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Ferroptosis and Sarcopenia-Osteoporosis after Menopause: Research Status, Traditional Chinese Medicine Strategies, and Prospects

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Abstract: ***Ferroptosis, a precisely regulated cell death mechanism, is distinguished by its intimate link to iron overload and lipid peroxidation processes, playing a pivotal role in the pathological progression of a wide range of diseases. In postmenopausal women suffering from osteoporosis, reduced muscle strength and impaired balance lead to a heightened risk of fragility fractures, markedly diminishing their quality of life. Recent groundbreaking research has underscored the crucial role of the ferroptosis mechanism in the initiation and progression of musculoskeletal diseases. This discovery not only enriches our understanding of disease mechanisms but also heralds ferroptosis pathways as novel and promising therapeutic targets for treating these conditions. Traditional Chinese Medicine (TCM) has exhibited remarkable efficacy in managing musculoskeletal diseases, with studies validating its ability to modulate ferroptosis mechanisms and profoundly impact disease regulation. This portends vast research potential and significant therapeutic promise for the future. By delving deeper into the interplay between ferroptosis and sarcopenia-osteoporosis in postmenopausal women, and by developing innovative therapeutic strategies and TCM interventions, we aspire to forge new pathways for the treatment of sarcopenia-osteoporosis in this patient population.***

Keywords: Ferroptosis, Traditional Chinese Medicine (TCM), Sarcopenia-Osteoporosis, Postmenopausal Women**.**

1. Introduction

Classical modes of cell death can be categorized into Accidental Cell Death (ACD) and Regulated Cell Death (RCD). ACD is primarily induced by accidental physical or chemical insults that exceed the scope of intracellular molecular control mechanisms. In contrast, RCD involves multiple genetically defined effector molecules and precise molecular regulatory cascades, significantly impacting development, tissue homeostasis, and the onset of various diseases, with apoptosis being its primary form [1]. In recent years, with the deepening of research, increasingly abundant evidence has shown that non-apoptotic forms of RCD, including necrosis, autophagy, pyroptosis, and ferroptosis, play vital roles in numerous diseases. Ferroptosis, a non-apoptotic mode of cell death, is characterized by the accumulation of iron-dependent reactive oxygen species (ROS) within cells, leading to lipid peroxidation (LPO) and ultimately cell death. This unique form of cell death is intimately associated with numerous pathophysiological processes, especially in musculoskeletal diseases (MSKs) such as rheumatoid arthritis, osteoarthritis, spinal cord injury, osteoporosis (OP), and sarcopenia (SP). Postmenopausal Osteoporosis (PMO), a common skeletal disease related to aging, frequently coexists with sarcopenia in postmenopausal women, manifested as reduced skeletal muscle mass and impaired muscle strength and function. Both muscle and bone originate from mesenchymal stem cells (MSCs), thus sharing developmental homology at the tissue level. Functionally, the decline of these two tissues is closely interconnected, jointly contributing to increased fall risk, fracture susceptibility, and gradual loss of overall physical function [2]. Current research has revealed that postmenopausal sarcopenia-osteoporosis in women is closely related to iron overload and lipid peroxidation, further highlighting the potential role of ferroptosis in the development of these diseases. At present, clinically targeted therapeutic drugs are still lacking, whereas traditional Chinese medicine (TCM) boasts advantages such as high safety, multi-target, and multi-pathway effects. In light of this, the authors comprehensively discuss the role of ferroptosis mechanisms in postmenopausal sarcopenia-osteoporosis in women and the current status of TCM interventions, aiming to open up new avenues for the prevention, treatment, and new drug development of this disease. We hope that this study can provide valuable reference for subsequent research and practice.

2. Overview of Ferroptosis

In 2002, Dolma et al. [3] delved into the study of epithelial cell lines expressing oncogenic Ras (RasV12) and successfully discovered a novel compound named erastin. This compound induced a unique form of cell death that markedly differed from canonical apoptosis processes, such as nuclear fragmentation, DNA laddering, and the activation of cystein-asparate protease (Caspase). Dixon et al. [4] found that similar to glutamate, erastin inhibited the cystine / glutamate antiporter (system xc-) to block cystine uptake, thereby creating a deficiency in cellular antioxidant defenses. This ultimately led to the accumulation of iron-dependent reactive oxygen species (ROS) within cells, causing cell death. Consequently, ferroptosis was formally recognized as a novel type of regulated cell death (RCD) in 2012.

3. Ferroptosis and Postmenopausal Osteoporosis

3.1 Iron Metabolism

Iron overload caused by abnormal iron metabolism is one of

the primary characteristics of ferroptosis. Extracellular Fe3+ binds to transferrin (Tf) and enters cells through the transferrin receptor 1 (TfR1). Inside the cell, the metalloprotease six-transmembrane epithelial antigen of prostate 3 (STEAP3) reduces Fe^{3+} to Fe^{2+}, which is then transported into the labile iron pool (LIP) in the cytoplasm by the recombinant divalent metal transporter 1 (DMT1). Excess iron in the LIP is stored in ferritin complexes (ferritin heavy chain 1: H or ferritin light chain: L). The degradation of ferritin is mediated by nuclear receptor coactivator 4 (NCOA4), which binds to ferritin and promotes its autophagic degradation during ferritinophagy. Under conditions of intracellular iron deficiency, NCOA4-mediated ferritinophagy supplies iron to mitochondria via intracellular iron release to maintain their function [5]. Studies have shown that excessive autophagy during NCOA4-mediated ferritinophagy can lead to the degradation of ferritin and the release of large amounts of free iron, thereby accelerating the process of ferroptosis [6]. Ferritinophagy is related to interactions between autophagosomes, autolysosomes, and lysosomes, which are regulated by autophagy-related (ATG) proteins. Lysosomes are considered the primary cellular organelles involved in ferroptosis. When lysosomes are damaged, they release more free iron ions, exacerbating cellular oxidative stress and promoting ferroptosis [7]. Intracellular Fe2+ is expelled from the cell through ferroportin 1 (FPN1), and the interaction between hepcidin and FPN1 is a crucial mechanism for regulating extracellular iron homeostasis. Ferritin acts as a buffer to regulate intracellular iron balance. In pathological states, excessive Fe2+ in the cytoplasm generates reactive oxygen species (ROS) through the Fenton reaction [8], which are toxic to cells, damaging cell membranes, proteins, and nucleic acid structures, ultimately leading to tissue damage and apoptosis.

3.2 Iron Accumulation after Menopause

Clinically, serum ferritin (SF) is commonly used as an indicator of iron homeostasis in the body. Ferritin, a soluble protein present in all cells of the body, can bind approximately 4500 Fe3+ ions per molecule. At the age of 18, SF levels are significantly higher in males than in females. With age, SF levels tend to stabilize in males while they increase after menopause in females, and the proportion of females with elevated SF levels across all age groups increases significantly with age [9]. Both clinical and animal studies have observed a coexistence of iron accumulation and osteoporosis following a significant decrease in estrogen levels. In other words, the decrease in estrogen levels in postmenopausal women seems to be correlated with abnormal iron accumulation and decreased bone mineral density. A cross-sectional study involving 76 postmenopausal women with hip fragility fractures revealed an important finding: these patients exhibited iron overload after menopause, which was directly associated with increased bone turnover activity, ultimately leading to a significant reduction in bone mass [10]. Liu found that female rats subjected to ovariectomy (OVX) and administered ammonium ferric citrate (FAC) as an iron donor showed significant iron accumulation, manifested by increased serum iron levels and tibial iron content. Additionally, BMD significantly decreased in OVX rats, and the BMD decline was further exacerbated in the FAC group compared to OVX rats without FAC administration. These findings suggest that iron accumulation is an independent risk factor for osteoporosis in postmenopausal women [11].

3.3 Ferroptosis and Osteoporosis

Bone cells are primarily composed of osteocytes, osteoblasts (OBs), and osteoclasts (OCs). Osteocytes are the most abundant cell population in bone, accounting for 90-95% of all bone cells [12]. OBs originate from bone marrow-derived mesenchymal stem cells (BMSCs), which produce bone matrix and play a dominant role in bone formation. Osteocytes are considered fully differentiated OBs [13]. OCs, derived from the monocyte/macrophage lineage of hematopoietic cells, are rich in mitochondria and lysosomes, leading to bone resorption. The homeostasis between OCs and OBs promotes a balance between bone resorption and bone formation, facilitating bone remodeling and maintaining bone as a dynamic tissue to perform its normal functions [14]. Ferroptosis disrupts the balance of bone metabolism by acting on different bone cell types, ultimately leading to bone loss.

3.3.1 Ferroptosis occurs in osteoblasts

Studies have found that in a mouse model with the C326S mutation knock-in of ferroportin (FPN), impaired FPN function hinders normal iron transport and metabolism, leading to iron overload. This process disrupts the Hepcidin/FPN regulatory axis, ultimately resulting in axial bone loss due to suppressed bone formation [15]. The destabilization of the Hepcidin/FPN axis leads to iron overload in osteoblasts (OBs), and this suppression of bone formation may be closely related to ferroptosis. Numerous studies indicate that ferroptosis is involved in bone loss caused by iron overload in OBs. Zhang H et al. [16] discovered that iron overload increases the accumulation of NADPH oxidase 4 (NOX4), leading to increased lipid peroxide (LPO) accumulation in OBs and triggering ferroptosis. The mechanism involves iron binding to an iron-responsive element (IRE)-like sequence within the NOX4 locus, which causes iron regulatory protein 1 (IRP1) to dissociate from the IRE-like sequence, thereby activating NOX4 transcription and causing significant mitochondrial dysfunction. A study [17] reported that iron overload induces reactive oxygen species (ROS) production in MC3T3-E1 cells, blocks the PI3K/AKT and JAK/STAT3 signaling pathways, and activates p38 MAPK, subsequently leading to G1 phase arrest and autophagy in MC3T3-E1 cells. The mechanism may be related to iron overload inhibiting AKT activity, upregulating p27 expression, and decreasing p-GSK-3β, which reduces the phosphorylation and degradation of Cyclin D1, a crucial protein for advancing the cell cycle from G1 to S phase, and inhibiting the activation of Stat3 transcription factor and its target genes. Xia et al. [18] cultured MC3T3-E1 cells with different concentrations of FAC and found that cell proliferation decreased gradually with increasing FAC concentrations. In iron-overloaded OBs, iron overload strongly suppressed the expression of dual-specificity phosphatase 14 (DUSP14), while the specific inhibitor of PI3K/Akt, LY294002, increased DUSP14 levels in OBs. Previous studies have shown that DUSP14 knockout increases ROS production and accelerates ferroptosis in cells [19]. This suggests that iron overload may affect OBs growth and apoptosis by inhibiting the PI3K/AKT/FOXO3a/DUSP14

signaling pathway and suppressing DUSP14 expression. This signaling pathway plays a crucial role in OBs defense against iron overload, and DUSP14 may be a novel component in this pathway. Luo [20] et al. reported that iron overload in OBs inhibits classical Wnt signaling by downregulating Wnt target gene expression and inhibiting transcription of the Wnt reporter gene TopFlash construct, thereby triggering ferroptosis and impairing OBs differentiation. Xu P [21] et al. showed that activation of the vitamin D receptor (VDR) activates a key signaling pathway, Nuclear factor erythroid 2-related factor 2 (Nrf2)/Glutathione peroxidase 4 (GPX4), which downregulates LPO levels and alleviates ferroptosis in OBs. Further research revealed that knocking out Nrf2 or adding GPX4 inhibitors (RSL-3) abolished the protective effect of active vitamin D (1,25-dihydroxyvitamin D3, 1,25(OH)2D3) against D-galactose (D-gal)-induced ferroptosis in mouse OBs. When VDR was knocked out in mice, not only did OBs exhibit ferroptosis, but the Nrf2/GPX4 protective pathway was also significantly inhibited. This implies that the normal functioning of the Nrf2/GPX4 pathway is crucial for vitamin D to protect OBs from ferroptosis.

3.3.2 Ferroptosis occurs in osteoclasts

Osteoporosis primarily stems from the excessive activity of osteoclasts (OCs), cells responsible for bone decomposition and resorption, leading to rapid bone loss. As bone mass decreases and intertrabecular spaces widen, bones become fragile and porous, triggering osteoporosis [22]. The RANKL (Receptor Activator of Nuclear Factor-κB Ligand)/RANK (Receptor Activator of Nuclear Factor-κB)/NF-κB (Nuclear Factor-kappa B) signaling pathway plays a crucial role in OCs differentiation. The interplay between RANK and RANKL not only promotes OCs differentiation and formation but also regulates their metabolism and apoptosis [23]. J. Yang [24] observed that under FAC culture conditions, MLO-Y4 osteoblast-like cells exhibited iron overload accompanied by cytotoxicity, significantly upregulating RANKL gene expression and protein secretion. Exposure of OCs to conditioned media from iron-overloaded MLO-Y4 osteoblasts significantly enhanced their formation, differentiation-related gene expression, and bone resorption capabilities. This finding suggests that iron overload promotes osteoclast differentiation by inducing increased RANKL production in osteoblasts, thereby accelerating bone loss.

Xue C [25] discovered that aconitine (AC), as a modulator, inhibits the NF-κB signaling pathway by suppressing the degradation of IKB (Inhibitor of Nuclear Factor-κB) and the phosphorylation of its downstream p65 subunit. This inhibition regulates the expression of GPX4 and Acsl4, thereby preventing ferroptosis in OCs. In conditions of iron overload, ROS accumulation activates Nrf2 and its downstream antioxidant and iron metabolism genes, leading to the upregulation of FPN1 (Ferroportin 1) and Ft, which decrease intracellular iron levels. This enhancement of antioxidant capacity and promotion of OCs differentiation suggest that targeting Nrf2-induced ferroptosis in OCs may inhibit osteoclastogenesis, mitigating bone loss caused by iron overload [26]. Wang [27] found that FPN gene deficiency in mature OCs and their precursors results in a mild increase in intracellular iron levels. In female mice, FPN deficiency specifically in osteoclast precursors, but not mature OCs, promoted OCs generation and bone loss. In vitro experiments revealed that elevated iron ion concentrations stimulate the proliferation of macrophages (OC precursors) and enhance the expression of two crucial transcription factors for osteoclast differentiation, PGC-1β and NFATc1.

3.3.3 Ferroptosis occurs in BMSCs

BMSCs possess multipotency, capable of differentiating into osteoblasts, adipocytes, myocytes, or chondrocytes depending on specific factors present in the microenvironment [28]. Ferroptosis affects BMSCs through multiple mechanisms, leading to bone loss. Balogh et al. [29] found that iron overload increased ferritin expression in BMSCs in a dose-dependent manner, decreased the expression of osteocalcin (OCN), runt-related transcription factor 2 (Runx2), and alkaline phosphatase (ALP), thereby inhibiting osteogenic differentiation of BMSCs. In 2018, a study reported [30] that iron overload suppressed the proliferation of MSCs in mouse bone marrow cells, leading to a reduction in the number of OBs and decreased expression of osteogenic-related genes such as Runx2 and OCN, attributed to the depletion of precursor OBs and upstream MSCs. Further research [31] revealed that Runx2 is a crucial transcription factor regulating BMSCs differentiation towards OBs. Runx2 stabilizes its own protein by activating the Fgf signaling pathway, activates its promoter and OB-specific enhancers through factors such as Tcf7, Ctnnb1, and Dlx5, and responds to parathyroid hormone (Pth) to increase its activity and mRNA expression, thereby enhancing its own expression and activity, promoting BMSCs proliferation, and expressing OCN and ALP to drive differentiation towards the osteoblast lineage. Li M discovered [32] that dexamethasone (DEX) activates the ferroptosis pathway, downregulating the expression of ferroptosis-related markers in BMSCs such as GPX4, system xc-, and ferroptosis suppressor protein 1 (FSP1), exacerbating lipid peroxidation (LPO) and disrupting normal iron metabolism functions. This ultimately leads to a massive accumulation of intracellular reactive oxygen species (ROS), triggering ferroptosis in cells. The study also elucidated that melatonin (MT) protects against glucocorticoid (GCs)-induced osteoporosis by inhibiting DEX-induced ferroptosis through activation of the PI3K/Akt/mTOR signaling pathway.

4. Ferroptosis and Postmenopausal Sarcopenia

4.1 Decline in Estrogen and Sarcopenia

Estrogens, including estradiol, estriol, and estrone, are vital hormones that directly and indirectly regulate bone and skeletal muscle metabolism and function through estrogen receptors (ERs). The sharp decline in estrogen levels during female menopause often leads to osteoporosis and sarcopenia [33]. Research has shown that estradiol (E2) not only directly binds to ERs in skeletal muscle but also indirectly participates in muscle metabolism by regulating the secretion of growth hormone (GH) and insulin-like growth factor 1 (IGF-1). Furthermore, estrogens play a pivotal role in regulating carbohydrate and lipid metabolism, which may impact skeletal muscle composition in postmenopausal women by promoting muscle glycogenolysis and inducing lipid

oxidation [34]. The potential regulatory effects of ERs and estrogen-related receptors (ERRs) on mitochondrial function and metabolism in muscle satellite cells (MuSCs) are crucial for muscle physiology. Collins et al. [35] demonstrated that estrogens are essential for maintaining the number of MuSCs in female mice and humans, and E2 deficiency-mediated MuSC loss impairs their self-renewal and differentiation.

4.2 Ferroptosis and Sarcopenia

Oxidative stress and mitochondrial dysfunction are salient indicators of skeletal muscle aging, where iron overload acts as a critical potential catalyst in this process, potentially accelerating skeletal muscle aging further [36]. In brief, excessive iron levels may exacerbate both pathological states, thereby accelerating skeletal muscle senescence. Iron overload facilitates the participation of excessive free Fe^{2+} in the Fenton reaction, generating substantial amounts of highly reactive ROS that pose a significant threat to the cellular internal environment. ROS accumulation not only leads to structural damage to RNA and DNA but also triggers protein conformational abnormalities and LPO, ultimately resulting in severe cellular damage and inducing apoptosis. Recently, numerous studies have observed these processes to be significant in skeletal muscle tissues and cells as well. Research has shown that abnormally elevated ROS levels in skeletal muscle can inhibit the MAPK signaling pathway, leading to impaired muscle regeneration in mouse models, manifested as delayed muscle regeneration, reduced regenerated muscle fiber size, and decreased expression of myoblast differentiation markers. Furthermore, a high ROS environment activates multiple gene expression programs associated with muscle atrophy and enhances the activity of the ubiquitin-proteasome system, a primary pathway for intracellular protein degradation, directly contributing to accelerated protein hydrolysis [37][38]. Huang et al. [39] observed significant iron overload in skeletal muscle cells of 40-week-old SAMP8 male mice, with a notable reduction in muscle mass compared to 8-week-old mice, accompanied by increased expression levels of the muscle atrophy markers Fbxo32 and Trim63. Further in vitro experiments revealed that the cell viability of C2C12 myoblasts negatively correlated with FAC concentration in the culture environment, akin to the iron death phenomenon induced by erastin, with FAC treatment significantly increasing LPO levels. To validate the role of iron overload in skeletal muscle ferroptosis, researchers employed the ferroptosis-specific inhibitors ferrostatin-1 (Ferr-1) and deferoxamine (DFO), both of which significantly reversed ferroptosis in mouse skeletal muscle cells and C2C12 myoblasts. Further analysis revealed that iron-accumulation-induced ferroptosis may reduce cell numbers by increasing LPO and inhibit myoblast differentiation into myotubes. The underlying mechanism could involve iron overload downregulating GPX4 expression and activating the p53 signaling pathway, which modulates the expression of SLC7A11, a component of the cystine/glutamate antiporter (system xc-), ultimately inducing ferroptosis under ROS-induced stress conditions. Skeletal muscle cells are rich in mitochondria, which not only provide energy for muscle contraction but also balance intracellular oxidative reactions and regulate catabolic pathways [40]. Mitochondrial dysfunction leads to an energy crisis, orchestrates ferroptosis, and influences cellular redox status. For instance, the ferroptosis agonist erastin directly targets mitochondrial anion channels to induce ferroptosis [41]. Previous studies have shown that oxygen radicals generated by iron accumulation can cause mitochondrial RNA peroxidation, inducing the opening of the mitochondrial permeability transition pore (mPTP), releasing cytochrome C into the cytoplasm, activating caspase-3, and ultimately leading to skeletal muscle cell apoptosis [42]. Mitochondrial dynamics regulatory processes, such as fission, fusion, and autophagy, are essential for maintaining mitochondrial quality control and are regulated by various molecules (e.g., DRP1, FIS1, MFN1/2, OPA1, PINK1, and FUNDC1), all of which participate in ferroptosis [43]. Singh et al. [44] proposed that mitophagy, ferritinophagy, and lysosomal destabilization may play pivotal roles in ferroptosis. Studies have found that Nrf2 is a crucial hub gene regulating ferroptosis and mitochondrial dynamics, exerting multiple regulatory effects on mitochondrial biogenesis, fission, fusion, and autophagy [45][46], providing new insights into this process.

5. The Treatment Strategy of Traditional Chinese Medicine in Preventing and Treating Sarcopenia-osteoporosis Through Intervening Ferroptosis Pathway

Traditional Chinese medicine (TCM) boasts unique advantages in treating sarcopenia-osteoporosis post-menopause, including abundant resources, high safety, multi-target effects, and multi-pathway mechanisms. With the advancement of modern molecular biology, current research focuses on exploring the progress in preventing and treating sarcopenia-osteoporosis at the molecular level through interventions such as TCM monomers/active ingredients and TCM compound prescriptions, specifically targeting the ferroptosis pathway.

5.1 TCM Monomers/active Ingredients

The traditional Chinese medicine Fructus Ligustri Lucidi (FLL) possesses the function of nourishing the liver and kidneys, and can be used to treat symptoms such as weakness in the loins and knees, dizziness with tinnitus, and premature graying of hair caused by yin deficiency of the liver and kidneys. Jiang et al. [47] discovered that multiple components in FLL and wine-steamed FLL (WFLL) can simultaneously target the common pathways of iron overload and postmenopausal osteoporosis (PMOP), demonstrating unique pharmacological effects. WFLL exhibits a dual regulatory effect in reducing iron overload and promoting bone metabolism. Further validation through rat model experiments showed that both FLL and WFLL significantly reversed the pathological state of PMOP, evidenced by enhanced bone formation markers (e.g., ALP, OPG, OGN), improved iron metabolism indicators (e.g., hepcidin, ferritin), and optimized bone microstructure (e.g., BMD, BV/TV, Tb. Th, Tb. N). Additionally, the study found that WFLL increased the expression of key genes (e.g., Hep, BMP-6) and proteins (e.g., p-Smad1/5, Smad4) related to the BMP-Smad pathway. Icariin (ICA), the primary active ingredient of Epimedium brevicornum, significantly reduced ROS levels in osteoblasts (OBs) induced by erastin, downregulated SLC7A11 and GPX4 expression, and upregulated Nrf2, NQO-1, HO-1,

Runx2, ALP, OPG, and OCN expression, indicating its inhibition of ferroptosis in OBs through antioxidant mechanisms. Further X-ray and Micro-CT analysis revealed that ICA increased trabecular bone number, promoted callus formation and bone remodeling in osteoporotic fracture models, upregulated GPX4, Nrf2, and Runx2 expression at fracture sites, and significantly reduced the expression of the apoptotic gene Bax, collectively promoting fracture healing [48].Li et al. [49] conducted an intervention study using the medicinal pair of Eucommia ulmoides and Dipsacus asper on ovariectomized osteoporosis (OVX-OP) model rats, showing that this pair significantly increased femoral bone mineral density in the model rats. In-depth analysis revealed abnormal upregulation of ferroptosis-related proteins NOX1 and p53, and downregulation of GPX4 and ferritin heavy chain 1 (FTH1) in the model rats. Intervention with the Eucommia - Dipsacus pair reversed these phenomena by inhibiting NOX1 and p53 protein expression and promoting GPX4 and FTH1 protein expression, potentially improving osteoporosis by regulating the balance of ferroptosis-related proteins. Resveratrol, a non-flavonoid polyphenol compound, exhibits significant anti-inflammatory and antioxidant capabilities. Studies have shown that it effectively promotes motor function recovery and exerts neuroprotective effects after spinal cord injury (SCI). Further research found that resveratrol inhibits the expression of ferroptosis-related proteins and ions, thereby reducing cellular damage. Additionally, it improves mitochondrial morphological changes. Notably, when using the Nrf2 inhibitor ML385, the inhibitory effect of resveratrol on ferroptosis-related genes was significantly reversed, revealing its mechanism of inhibiting ferroptosis through the Nrf2/GPX4 signaling pathway [50].Artificial tiger bone powder (JTG) demonstrates remarkable efficacy in treating osteoporosis by downregulating the activity of key molecules such as arachidonate 15-lipoxygenase (ALOX15), long-chain acyl-CoA synthetase 1 (LACS1), transferrin (Tf), and CREB-binding protein, effectively suppressing lipid peroxidation (LPO) and iron accumulation, and negatively regulating ferroptosis. This mechanism is crucial for reversing bone loss and trabecular microstructural damage in osteoporotic rats [51].

In summary, the Chinese medicine monomers/active ingredients such as Ligustrum lucidum, icariin, Eucommia ulmoides-Dipsacus asperoides drug pair, resveratrol, and artificial tiger bone powder can all play a role in the treatment of musculoskeletal diseases by inhibiting ferroptosis, demonstrating the enormous potential of various effective components of traditional Chinese medicine in the prevention and treatment of sarcopenia-osteoporosis after female menopause.

5.2 Traditional Chinese Medicine Compound Prescription

The spleen is the foundation of postnatal life, while the kidney is the foundation of prenatal life. Under physiological conditions, the spleen and kidney complement each other, leading to plump muscles and strong bones. However, under pathological conditions, when they restrict each other, it may lead to "muscle flaccidity" and "bone withering," which is the pathological state of sarcopenia-osteoporosis [52]. Traditional Chinese Medicine (TCM) approaches to treating sarcopenia - osteoporosis should primarily focus on invigorating the spleen and nourishing the kidney [53][54]. Studies have found that Zuogui Pill can reduce oxidative damage in osteoblasts by activating the Nrf2/HO-1 signaling pathway [55]. Erxiantang can increase the phosphorylation of Akt in TNF-α-induced osteoblasts, activate the expression of Nrf2 and HO-1, and protect osteoblasts from TNF-α-induced apoptosis [56]. Zhang Yili et al. [57] found that Bugushengsui Formula significantly improves bone mineral density in OP model rats, optimizes the microstructure of cancellous bone, and exerts anti-OP effects through the following mechanisms: upregulating serum superoxide dismutase (SOD) activity, klotho protein, and Hepcidin levels, while reducing malondialdehyde (MDA), fibroblast growth factor 23 (FGF23), and ferritin content. This process enhances antioxidant enzyme activity, alleviates oxidative stress, corrects iron overload in the body, and thereby regulates ferroptosis pathways.

6. Conclusion and Prospects

Since the introduction of ferroptosis as a novel form of programmed cell death in 2012, its intricate regulatory mechanisms across various diseases have gradually emerged as a research focus. Ferroptosis encompasses a complex pathological network where individual mechanisms operate independently yet intertwine, forming a unique regulatory system. In the realm of women's health, the steep decline in estrogen levels post-menopause is intimately linked to the pathological progression of osteoporosis and sarcopenia, with ferroptosis playing an increasingly pivotal role in this process. Current research indicates that intervening in ferroptosis pathways can effectively slow the progression of sarcopenia-osteoporosis, offering a novel perspective for therapeutic strategies.

At the forefront of cell biology and chemical biology, the exploration and development of novel ferroptosis inhibitors and activators are ushering in a new era of precision targeted therapy against this pathological process. However, the current understanding of iron metabolism disorders and the specific mechanisms of ferroptosis in the pathological state of the musculoskeletal system remains limited, with numerous core scientific questions awaiting further exploration and answers. Therefore, deepening the research on the interplay between iron metabolism and ferroptosis in sarcopenia-osteoporosis holds immense value for advancing innovative therapeutic strategies.

Traditional Chinese Medicine (TCM), as a treasure trove of ancient medicine, demonstrates potential for multi-dimensional and multi-targeted regulation of ferroptosis. Nevertheless, current research primarily focuses on the direct impact of TCM monomers or active ingredients on ferroptosis, while clinical and basic research on TCM formulas in modulating ferroptosis is relatively scarce. Given the complexity of TCM formulas, their extensive range of targets, and the unclear molecular mechanisms, the deep connections between TCM, ferroptosis, and sarcopenia-osteoporosis require further elucidation.

Looking ahead, it is crucial to leverage modern technological tools such as network pharmacology to foster interdisciplinary

collaboration, enabling precise dissection of disease pathologies and tapping into the potential of TCM. By strengthening basic research and clarifying the specific pathways and molecular mechanisms of TCM in regulating ferroptosis, we can provide a solid theoretical foundation and research guidance for the application of TCM in the treatment of sarcopenia-osteoporosis post-menopause. Concurrently, this endeavor will pave new avenues for drug development, accelerating the modernization and international integration of TCM.

Fund Project

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