing oxidative stress (Yadav & Dabur, 2023), inhibiting inflammation (Yadav & Dabur, 2023), and improving mitochondrial function (Chen et al., 2017). This supports ursolic acid as a promising therapeutic candidate for sarcopenia. However, despite promising preclinical results, clinical translation remains limited. Most studies have been conducted in animal models or in vitro systems (Kwak & Kwon, 2019), with scarce human trials, necessitating research on optimal dosing, safety, and long-term benefits (Pitaloka et al., 2024).

Pathway	Glucocorticoid Effect	Ursolic Acid Effect
IGF-1/Akt/mTOR	Inhibits ↓	Activates ↑
FOXO Transcription Factors	Activates ↑	Inhibits ↓
Atrogin-1 / MuRF1	Upregulates ↑	Suppresses ↓
NF-κB Inflammation	Stimulates ↑	Attenuates ↓
Reactive Oxygen Species	Promotes ↑	Reduces ↓
Mitochondrial Biogenesis (PGC-1α)	Impairs ↓	Enhances ↑
Myostatin	Induces ↑	Downregulates ↓

Figure 8: *Head-to-head comparison of glucocorticoid-induced catabolic pathways and the counteracting protective effects of ursolic acid in skeletal muscle.*

Comparative Evaluation of Ursolic Acid and Other Phytochemicals

The therapeutic potential of plant-derived compounds in sarcopenia has been explored recently (Bagherniya et al., 2022). Several phytochemicals protect skeletal muscle from degeneration (Nikawa et al., 2021), including resveratrol, curcumin, epicatechin, and quercetin. Resveratrol, found in grapes, activates AMPK and stimulates mitochondrial biogenesis (Tao et al., 2023), improving muscle function (Baltaci et al., 2016). However, its anabolic effects are modest compared to ursolic acid (Novelle et al., 2015). Curcumin has anti-inflammatory properties and may reduce muscle wasting by inhibiting NF-κB signalling (Jin & Li, 2006), but its influence on muscle hypertrophy is limited (Alamdari et al., 2008). Epicatechin inhibits myostatin signalling and promotes muscle growth (Gutierrez-Salmean et al., 2013), though evidence remains limited (Shahidi et al., 2019). Ursolic acid activates anabolic pathways (Kunkel et al., 2012), inhibits proteolysis (Kang et al., 2019), reduces oxidative stress, suppresses inflammation (Yadav & Dabur, 2023), and enhances mitochondrial metabolism (Chen et al., 2017), making it promising as a therapeutic candidate (Al-kuraishy et al., 2022).

Table 4: *Comparison of Ursolic Acid with Other Phytochemicals in Sarcopenia Research*

S.N.	Compound	Source	Mechanisms	Evidence level
1.	Ursolic acid	Apple peel, rosemary, tulsi, plumeria	Akt/mTOR activation, FOXO inhibition	Strong preclinical
2.	Resveratrol	Grapes	AMPK activation, mitochondrial biogenesis	Moderate
3.	Curcumin	Turmeric	Anti-inflammatory, antioxidant	Moderate
4.	Epicatechin	Cocoa	Myostatin inhibition	Emerging
5.	Quercetin	Fruits and vegetables	Antioxidant, mitochondrial protection	Limited

Translational Challenges and Future Perspectives

Despite strong experimental evidence supporting ursolic acid's ability to combat sarcopenia, its clinical application remains limited. Transitioning a promising bioactive compound from laboratory research to clinical use involves evaluating pharmacokinetics, safety, formulations, and clinical trials. Before therapeutic utilization, several pharmacological challenges need to be overcome. A major obstacle is its low water solubility, which hinders gastrointestinal absorption when taken orally. Ursolic acid is highly lipophilic and dissolves poorly in aqueous environments (Pironi et al., 2017), leading to low oral bioavailability (Eloy et al., 2012). Additionally, ursolic acid undergoes first-pass metabolism in the liver and intestines. Metabolic enzymes transform it into metabolites (Hu et al., 2018) with diminished biological activity, reducing therapeutic effectiveness (Kadsanit et al., 2024). Ursolic acid's short plasma half-life requires frequent dosing to maintain therapeutic levels (Miatmoko et al., 2021). High doses could raise safety concerns (Al-kuraishy et al., 2022), necessitating optimized delivery methods.

Table 5: *Pharmacokinetic Challenges of Ursolic Acid*

S.N.	Challenge	Mechanism	Impact on therapy
1.	Poor aqueous solubility	Lipophilic structure	Limited gastrointestinal absorption
2.	Low oral bioavailability	Poor dissolution and absorption	Reduced systemic exposure
3.	First-pass metabolism	Hepatic metabolism	Reduced active compound levels
4.	Rapid clearance	Short plasma half-life	Need for higher or repeated doses
5.	Limited tissue targeting	Non-specific distribution	Reduced skeletal muscle concentration

To address these limitations, researchers have investigated advanced drug delivery systems to enhance ursolic acid's bioavailability and stability. Nanoparticle-based formulations represent a promising strategy, improving drug solubility and enabling targeted delivery to specific tissues (Miatmoko et al., 2021; Wang et al., 2021). Studies show that nanoparticle formulations significantly boost ursolic acid's bioavailability and therapeutic efficacy (Wang et al., 2021). Liposomal delivery systems encapsulate ursolic acid within lipid bilayers, enhancing

drug solubility and cellular uptake while ensuring sustained release. Phospholipid complexes improve solubility and absorption in the gastrointestinal tract (Ittadwar & Puranik, 2016). Polymeric nanoparticles and micellar systems enhance ursolic acid pharmacokinetics by increasing stability and tissue targeting (Wang et al., 2021). These technologies may enable therapeutic formulations for clinical use. Clinical validation remains crucial, as most studies on anti-sarcopenic effects have been conducted in cell cultures or animal models (Liu et al., 2024; Moro et al., 2016, p. 805), which cannot fully predict human outcomes.

Table 6: *Advanced Drug Delivery Strategies for Ursolic Acid*

S.N.	Formulation	Description	Advantages
1.	Nanoparticles	Drug encapsulated in nano-carriers	Improved solubility and bioavailability
2.	Liposomes	Phospholipid bilayer vesicles	Enhanced cellular uptake
3.	Phytosomes	Complex with phospholipids	Improved gastrointestinal absorption
4.	Polymeric nanoparticles	Biodegradable polymer carriers	Sustained drug release
5.	Micellar systems	Surfactant-based carriers	Increased solubility

Future clinical research should prioritize randomized controlled trials to assess ursolic acid supplementation's effects on muscle mass and function in individuals at risk of sarcopenia. Using dual-energy X-ray absorptiometry (DXA), magnetic resonance imaging (MRI), and muscle biopsies could provide insights into ursolic acid's impact on muscle physiology. Research should explore ursolic acid in combination therapy. Given sarcopenia's multifactorial nature (Walston, 2012), combining ursolic acid with exercise or nutritional supplements might offer synergistic benefits. Safety evaluation remains crucial. While ursolic acid is generally safe in common dietary sources (Seo et al., 2018; Shaikh et al., 2021), high doses may cause adverse effects (Al-kuraishy et al., 2022). Long-term safety assessments are necessary before large-scale trials. Ursolic acid's ability to modulate multiple molecular pathways (Al-kuraishy et al., 2022) makes it promising for sarcopenia treatment.

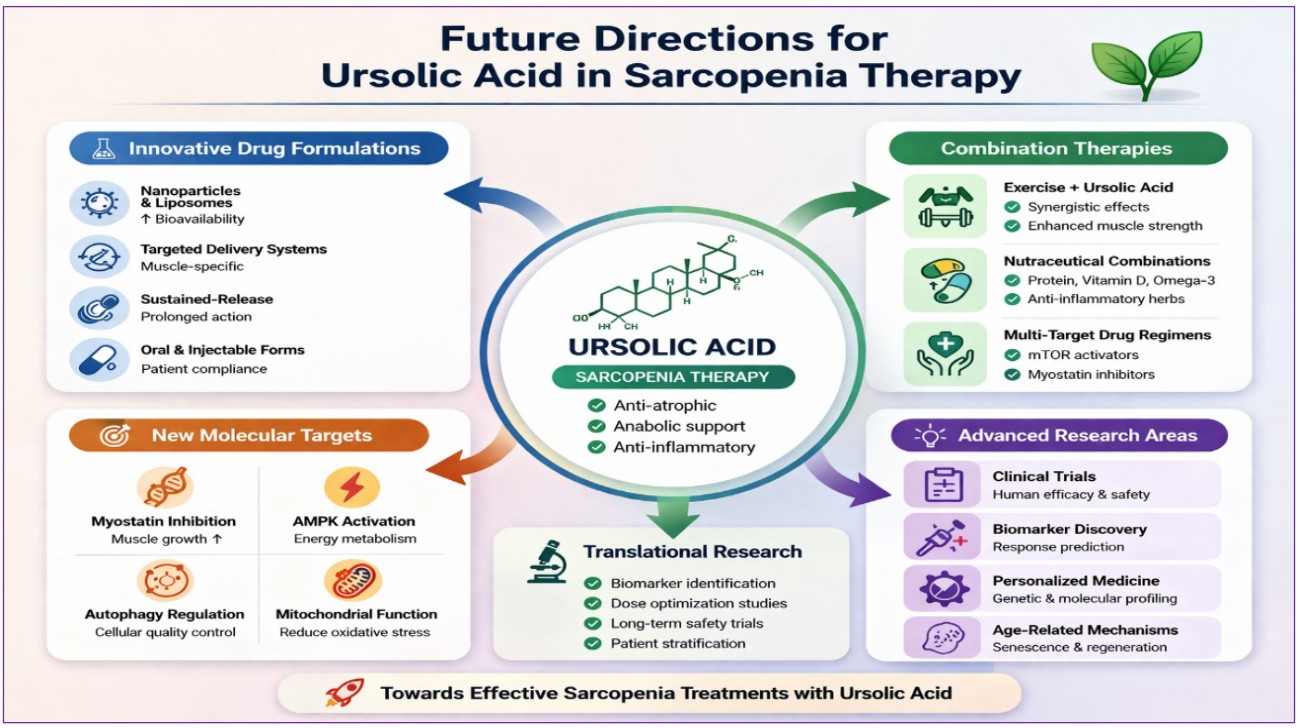

Figure 9: *Multi-target mechanisms of ursolic acid, including activation of anabolic pathways, inhibition of proteolysis, and reduction of oxidative stress and inflammation.*

Discussion

The current review underscores the complex nature of glucocorticoid-induced sarcopenia and stresses the importance of therapeutic strategies that target multiple pathways. Chronic exposure to glucocorticoids disrupts skeletal muscle homeostasis by suppressing anabolic signalling, activating proteolytic systems (Schakman et al., 2013), inducing oxidative stress, and impairing mitochondrial metabolism (Gupta & Mohan, 2013). These processes accelerate muscle protein degradation (Schakman et al., 2013) and hinder muscle regeneration.

Traditional pharmacological treatments for sarcopenia show limited effectiveness (Kwak & Kwon, 2019) by targeting single molecular pathways (Yoon & Kwon, 2021). Phytochemicals with pleiotropic effects hold promise due to their influence on multiple signalling networks. Ursolic acid has attracted scientific interest as it activates IGF-1/Akt/mTOR signalling (Kunkel et al., 2012; Yadav & Dabur, 2023), suppresses FOXO-mediated transcription (Makanae et al., 2019; Yadav & Dabur, 2023), and enhances mitochondrial biogenesis (Yadav & Dabur, 2023), improving muscle metabolism in experimental models (Tueller et al., 2017). However, poor solubility and bioavailability (Eloy et al., 2012; Makeen & Al-Bratty, 2023) limit its therapeutic potential, though nano-delivery systems may help overcome these challenges.

Future research should focus on evaluating ursolic acid supplementation through clinical trials in individuals at risk of sarcopenia, particularly those undergoing glucocorticoid therapy. Combining ursolic acid with exercise and nutritional interventions may offer synergistic benefits.

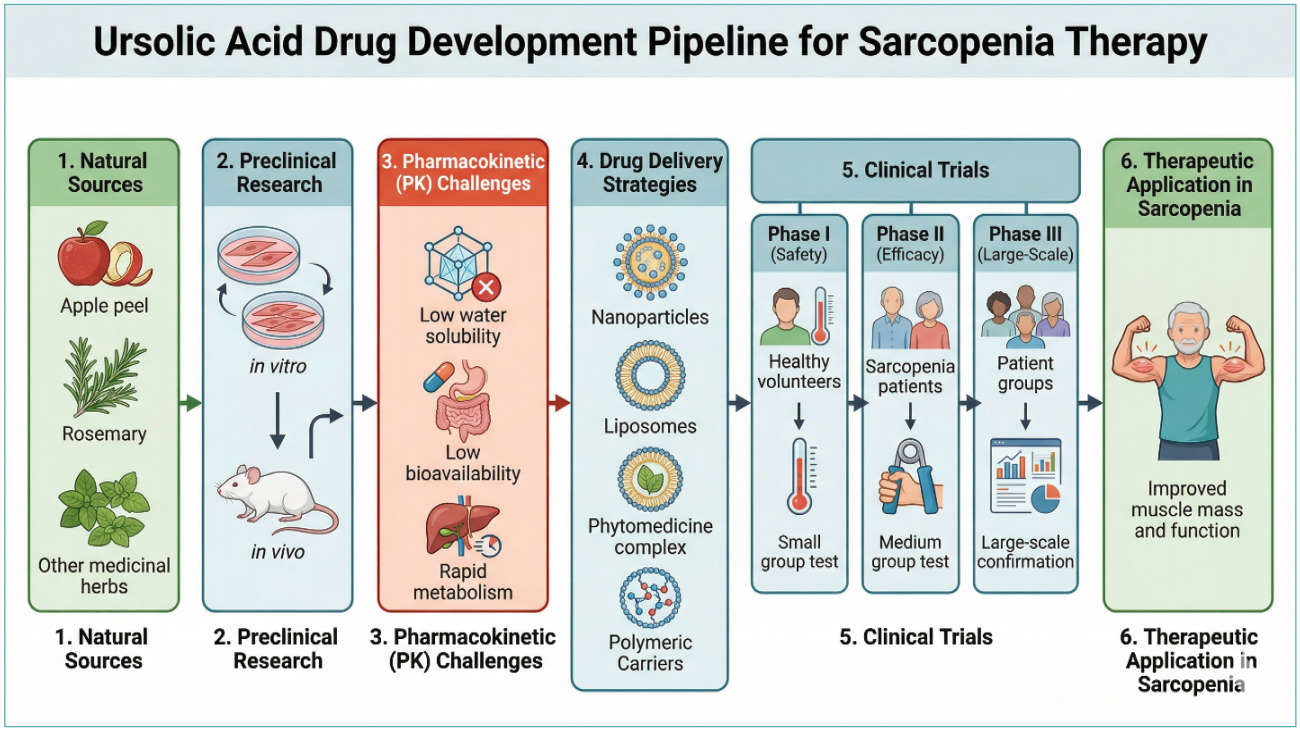

Figure 10: *Drug development pathway of ursolic acid from natural sources to clinical application in sarcopenia, highlighting pharmacokinetic challenges and advanced delivery strategies.*

Table 7: *Research Gaps and Future Directions in Ursolic Acid Research*

S.N.	Research area	Current limitations	Future directions
1.	Clinical evidence	Limited human studies	Conduct randomized clinical trials
2.	Pharmacokinetics	Poor bioavailability	Develop nano formulations
3.	Dose optimization	Limited pharmacodynamic data	Establish therapeutic dosing ranges
4.	Safety evaluation	Limited long-term studies	Conduct chronic toxicity studies
5.	Combination therapy	Limited investigation	Evaluate synergy with exercise and nutrition

Conclusion

Sarcopenia represents a significant health challenge associated with aging and chronic disease. Glucocorticoid-induced sarcopenia is particularly concerning due to the widespread use of corticosteroids and their catabolic effects on muscle tissue. This condition involves the disruption of molecular pathways, including the suppression of anabolic signalling, activation of proteolytic systems, oxidative stress, mitochondrial dysfunction, and inflammatory signalling. Ursolic acid emerges as a promising bioactive compound capable of modulating these mechanisms. Research indicates that it activates anabolic signalling, suppresses proteolytic gene expression, reduces oxidative stress, inhibits inflammatory pathways, and enhances mitochondrial function. Although the majority of evidence is derived from preclinical studies, advancements in drug delivery and clinical research may facilitate the development of ursolic acid-based therapies for sarcopenia. Future investigations in molecular pharmacology, pharmaceutical formulation, and clinical trials are essential for translating the potential of ursolic acid into effective interventions.

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