Chinese Journal of Natural Medicines

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Citation: Jianjian Zhuang, Wenjie Yang, Yiming Jiang, Yang Chen, Xiaoli Ye, Yangling Li, Nengming Lin, Effect and mechanism of Chinese medicine on inhibiting the senescence of mesenchymal stem cells, Chinese Journal of Natural Medicines, 2026, 24(1), 1–12. doi: 10.1016/S1875–5364(26)61072–2.

View online: https://doi.org/10.1016/S1875–5364(26)61072–2

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Review

Effect and mechanism of Chinese medicine on inhibiting the senescence of mesenchymal stem cells

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ARTICLE INFO

Article history:
Received 8 March 2025
Revised 10 May 2025
Accepted 17 June 2025
Available online 20 January 2026

Keywords:
Mesenchymal stem cells
Inhibiting
Senescence
Chinese medicine
Natural compounds

ABSTRACT

Mesenchymal stem cells (MSCs) are pluripotent stem cells isolated from human tissues. Due to their strong self-renewal capacity, pluripotency, and immunomodulatory properties, MSCs have garnered significant attention in cell therapy and tissue regeneration. However, cellular senescence induced by replication or external stimuli can impair MSC proliferation and differentiation, making it crucial to develop interventions that delay or reverse the senescence process. From a traditional Chinese medicine perspective, senescence stems from spleen and stomach deficiency, kidney deficiency, and related factors; thus, medicines that tonify the kidney and promote Qi and blood circulation play vital roles in anti-senescence therapy. Chinese medicine, characterized by low toxicity and multi-target, multi-functional properties, has become prominent in anti-senescence research. This paper examines the MSC senescence process by discussing its causes, characteristics, and mechanisms, then summarizes how active ingredients in herbal medicines and natural compounds reverse MSC senescence, facilitating the discovery of additional anti-senescence Chinese medicines and their effective components.

1. Background

Stem cells, as undifferentiated cells, possess the capacity for self-renewal and differentiation into other cell types. Human stem cells comprise two categories: embryonic stem cells and adult stem cells. Compared to embryonic stem cells, adult stem cells exist in highly differentiated tissues and are essential for maintaining and repairing adult tissues and organs [1]. Among adult stem cells, mesenchymal stem cells (MSCs) are pluripotent stem cells isolated from various human tissues that can differentiate into mesodermal cells and other ectodermal cells [2, 3]. In 2006, The International Society for Cellular Therapy (ISCT) established three criteria for MSC identification: 1) plastic adhesion; 2) expression of cluster of differentiation 105 (CD105), CD73, and CD90 surface antigens; 3) *in vitro* differentiation potential into multiple lineages, including osteoblasts, adipocytes, and chondroblasts [4]. Given their robust self-renewal capacity, pluripotency, and immunomodulatory properties, MSCs have attracted significant attention in cell therapy and tissue regeneration. MSCs contribute to tissue regeneration and repair through their multi-differentiation potential, maintaining cellular renewal. During immune reconstitution, MSCs produce cytokines that suppress T cell proliferation and immune responses through cell-cell interactions. These properties have led to widespread MSC applications in angiogenesis, neurogenesis, tissue repair, and wound healing.

Accumulating evidence indicates that mesenchymal stem cells (MSCs) derived from aged donors exhibit reduced proliferative and differentiation capacities compared to those from younger individuals, significantly compromising their regenerative potential [5, 6]. Therefore, strategies to compensate for the functional decline of MSCs through *in vitro* passage expansion and *in vivo* transfusion are critical for their therapeutic application. However, MSCs possess inherently limited proliferative capacity under *in vitro* conditions, influenced by factors including cell source, isolation and culture techniques, cellular state, and donor age [7]. Prolonged *in vitro* culture further accelerates cellular senescence, leading to phenotypic and functional heterogeneity between preclinical models and clinical applications, which has become a major obstacle to MSC clinical translation [8]. These findings underscore the importance of controlling MSC quality and developing rejuvenation strategies to facilitate clinical translation and application [9, 10]. Therefore, advancing the clinical efficacy of MSC-based therapies requires a comprehensive understanding of the molecular mechanisms underlying MSC senescence, alongside the development of targeted interventions to delay or reverse this process.

Traditional Chinese herbal medicine has an extensive history in Asian countries. Research indicates that traditional Chinese medicine can regulate the differentiation, proliferation, and mi-

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https://doi.org/10.1016/S1875-5364(26)61072-2

gration of MSCs, which has been extensively studied in nerve-like cell differentiation [11], osteoarthritis [12], and liver fibrosis [13]. Leveraging the anti-inflammatory properties of MSCs, the combination of traditional Chinese medicine and MSCs demonstrates efficacy in treating atherosclerosis and other inflammatory conditions [14, 15]. Furthermore, MSCs possess immunomodulatory effects, and UC-MSCs treated with traditional Chinese medicine enhance the immunosuppressive capabilities of MSCs in acute graft-versus-host disease following hematopoietic stem cell transplantation [16]. Traditional Chinese medicine has also gained significant attention in anti-senescence research. According to traditional Chinese medical theory, senescence is attributed to factors such as spleen and stomach dysfunction, kidney deficiency, and impaired Qi and blood circulation. Consequently, herbal therapies that tonify the kidney and regulate Qi and blood flow are considered fundamental in delaying aging processes [17]. Increasing research attention has focused on *Panax ginseng* [18], *Ganoderma* spp. [19], *Astragalus membranaceus*, and *Dioscorea opposita* [20, 21]. Chinese medicine comprises diverse active natural products characterized by low toxicity, multiple targets, and multi-functional properties, making it a prominent field in anti-senescence research [22]. This review examines the characteristics and mechanisms of MSC senescence, summarizes recent advances in Chinese medicine and natural active substances in inhibiting MSC senescence, and discusses the current challenges and future directions for advancing Chinese medicine-based anti-senescence strategies.

2. Characteristics, types of senescent MSCs

Morphologically, senescent cells typically exhibit increased size and flatness, with granular cytoplasm and disproportionate growth between cytoplasm and nucleus. Additionally, cell adhesion to plastic surfaces decreases due to excessive actin fiber formation during senescence [23, 24]. At the cellular mechanism level, senescence-associated β-galactosidase (SA-β-gal) activity increases, serving as a primary detection method for evaluating cellular senescence [25]. Tumor suppressor genes *p21* and *p16* accumulate in senescent cells, maintaining cellular deoxyribonucleic acid (DNA) integrity and inducing irreversible cell cycle arrest [26]. Senescent cells produce and secrete various senescence-related secretory phenotypic factors (SASP) and exosomes that transmit senescence signals [27]. Functionally, senescent MSCs demonstrate reduced or lost proliferation capacity, oriented osteogenic differentiation, and enter a quiescent state. Their immunosuppressive and migration capabilities also decline (Fig. 1) [23].

Young cells progressively become senescent MSCs through development, replication, and stress stimulation. Developmental senescence occurs during mammalian sperm-to-embryo development [28]. This process proceeds without DNA damage or activation of ataxia-telangiectasia mutated (ATM) and ataxia telangiectasia and Rad3-related (ATR). This form of senescence depends on p21CIP1 expression and resembles oncogene-induced senescence (OIS) [29]. Under standard culture conditions, replicative senescence represents another form of MSC senescence, characterized by telomere shortening or structural changes [30, 31]. Additionally, stress-induced premature senescence is triggered by various external stimuli, such as oncogene activation [32], oxidative stress [33], and exposure to chemotherapeutic agents [34]. These stimuli activate senescence-associated pathways, including ATR-p53-p21CIP1 and p16Ink4a. Unlike replicative senescence, which occurs due to telomere attrition, SIPS leads to irreversible growth arrest well before the cells reach their replicative limit (Fig. 2).

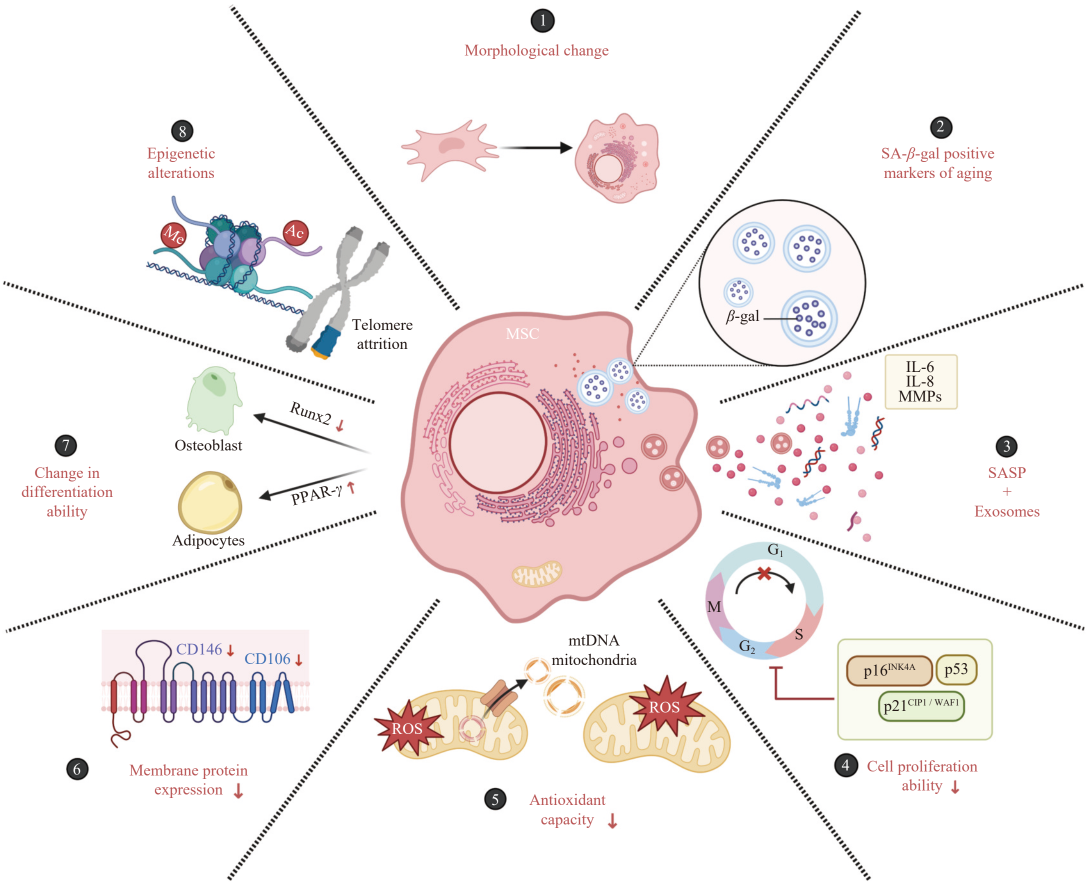

Fig. 1 Characteristics of senescent MSCs. Senescent MSCs exhibit distinct features at the morphological, molecular, and cellular levels. Morphologically, they display enlarged, flattened cell shapes. At the molecular level, hallmarks include cell cycle arrest, elevated SA-β-gal expression, altered secretion of SASP factors and exosomes, epigenetic modifications, and changes in membrane protein expression. At the cellular level, senescent MSCs show reduced proliferative and differentiation capacities.

3. Mechanisms of senescent MSCs and herbal medicine intervention

The mechanisms underlying cellular senescence primarily involve the activation of the DNA damage response (DDR), telomere shortening, and epigenetic alterations at the cellular level, as well as mitochondrial dysfunction at the organelle level. Nuclear DNA damage is a central trigger for senescence, particularly double-strand breaks, which initiate the DDR pathway. Activation of this pathway leads to cell cycle arrest *via* checkpoint signaling, thereby preventing the propagation of damaged DNA and contributing to the establishment of a senescent phenotype. Telomeres, the specialized nucleoprotein structures located at the ends of eukaryotic chromosomes, are maintained by telomerase—a ribonucleoprotein enzyme complex that extends telomeric DNA. In the absence of sufficient telomerase activity, telomeres progressively shorten with each cell division, ultimately triggering DNA damage responses and constituting a fundamental mechanism of MSC senescence. In addition to telomere attrition, epigenetic alterations are key regulators of MSC senescence. Senescent MSCs exhibit aberrant epigenetic modifications, including changes in DNA methylation and histone methylation/acetylation, which disrupt gene expression patterns critical for maintaining stem cell self-renewal, survival, and differentiation potential. These epigenetic dysregulations contribute significantly to the establishment and maintenance of the senescent phenotype. At the organelle level, mitochondrial dysfunction plays a central role in MSC senescence. Key mitochondrial alterations include increased accumulation of reactive oxygen species (ROS), changes in mitochondrial mass and membrane potential, morphological abnormalities, and impaired energy metabolism. Together, these cellular and organellar factors orchestrate the onset and progression of MSC senescence (Fig. 3).

In recent years, herbal medicine has emerged as a prominent field in anti-senescence research, offering advantages through natural products with minimal side effects, multiple components, targets, and pathways. Herbal medicine primarily ameliorates MSC senescence by addressing DNA damage, telomere length, and epigenetic changes. Additionally, it directly reduces ROS levels or activates autophagy by enhancing various antioxidant enzyme activities, thereby reducing oxidative damage in bone marrow MSCs (hBM-MSCs) and improving senescent MSCs. In traditional herbal medicine theory, kidney essence deficiency is considered the root of senescence; as kidney essence gradually depletes, signs of senescence become more apparent. The following sections examine recent advances in herbal medicine's role in inhibiting and reversing BM-MSC senescence, categorized by traditional medicinal properties such as tonifying Qi, addressing de-

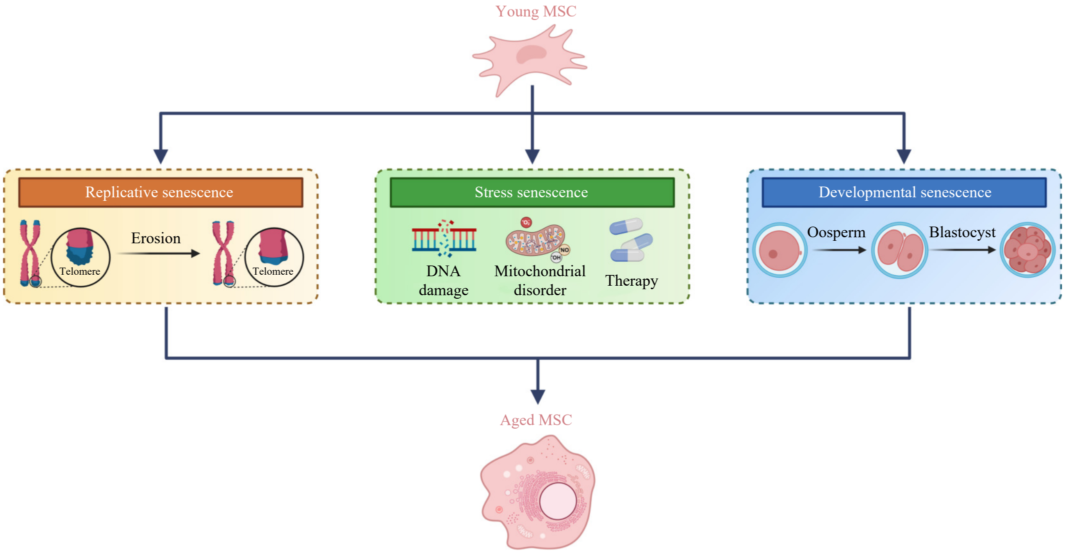

Fig. 2 Classification of senescence MSCs. Young MSCs can transition into a senescent state through replicative senescence, stress-induced senescence, and developmental senescence.

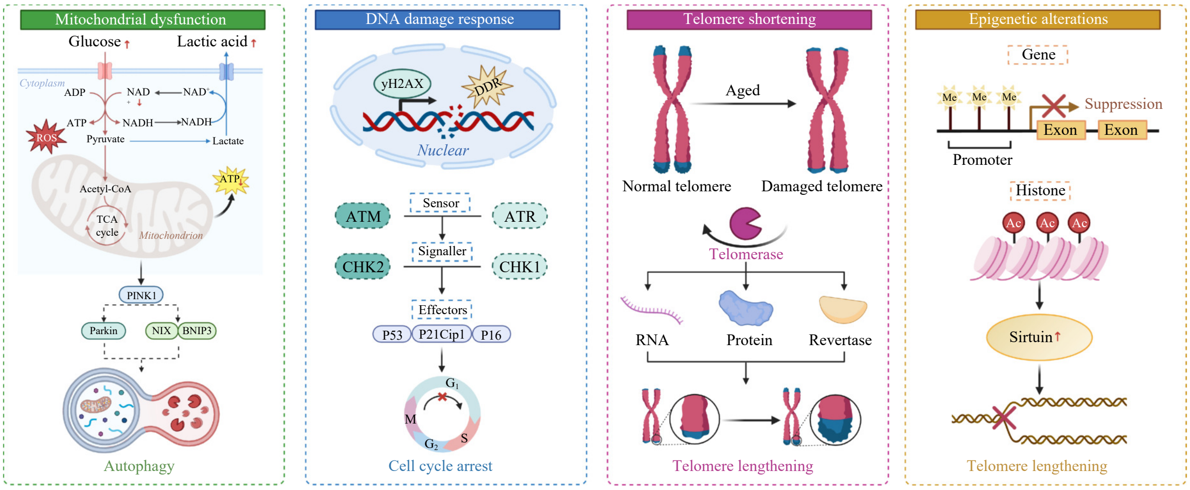

Fig. 3 Mechanisms underlying MSC senescence. MSC senescence is driven by mitochondrial dysfunction, DDR, telomere shortening, and epigenetic alterations.

ficiency, clearing heat, promoting blood circulation, removing blood stasis, and stopping bleeding.

3.1. DNA damage and herbal medicine intervention

Nuclear DNA damage represents a common trigger for cellular senescence activation. DNA double-strand breaks typically activate the DDR pathway, which halts the cell cycle through DDR checkpoints (ATM and ATR), human checkpoint kinase 1 (CHK1), and human checkpoint kinase 2 (CHK2) [35]. When DNA damage remains unrepaired, cells enter senescence-induced proliferation arrest, while checkpoint inhibition enables senescent cells to resume cell cycle progression. The DDR cascade activates tumor suppressor protein p53, which subsequently induces expression of cell cycle blocking proteins [36], including p21Cip1 and p16. While p21Cip1 activation occurs during early senescence, p16 activation manifests in late senescence [26], with both proteins working sequentially to induce permanent cellular senescence.

DNA damage in MSCs is commonly induced by oxidative stress, chemical agents, ionizing radiation, and other environmental or physiological factors. Among these, oxidative stress is the predominant contributor, where elevated levels of ROS or exposure to sublethal concentrations of exogenous H_2O_2 can impair DNA integrity. This oxidative damage disrupts DNA synthesis, reduces cell proliferation and differentiation capacity, and ultimately promotes the onset of cellular senescence in MSCs [37]. Generally, antioxidants can inhibit oxidative stress-induced cellular senescence. For instance, Qi-tonifying compounds ginsenoside Rg1 and Rb1 reduce DNA damage and DDR formation through the p53-p21WAF1/CIP1 and p16INK4ARb signaling pathways, thereby inhibiting MSC senescence [38]. Curcumin, an herb known for activating blood circulation, reduces ROS production and oxidative stress by activating nuclear factor E2-related factor 2 (NRF2) expression and AMP-activated protein kinase (AMPK) signaling pathway to maintain mitochondrial function [39]. These studies demonstrate that herbal medicine can inhibit DNA damage-induced DDR and suppress MSC senescence through key proteins p53, p21, and p16.

3.2. Cellular telomeres and telomerase activity and herbal medicine intervention

Telomeres constitute specialized structures at chromosome ends in eukaryotic cells. Without telomere repair mechanisms, progressive telomere shortening during DNA replication represents a fundamental endogenous mechanism in MSC senescence [40]. Telomerase, a riboprotease capable of extending telomere ends, comprises ribonucleic acid (RNA) and protein components containing primer-specific sites. Using its intrinsic RNA as a template, telomerase synthesizes telomere DNA and adds it to chromosome ends, effectively lengthening telomeres. Telomerase activity loss results in telomere shortening, and cells cease division and enter senescence when telomere DNA diminishes by several thousand bases [41].

Curcumin, an herb that activates blood circulation, is a fat-soluble natural active ingredient extracted from turmeric rhizome. Curcumin reduces ROS production and oxidative stress by activating NRF2 expression and the AMPK signaling pathway to maintain mitochondrial function. Additionally, it promotes MSC proliferation by increasing TERT activity and activating the PI3K-AKT signaling pathway [39, 42]. The Qi-tonifying combination of Astragalus alcohol and astragaloside influences telomere length and telomerase activity in human umbilical cord mesenchymal stromal cells [43]. *O. caudata* aqueous extract, from the Leguminosae family, decreases mitochondrial superoxide levels, DNA double-strand breaks, and telomere shortening in hADMSCs subjected to doxorubicin-induced senescence [44]. These studies demonstrate that herbal medicine primarily alleviates senescence by affecting telomerase activity and telomere length.

3.3. Epigenetic changes and herbal medicine intervention

Epigenetic changes serve as significant drivers of MSC senescence. Research indicates that abnormal epigenetic modifications, including DNA methylation, histone methylation, and acetylation, occur during MSC senescence. These epigenetic changes influence MSC survival and differentiation by disrupting gene expression [45]. Choi et al. discovered that genes associated with DNA replication and cell cycle in 15th-generation MSCs exhibited more hypermethylated 10 kb promoters compared to 5th-generation MSCs, with promoter hypermethylation resulting in decreased gene transcription [46].

Beyond gene-level hypermethylation modifications, histone acetylation and deacetylation maintain chromatin relaxation or aggregation at the protein level. The MSC senescence process involves histone H3 lysine-9 acetylation and lysine-14 acetylation. These histone modifications ultimately affect gene expression [47]. Deacetylase may mitigate protein acetylation's regulatory effect on MSC senescence. Recent studies reveal that SIRT, a NADH-dependent protein deacetylase, significantly regulates age-related diseases. Wang et al. demonstrated that exogenous nicotinamide adenine dinucleotide $(NAD)^+$ delays D-galactose (D-Gal) induced senescence in healthy Sprague Dawley (SD) rats derived MSCs through SIRT1 signaling [48]. These findings indicate that epigenetic modification at both gene and protein levels significantly regulates MSC senescence. For instance, berberine, an isoquinoline alkaloid from Coptidis Rhizoma, enhances antioxidant enzyme activity by promoting NAD^+-SIRT1 signaling pathway and activates AMPK signaling pathway to reduce ROS levels, thereby decreasing oxidative stress. The mTOR-p70S6K1/2 signaling pathway inhibition reduces oxidative stress damage to mitochondria and preserves mitochondrial function. Additionally, berberine inhibits inflammatory factor secretion and regulates autophagy, ultimately inhibiting senescent BM-MSCs [49]. Epigallocatechin-3-gallate prevents cellular senescence in H_2O_2-exposed human MSCs (hMSCs) by decreasing acetyl-p53 and p21 protein levels [50]. Camphorone, camphor's main active component, inhibits MSC senescence by increasing beclin1 protein expression, reducing p62 protein expression, promoting AMPK/SIRT1 pathway activation, and activating autophagy [51]. In conclusion, herbal medicine significantly inhibits MSC senescence by regulating senescence-related proteins through acetylation.

3.4. Mitochondrial dysfunction and herbal medicine intervention

Mitochondria, serving as cellular respiratory centers, play crucial roles in cell metabolism and signal transduction. Senescent cells frequently experience mitochondrial dysfunction, primarily caused by mitochondrial ROS accumulation, which subsequently intensifies senescence [52]. Mitochondrial dysfunction in senescent cells manifests through changes in mitochondrial mass, membrane potential, morphology, and energy metabolism. For instance, replicative senescence of MSCs exhibits prolonged mitochondrial morphology and impaired function, with severely senescent MSCs potentially developing discrete and fragmented mitochondria [53, 54].

Research indicates that stem cells primarily depend on mitochondrial glycolysis for energy metabolism. Mitochondrial dysfunction, including respiratory chain abnormalities and metabolic disorders, is associated with senescent MSCs, manifesting in several aspects: NAD^+ consumption, lactic acid accumulation, increased glucose consumption, and decreased adenosine triphosphate (ATP) production [55]. The principal factors regulating mitochondrial energy metabolism in MSCs include hypoxia-inducible factor 1α (HIF-1α), peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α), sirtuin, manganese superoxide dismutase (SOD2), and AMPK. For instance, SIRT1 molecules influence MSC senescence by regulating mitochondrial biogenesis and metabolic efficiency through control of transcription factors p53 and nuclear factor kappa B (NF-κB) [56].

Mitophagy represents a mitochondrial quality control process that maintains mitochondrial and cellular homeostasis. This process occurs through the selective encapsulation and degradation of mitochondria by autophagosomes. Typically, ROS and external stimulation of cellular senescence induce membrane potential depolarization-mediated mitochondrial damage, triggering mitophagy [57]. The elimination of damaged mitochondria through activated mitophagy serves a crucial regulatory function in maintaining microenvironment homeostasis and delaying senescence. The most extensively studied activation of mitophagy involves the ubiquitin-dependent signaling pathway of PTEN induced kinase 1 (PINK1)/Parkin, with research demonstrating that ROS and SIRT molecules can induce senescence by inhibiting Parkin-mediated mitophagy [58, 59]. Additionally, a ubiquitin-independent, receptor-mediated mitophagy pathway has been identified, in which autophagy receptor proteins, such as BCL2/adenovirus E1B 19 kDa-interacting protein 3-like (NIX), BCL2/adenovirus E1B 19 kDa-interacting protein 3 (BNIP3), and FUN14 domain-containing 1 (FUNDC1), anchor to the outer mitochondrial membrane and directly interact with microtubule-associated protein 1 light chain 3 (LC3). This interaction facilitates the recruitment of autophagosomal membranes and initiates mitophagy activation [60]. These two primary mechanisms of mitophagy regulation ensure mitochondrial internal stability. For instance, Buqi Astragalus's main active ingredients, including Astragalus polysaccharide, saponins, and isoflavones, reduce ROS levels by enhancing SOD expression, decreasing oxidative stress, regulating autophagy, improving mitochondrial function, and inhibiting BM-MSC senescence. Similarly, the Buqi compound glycyrrhizal chalcone D inhibits BM-MSCs by promoting autophagy through activation of the AMPK signaling pathway [61]. Curcumin, a traditional herb known for promoting blood circulation, reduces ROS production and mitigates oxidative stress by activating NRF2 expression and the AMPK signaling pathway, thereby preserving mitochondrial function [62]. Herbal medicine primarily inhibits ROS content by activating antioxidant enzymes and mitophagy to maintain mitochondrial stability, thereby inhibiting MSC senescence.

3.5. Autophagy and herbal medicine intervention

Autophagy serves a vital function in maintaining cellular growth stability. This process becomes significantly activated when cells experience oxidative stress, hypoxia, or nutrient deficiency. This mechanism effectively inhibits the accumulation of harmful substances resulting from cell injury and death. Additionally, senescence represents the gradual accumulation of cellular damage caused by low-intensity chronic stress, such as oxidative stress, establishing a close relationship between autophagy and cellular senescence. Studies of the senescence model have revealed corresponding changes in autophagy-regulating genes, including *LC3*, sequestosome 1 (*p62*), and autophagy-related (ATG) proteins [63].

Autophagy and senescence represent mammalian stress responses. However, autophagy's effect on senescence and its underlying mechanisms remain unclear. Regarding autophagy's role in delaying MSC senescence, Zhang et al. demonstrated that autophagy could delay D-Gal-induced senescence in MSCs derived from long bones of Sprague-Dawley rats through activation of the ROS/JNK/p38 signaling pathway [64]. Ma et al. found that autophagy activation enhances bone marrow osteogenic differentiation and proliferation of MSCs while reducing lipogenic differentiation to restore MSC senescence. Autophagy partially restores MSC characteristics and reduces bone loss in senescent mice through regulation of the ROS-p53 signaling pathway [65]. Recent research has also revealed that long-term culture induces MSC senescence, disrupting internal homeostasis of senescent MSCs, whereupon autophagy activates to maintain MSC survival [66]. These studies indicate autophagy's significant regulatory role in maintaining MSC internal balance.

Berberine, a heat-clearing drug, inhibits the secretion of inflammatory factors and regulates autophagy, ultimately inhibiting senescence in BM-MSCs. Curcumin, a compound that activates blood circulation and removes blood stasis, is a fat-soluble natural active ingredient extracted from turmeric rhizome. Curcumin activates NRF2 expression and AMPK signaling pathway, inhibits NF-κB signaling pathway and ERK1/2 phosphorylation, reduces ROS production and oxidative stress, thereby maintaining mitochondrial function and inhibiting SASP secretion. Curcumin also suppresses MSC senescence by promoting autophagy [42]. Resveratrol (RSV) is a natural polyphenol antitoxin that can inhibit BM-MSC senescence by enhancing cell metabolic balance and promoting autophagy [67]. These studies demonstrate that herbal medicine can affect cell senescence through autophagy regulation.

4. The effect and mechanism of herbal medicine and its active components on inhibiting MSC senescence

Traditional Chinese medicine attributes senescence primarily to Qi deficiency and blood stasis, with phlegm turbidity blocking collaterals. Therefore, nourishing blood and Qi are essential for anti-senescence in traditional Chinese medicine. This review summarizes the effects and mechanisms of traditional Chinese medicines against senescent MSCs in three categories: traditional Chinese herbs, Chinese herbal monomers (terpenes, phenols, flavonoids), and plant extractions. Currently, the anti-senescence effects of Chinese herbal medicine on MSCs are exerted across multiple biological levels, including the cellular, organelle, and extracellular environments. For example, individual herbal monomers such as ganoderic acid D (GA-D), ginsenoside Rg1, and camphorquinone (CQ) inhibit MSC senescence primarily by reducing mitochondrial reactive oxygen species (ROS), thereby preserving cellular homeostasis. In contrast, multi-herbal formulations such as Zuogui Wan (ZGW) and Guilu-Erxian Glue (GLEXG) modulate MSC senescence through regulation of the senescence-associated secretory phenotype (SASP) and exosome release. The specific molecular mechanisms by which these compounds inhibit MSC aging will be discussed in detail in the following sections (Fig. 4).

4.1. Traditional Chinese herb

Traditional Chinese herbal compounds have garnered increasing research attention and are widely employed as adjunct therapies in oncology, immunomodulation, endocrine regulation, and other areas. Their appeal lies in their multi-component, multi-target, and multi-effect characteristics, combined with low toxicity, minimal side effects, and strong synergistic potential. In recent years, these compounds have been increasingly explored in anti-senescence research, particularly in studies focused on mitigating MSC senescence [68-74].

Alpiniae Oxyphyllae Fructus (AOF), a renowned Chinese medicine from the Ginger family, is one of southern China's four famous medicines. AOF functions include nourishing the spleen to prevent diarrhea, reducing spittle, reinforcing kidney essence to decrease urination, and acting as a brain tonic to promote Qi and blood circulation for functional recovery. Pharmacological research demonstrates AOF's critical roles in treating Alzheimer's

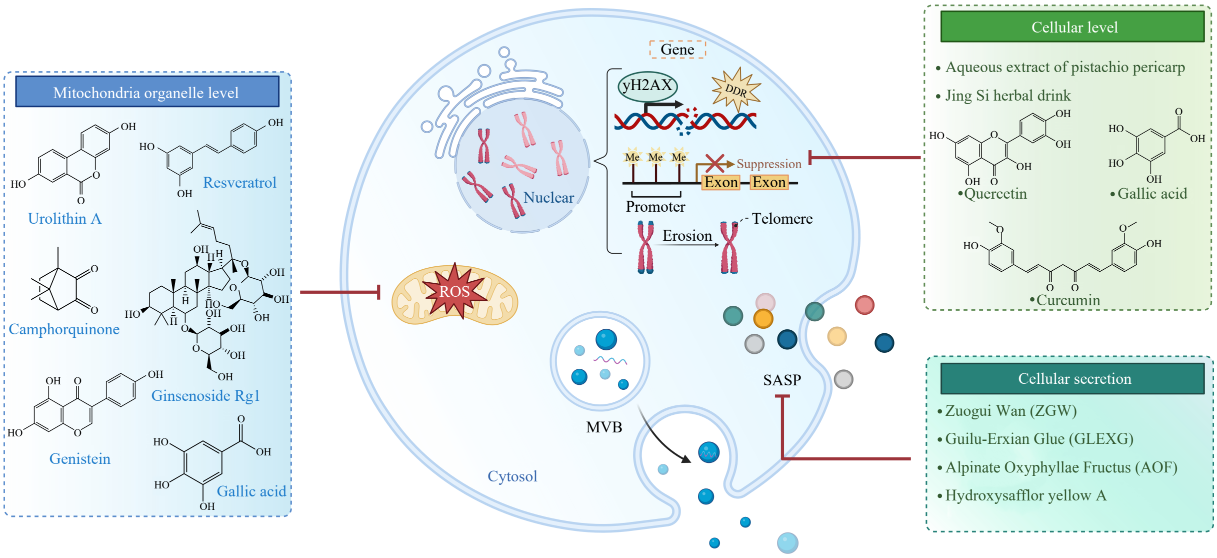

Fig. 4 Mechanisms of traditional Chinese medicine in inhibiting senescent MSCs. Traditional Chinese medicine, including herbal monomers, natural active compounds, and multi-herb formulations, exerts anti-senescence effects on MSCs at three biological levels: 1) the intracellular level, 2) the mitochondrial level, and 3) the extracellular level.

disease, stomach pain, ulcers, diarrhea, cardiac fibrosis, and tumors. Due to its anti-aging and sexual enhancement effects, AOF is utilized in Korea for treating various symptoms of hypertension and cerebrovascular diseases [68]. Recent studies have revealed AOF extract's anti-senescence effects in MSCs. Lin et al. investigated AOF's protective effect on senescence-related cardiac remodeling. AOF pretreatment of adipose-derived MSCs (ADMSCs) significantly reduced D-Gal-induced cardiac oxidative stress by activating the NRF2 pathway, with reduced ROS leading to inhibition of inflammatory signals (p-NF-κB and interleukin 6 (IL-6)) in senescent rats. Consequently, senescence-associated cardiac remodeling was restored [69]. Chang et al. confirmed that AOF-pretreated ADMSCs enhance cardiac repair function under senescence conditions, correlating with decreased expression of apoptosis and senescence markers (p21 and SA-β-Gal). Additionally, AOF and ADMSCs may restore senescent heart function by activating paracrine factors [70]. These studies indicate that AOF facilitates cardiac repair by regulating oxidative stress in senescent MSCs, reducing senescent cell numbers, and promoting MSC proliferation.

The herbal beverage Jing Si herbal drink (JS), based on Chinese herbal medicine, comprises eight Chinese herbs: mugwort leaf, tail leaf, ophiopogon, fish tail, platycodon, licorice, perilla, and chrysanthemum. Recent studies have demonstrated these herbs' anti-inflammatory, anti-viral, and immunomodulatory properties, as well as their ability to reduce organ damage [71]. Given that senescent cells exhibit increased inflammation, Shibu et al. demonstrated JS's anti-senescence effects on MSCs. Their study examined ADMSCs isolated from 16- and 24-week-old rats to evaluate JS's impact on cellular senescence. Following JS treatment, senescent ADMSCs showed decreased levels of DNA damage marker γ-H2AX and increased TERT nuclear accumulation. These findings validate JS's anti-senescence potential and expand understanding of its mechanism in MSCs, specifically through DNA damage reduction [72].

ZGW, a traditional prescription for kidney tonification, reflects the Chinese medical principle that kidney Qi fundamentally supports human growth, development, and reproductive function, with its depletion contributing significantly to senescence. Kang et al. examined ZGW's effects on MSC senescence. Their findings revealed that ZGW modulates Wnt/β-catenin signaling and suppresses age-related factors, thereby enhancing cellular proliferation, mitigating DNA damage, and reducing senescence-associated cytokine secretion, including high mobility group box 1 (HMGB1), matrix metalloproteinase-3 (MMP3), and IL-6, while maintaining MSCs' multi-directional differentiation capacity [73]. These results demonstrate ZGW's ability to inhibit MSC senescence through multiple mechanisms.

GLEXG, a Chinese herbal medicine designed to nourish blood and Qi and address kidney deficiency, has demonstrated clinical efficacy in treating elderly osteoarthritis patients' joint pain. Composed primarily of longtail, antler, wolfberry, and ginseng, GLEXG shows promising effects in addressing senescence, perimenopausal syndrome, and degenerative joint conditions. Yang et al. discovered that GLEXG dose-dependently upregulates type II/X collagen II, SOX9, and aggrecan expression, promoting MSC cartilage formation. Analysis of MSC exosome protein components revealed that GLEXG significantly reduces age-related protein expression, indicating exosome components' crucial role in delaying MSC senescence [74]. This research highlights GLEXG's role in controlling MSC senescence through exosome component regulation.

These studies highlight recent advances in Chinese herbal medicines that nourish blood and Qi for combating MSC senescence. At the cellular level, medicines such as AOF and ZGW inhibit MSC senescence and stimulate proliferation for renewal. Regarding cellular secretion, AOF and ZGW reduce paracrine factor release, including HMGB1, MMP3, and IL-6. GLEXG modulates senescent protein expression in exosomes to delay MSC senescence. At the molecular level, JS herbal medicine reduces DNA damage marker γ-H2AX expression and TERT nuclear accumulation processes. Traditional Chinese Medicine compounds thus demonstrate significant effects in inhibiting MSC senescence across cellular, molecular, and secretory levels.

4.2. Effective ingredients of herbal medicine

4.2.1. Terpenes

Terpenes comprise a class of isoprene derivatives widely distributed in nature, primarily isolated from plants, microorganisms, and marine organisms. These compounds exist in various oxygen-containing derivative forms, including alcohols, aldehydes, carboxylic acids, ketones, esters, and glycosides. Common plants such as ginseng, licorice, Astragalus, Bupleurum, and Reishi Mushroom contain high terpene levels. These compounds demonstrate significant regulatory functions in multiple therapeutic areas, including anticancer, anti-inflammatory, anti-allergic, antioxidant, anti-leukemic, anti-viral, and hypoglycemic effects, as well as cardiovascular and cerebrovascular disease prevention. Given these advantages, research progress regarding terpenes' role in inhibiting MSC senescence warrants examination [75].

Currently, extensive research examines the effects of terpenoids on MSC senescence. Ginsenoside, a glycoside compound based on triterpenoids or spiral steranes as ligands, is primarily extracted from ginseng as a monomeric component. Its mild and non-toxic properties have led to widespread applications in medicine, food, and cosmetics [76-79]. Ginsenosides possess a four-ring rigid steroid backbone similar to steroid hormones, and research demonstrates their hormone-like activity through nuclear receptor binding or hormone level modulation, thereby influencing various menopause-related diseases, inflammatory conditions, and cancers. Recent studies confirm that ginsenosides can counteract MSC senescence [80], with ginsenoside Rg1 being the most extensively studied saponin monomer component in MSC anti-senescence research. In 2020, Wang et al. discovered that ginsenoside monomeric Rg1 reduces Wnt pathway over-activation in senescent human bone marrow-derived MSCs (h-MSCs) by inhibiting GSK-3β phosphorylation and demonstrates the ability to regulate h-BMSC differentiation [81]. In 2021, this research group further investigated Rg1's anti-senescence mechanism in primary MSCs obtained from mouse femurs, confirming that Rg1 enhances MSC antioxidant capacity. The anti-senescence and antioxidant effects of Rg1 correlate with NRF2 signaling pathway activation, with AKT identified as the upstream molecule activating NRF2. AKT or NRF2 activation may serve as therapeutic targets for preventing MSC senescence [38]. In 2023, Ling et al. examined Rg1's effect on D-Gal-induced senescence of amniogenic MSCs (hAD-MSCs), finding that Rg1 inhibits hAD-MSC senescence rate and significantly reduces senescence proteins p16INK4a and p53/p21CIP1 expression. Rg1 also exhibits anti-senescence effects by inhibiting senescence factor insulin-like growth factor 1 (IGF-1) secretion [82]. In 2023, Che et al. investigated another saponin monomer molecule Rg2, revealing its ability to inhibit D-Gal-induced senescence and oxidative stress in porcine MSCs (pMSCs). Rg2 inhibits pMSC replicative senescence and maintains stemness by increasing autophagy activity through AMPK signaling pathway activation. These findings suggest a potential strategy for pMSC expansion *in vitro* [83]. This research indicates that ginsenosides such as Rg1 and Rg2 regulate differentiation and stemness at the cellular level, while Rg1 affects mitochondrial and lysosomal function at the organelle level. Additionally, Rg1 influences senescence factor secretion to inhibit MSC senescence.

Ganoderma lucidum represents a triterpenoid bioresource traditionally used as an anti-aging elixir in China and other oriental countries for millennia. GA-D, a triterpenoid compound extracted from *Ganoderma lucidum*, has broad applications in various diseases due to its excellent anti-inflammatory properties. In 2020, Xu et al. demonstrated that GA-D protected human amniotic MSCs (hAMSCs) from oxidative stress-induced senescence. GA-D significantly inhibits ROS production, *β*-galacsidase formation (an age-related marker), and senescence proteins p21 and p16 expression, while alleviating cell cycle arrest and enhancing telomerase activity in senescent hAMSCs. Mechanistic studies revealed that GA-D delayed hAMSC senescence through PERK/NRF2 signal activation [84]. In 2022, Yuan et al. further investigated GA-D's mechanism in inhibiting hAMSC senescence, identifying 14-3-3ε as GA-D's target. GA-D delayed MSC senescence by regulating both 14-3-3ε and the CaM/CaMKII/NRF2 axis in *in vivo* and *in vitro* senescence models [85]. This research elucidates the mechanism of triterpenoids in inhibiting MSC senescence. GA-D inhibits its senescence by alleviating cell cycle arrest and enhancing telomerase activity. These studies confirm that terpenoids resist MSC senescence by maintaining MSC differentiation, stemness, and proliferation.

CQ, a bicyclic monoterpenoid compound synthesized through continuous bromination oxidation of camphor, is found in essential oils from various herbs and utilized in traditional Chinese medicine for treating sprains, swelling, and inflammation. Research demonstrates that camphor's anti-aging properties enhance proliferation and anti-senescence effects in human primary dermal fibroblast cells while preventing UV-induced wrinkles in mouse skin. Studies by Maharajan et al. revealed that CQ inhibits senescence of human BM-MSCs and mouse heart tissue induced by H_2O_2 and D-Gal, activating the AMPK/SIRT1 signaling pathway and autophagy in both senescence models. Additionally, CQ decreases inflammatory marker gene expression in the heart tissue of D-Gal-induced senescence mice [51]. The above studies have confirmed that bicyclic monoterpenoid (CQ) plays an anti-senescence and heart-protecting role by activating autophagy. The study also expands a new approach to anti-senescence of terpenoids.

In summary, these studies demonstrate the anti-senescence effects of terpenes at multiple levels. At the intracellular functional protein level, terpenoids (saponins, CQ, *etc.*) directly inhibit p21 and p16 protein expression in senescent cells, while triterpenoid GA-D inhibits MSC senescence by enhancing telomerase activity. At the organelle level, saponin monomer molecules Rg2 and CQ target mitochondrial organelles and suppress cellular oxidative stress through the AMPK/SIRT1 mitophagy signaling pathway, thereby inhibiting MSC senescence. Regarding extracellular secretion proteins, Rg1 achieves anti-senescence effects through IGF-1 cellular factor secretion. These findings indicate that terpenoids inhibit MSC senescence through multiple mechanisms affecting cells, organelles, intracellular functional proteins, and extracellular secretion proteins.

4.2.2. Phenols

Polyphenols are secondary metabolites commonly found in Chinese herbs, vegetables, fruits, and other plant foods. These compounds exhibit dual mechanisms of action: they inhibit oxygen free radical generation by activating antioxidant enzymes, maintaining cell membrane integrity, and they alleviate the senescence process by suppressing pro-inflammatory factor-related inflammatory responses [86]. Common polyphenol compounds in Chinese medicine include curcumin, RSV, and quercetin. Recent research has demonstrated significant progress in understanding the anti-senescence effects of polyphenols on MSCs.

RSV, a natural polyphenol derived from peanuts, grapes, and other plants, blocks cell apoptosis, delays senescence, and extends lifespan by enhancing longevity gene *SIRT2* expression while suppressing tumor gene *p53*. Research exploring RSV's anti-senescence effects on MSCs reveals significant findings. Ali et al. demonstrated that RSV reduces SASP secretion and senescence-related gene expression (*p53*, *p16*, and *p21*) in human bone marrow MSCs (hBM-MSCs), while decreasing ROS content through increased expression of cellular antioxidation-related enzymes [heme oxygenase 1 (HMOX1) and SOD3]. RSV inhibits both adipogenic differentiation and age-related phenotypes in hBMSCs, consequently suppressing bone marrow adipose tissue (BMAT) formation, which originates from hBMSCs [87]. Alessio et al. found that picetanol, another natural polyphenol, counteracts MSC senescence by inhibiting p53-p21, RB1, and non-p53-dependent RB2-p16-p21-p27 signaling pathway activation in genotoxically-induced stress and replicative senescence models [88]. Lei et al. were the first to demonstrate the protective effects of resveratrol (RSV) against senescence in ADMSCs. Their study revealed that RSV significantly upregulates Pim-1 expression in senescent ADMSCs through activation of the PI3K/AKT signaling pathway. Moreover, they found that elevated Pim-1 levels in ADMSCs enhanced insulin secretion in INS-1 pancreatic *β*-cells when exposed to ADMSC-conditioned medium [89]. These studies elucidate the anti-senescence mechanisms of natural polyphenols (RSV, picetanol) in MSCs at cellular, organelle, and secretory levels.

Curcumin, a yellow pigment extracted from the rhizome of turmeric, is an active substance in acidic polyphenols. Curcumin exhibits multiple biological activities, including anti-oxidative, anti-inflammatory, anticancer, chemopreventive, and anti-neurodegenerative properties. Research has demonstrated its capacity to extend the mean lifespan of various aging model organisms, including *C. elegans*, *D. melanogaster*, yeast, and mouse. Deng et al. investigated curcumin's effect on canine bone marrow MSC (cBMSC) senescence and its underlying mechanism, discovering that curcumin increases the ratio of microtubule associated protein LC3-phosphatidylethanolamine conjugate (LC3II)/cytosolic form of LC3 (LC3I) and the expression of autophagy-related molecules autophagy-related gene 7 (*ATG7*) and *ATG12*. Additionally, the formation of autophagy vesicles and acid vesicles was enhanced. Consequently, autophagy inhibitors/activators modify the senescence state of canine BMSCs through regulation of the autophagy pathway, confirming curcumin's significant role in ameliorating cBMSC senescence through autophagy mechanisms [42]. In examining curcumin's impact on MSC lifespan, Pirmoradi et al. determined that curcumin significantly enhances rat adipose tissue-derived stem cells (rADSCs) proliferation. The treatment delays senescence onset and markedly reduces senescent cell numbers. Molecular analysis revealed significantly higher *TERT* gene expression in curcumin-treated cells compared to controls, with notably extended rADSC lifespan [90]. This research demonstrates how curcumin modulates senescence through cellular autophagy and proliferation regulation, while at the molecular level, it extends lifespan by enhancing TERT expression.

Urolithin A (UA), a natural metabolite of ellagitannin polyphenol compounds, demonstrates significant antioxidant, anti-inflammatory, and anti-senescence properties. Shi et al. examined UA's anti-senescence effects in H_2O_2-induced senescent nucleus pulposus-derived MSCs (NPMSCs), revealing that UA inhibits NPMSC cell cycle arrest, reduces SA-β-Gal activity, and decreases senescence-related protein and mRNA expression. UA preserves mitochondrial function and delays NPMSC senescence through SIRT1/PGC-1α pathway activation [91]. These findings indicate UA's capacity to regulate MSC senescence through modulation of cell proliferation and mitochondrial function.

Gallic acid (3,4,5-trihydroxybenzoic acid, GA), a natural polyphenolic compound widely present in plants, possesses significant medicinal properties, including anti-inflammatory and antioxidant effects. Shan et al. investigated GA's impact on Werner syndrome (WS) hMSC senescence, confirming reduced expression of senescence markers p16 and p21, increased telomere length, and inhibited DDR. Notably, GA treatment enhanced histone H3 Lys9 trimethylation (H3K9me3) in WS hMSCs. GA additionally upregulates nuclear membrane proteins lamin B1 (LB1) and lamina-associated polypeptide 2β (LAP2β), supporting heterochromatin structure maintenance. These findings establish GA's critical role in heterochromatin maintenance and reduction of physiological premature senescence in hMSCs [92].

In conclusion, natural polyphenols, including RSV, picetanol, and GA, inhibit MSC senescence by directly suppressing p53, p21, and p16 protein expression and senescence factor secretion. Curcumin extends rADSC lifespan through enhanced telomerase reverse transcriptase gene expression. GA increases *H3K9me3* in WS hMSCs, upregulating *LB1* and *LAP2β* expression and maintaining heterochromatin structure. At the cellular organelle level, RSV reduces ROS content by increasing antioxidant enzymes HMOX1 and SOD3 expression, thereby inhibiting hBMSC senescence. Urolithin A preserves mitochondrial function through SIRT1/PGC-1α pathway activation. Curcumin enhances canine BMSC condition by increasing autophagy. These findings demonstrate phenolic compounds' regulatory and inhibitory effects on senescence at cellular and organelle levels.

4.2.3. Flavonoids

Flavonoids are widely distributed throughout the plant kingdom and constitute one of the primary active components in Chinese herbs. These compounds exhibit numerous biological functions, including anti-oxidation, tumor suppression, inflammation reduction, immune enhancement, and anti-aging properties [93]. Recent research has demonstrated significant progress regarding the flavonoid components of herbal medicine in preventing MSC senescence. This review examines the anti-senescence properties of commonly used Chinese medicines containing flavonoids, including quercetin, genistein (extracted from soy products), and hydroxysafflor yellow A (extracted from saffron).

Quercetin represents a distinct subclass of flavonoids. This bioactive natural compound, structured as C6 (ring A)-C3 (ring C)-C6 (ring B), demonstrates potent antioxidant and anticancer properties. Quercetin shows considerable promise as an anti-aging agent. Preclinical and early clinical data from anti-aging studies indicate quercetin's effectiveness in preventing or reducing cancer formation. Geng et al. developed a premature senescence model using WS hMSCs to evaluate natural compounds that inhibit premature hMSC senescence. Their research revealed that quercetin mitigated cell senescence by enhancing cell proliferation and restoring heterochromatin structure in WS hMSCs. These findings suggest quercetin's potential as a therapeutic intervention for age-related diseases [94].

Genistein, an isoflavone isolated from soy products, targets estrogen-associated receptor alpha (ERRα). This compound functions as a cancer protective agent by promoting apoptosis and cell cycle arrest while inhibiting angiogenesis and metastasis. Additionally, it exhibits antioxidant and anti-inflammatory properties. These characteristics suggest genistein's potential application in treating age-related conditions such as metabolic diseases, osteoporosis, and Alzheimer's disease. MSC senescence represents a significant factor in postmenopausal osteoporosis (PMOP). Li et al. demonstrated that genistein inhibits the senescence of ovariectomized (OVX)-BMMSCs through ERRα-mediated mitochondrial biogenesis and mitophagy activation. Furthermore, genistein increased the expression of p16INK4a, SIRT3, and PGC1α in OVX rats. These findings establish the molecular foundation for developing genistein-based PMOP treatment strategies [95].

Hydroxyl safflower yellow A (HSYA), the principal active component of edible safflower, demonstrates anti-inflammatory and antioxidant properties. In China, HSYA is frequently employed in treating cardiovascular and cerebrovascular diseases, functioning to eliminate oxygen-free radicals, decrease inflammatory infiltration, and inhibit apoptosis. Song et al. demonstrated that HSYA could delay the senescence process of D-Gal-induced MSCs by alleviating oxidative stress through increased SOD activity and reduced malondialdehyde (MDA) and ROS levels. Additionally, HSYA significantly decreased the secretion of senescence cytokines, tumor necrosis factor-α (TNF-α) and IL-1β, by activating the NF-κB signaling pathway [96]. These findings indicate that HSYA's anti-senescence effects correlate closely with its anti-inflammatory and antioxidant properties.

Research demonstrates that flavonoids effectively counter cell senescence through multiple mechanisms. At the cellular level, quercetin mitigates senescence by enhancing overall cell proliferation capacity. At the organelle level, genistein inhibits OVX-BMMSC senescence *via* ERRα-mediated mitochondrial biogenesis and mitophagy activation. Similarly, hydroxysafflor yellow A delays D-Gal-induced MSC senescence by modulating mitochondrial SOD activity and reducing oxidative stress. Regarding extracellular secretion, hydroxysafflor yellow A reduces senescence factor secretion (TNF-α and IL-1β) through activation of the NF-κB signaling pathway. These findings demonstrate flavonoids' capacity to inhibit MSC senescence at both cellular and mitochondrial levels.

4.3. Plant extracts

Plant extracts comprise biological small molecules or macromolecules obtained by separating and purifying one or more effective components from plant raw materials through physical, chemical, and biological methods [97, 98]. These extracts contain complex chemical compositions, including polysaccharides, polyphenols, volatile oils, alkaloids, and other secondary metabolites, exhibiting various functions such as anti-oxidation, anti-viral activity, anti-tumor effects, and immune enhancement. Recent studies have demonstrated notable progress in understanding plant extracts' role in preventing MSC senescence.

Studies have demonstrated that polysaccharides from *U. pinnatifida* serve an essential role in both nutritional and medicinal applications. *U. pinnatifida* has garnered significant attention for its pharmacological properties in preventing various conditions, including inflammation, cancer, and other diseases. Jeong et al. examined the anti-senescence effects of *U. pinnatifida* ethanol extract (UP-Ex) on hBM-MSCs. Their findings indicated that UP-Ex inhibited ROS-induced oxidative damage in hBM-MSCs by enhancing the activities of SOD1, SOD2, and catalase, suggesting UP-Ex could ameliorate functional decline in senescent stem cells. This may lead to enhanced therapeutic outcomes in stem cell therapy [99].

Pistachio represents a substantial source of phenolic, antioxidant, and anti-inflammatory compounds. Extensive research has examined the antioxidant and anticancer properties of pistachio pericarp extract. Askari et al. demonstrated that the aqueous extract of pistachio pericarp (AEPP) enhanced cell proliferation and decreased senescence in a concentration-dependent manner. Furthermore, telomere length, telomerase activity, and anti-senescence gene expression increased significantly with AEPP treatment in a dose-dependent fashion. Given its high safety profile and anti-senescence effects, AEPP shows promise as a potential therapeutic agent for mitigating bone marrow-derived MSC senescence [100].

Plant extracts inhibit MSC senescence primarily through cellular and intracellular functional protein mechanisms. At the cellular level, AEPP delays senescence by enhancing overall cell proliferation. Regarding intracellular functional proteins, *U. pinnatifida* exhibits anti-senescence effects primarily by increasing antioxidant enzyme activities of SOD1, SOD2, and catalase. Additionally, AEPP delays MSC senescence through regulation of telomerase activity and anti-aging gene expression. These plant extracts demonstrate promising effects in alleviating MSC senescence, establishing a foundation for future development of additional plant extracts.

The aforementioned studies indicate that traditional Chinese medicines that nourish blood and Qi inhibit MSC senescence through antioxidant and anti-inflammatory mechanisms. The anti-senescence mechanisms operate at three distinct levels. At the cellular level, traditional Chinese medicine exhibits anti-senescence effects by modulating cell proliferation, differentiation, and stemness. Additionally, it reduces senescent protein expression. At the organelle level, TCM demonstrates anti-senescence effects through enhanced mitochondrial antioxidant activity and regulation of autophagy to inhibit MSC senescence. At the extracellular level, TCM suppresses MSC senescence by inhibiting senescence-related secretory factors and exosomes (Table 1).

5. Summary and future perspectives

MSCs represent one of the most extensively studied adult stem cell types. Their accessibility, immunomodulatory properties, and therapeutic potential in regenerative medicine have led to clinical research applications across various diseases, particularly degenerative and age-related conditions. However, the continuous senescence of MSCs both *in vivo* and *in vitro* inhibits their proliferation and diminishes their functional activity, presenting a significant challenge for clinical applications. Analyzing the causes and specific mechanisms of MSC senescence, and developing corresponding preventive or reversal measures, is crucial for addressing this limitation.

MSC senescence occurs through multiple pathways. This review categorizes the causes into three main types: replicative senescence, stress-induced premature senescence (including oncogenic, oxidative stress, and treatment-induced), and developmental senescence. Among stress-induced premature senescence factors, oxidative stress and excessive ROS production are particularly significant. While inhibiting ROS production theoretically could prevent premature senescence, ROS serves essential regulatory functions in normal cellular processes. Therefore, targeting excess ROS elimination has limitations, whereas modulating anti-senescence SIRT family molecules that regulate MSC activity appears more promising and safer [101]. Current interventions using small molecule inhibitors or gene modification target various signaling pathways but present dose-dependent toxicity or off-target effects. Given increasing health consciousness, non-toxic or low-toxic traditional Chinese medicines and their active ingredients with anti-senescence properties represent an important future direction [102]. This review examines recent advances in Chinese medicine and its active components in preventing MSC senescence. Terpenoids, phenols, and flavonoids emerge as the most studied components, functioning at mitochondrial, cellular, and secretory levels. Recent research highlighting the role of MSC paracrine substances, such as exosomes, in anti-senescence provides novel mechanistic insights regarding Chinese medicine's anti-senescence properties. This foundation enables new approaches to prevent MSC senescence [103]. Additionally, identifying and isolating compounds with similar structures from natural sources could yield novel anti-aging active ingredients (Fig. 5).

Research on Chinese medicine's anti-MSC senescence effects remains at cellular and animal experimental stages, requiring further clinical studies before practical application. Moreover, the complex composition of herbal medicine compounds necessitates bioinformatics analysis to understand multi-component and multi-target interactions, advancing herbal medicine research [104]. Current basic studies predominantly focus on cell populations, overlooking single-cell heterogeneity in MSCs. Advanced technologies like single-cell RNA sequencing and spatial transcriptomics enable deeper understanding of MSC senescence mechanisms. While p16 and p21 serve as common transcriptional senescence markers, their expression varies across senescent cells depending on pathological status, tissue location, and microenvironment. Single-cell/nuclear RNA-seq methods effectively study senescence heterogeneity, though each has limitations. Single-cell RNA-seq provides comprehensive transcriptome analysis but may miss larger or sensitive senescent cells. Single-nuclear RNA-seq captures all cell types but with potentially reduced sensitivity due to lower nuclear mRNA abundance. Spatial transcriptomics offers advantages by capturing all senescent cell types while providing crucial spatial information, facilitating more accurate identification and characterization of senescent cells and potential new markers [105].

6. Conclusion

This review examined the biological characteristics, types, and molecular mechanisms of MSC senescence, with particular emphasis on recent advances in safe, low-toxicity herbal medicines and their compounds in combating MSC senescence. Research has demonstrated that herbal medicines can mitigate MSC senescence by influencing DNA damage, telomere length, and epi-

Table 1 Summary the mechanism of traditional Chinese medicine on inhibiting senescence of MSC.

Function	Compound	Classification	Models	Mechanism	Ref.
Mitochondrial function	Ginsenoside Rg1	Terpenoids	MSC	PI3K/AKT-NRF2↑	38
	Ginsenoside Rg2	Terpenoids	Porcine MSCs	AMPK↑, NRF2↑	83
	AOF	Chinese medicine	ADMSC	NRF2↑, ROS↓	69
	Ganoderic acid D	Terpenoids	HAMSC	PERK/NRF2↑ CaM/CaMKII/Nrf2↑	84–85
	Resveratrol	Polyphenol	MSC	HMOX1↑, SOD3↑ ROS↓	87
	Genistein	Isoflavone	MSC	ERRα↑ SIRT3↑ PGC1α↑	95
	UP-Ex	Chinese medicine	HMSC	ROS↓ SOD1, SOD2↑ CAT↑	99
Autophagy	Curcumin	Polyphenols	Canine BMSC	LC3II/ LC3I↑ ATG7↑ATG12↑	42
	Camphorquinone	Terpenoids	HMSC	AMPK/SIRT1↑	61
Telomerase activity	Pistachio	Chinese medicine	MSC	TRF1, RAP1↑	100
	JingSi herbal	Chinese medicine	ADMSC	TERT↑	72
	Curcumin	Phenols	Rats ADMSC	TERT↑	90
Heterochromatin architecture	Quercetin	Flavonoid	WS-HMSC	Heterochromatin architecture ↑	94
	Gallic acid	Benzoic acid	WS-HMSC	H3K9me3↑ LaminB1↑, LAP2β↑	92
SASP	Zuogui Wan	Chinese medicine	MSC	HMGB1, MMP3, IL-6↓	73
	Resveratrol	Polyphenol	MSC	IL1α, IL1β, IL-6 TNFα↓	87
	AOF	Ginger family	ADMSC	NF-κB↓, IL-6↓	69
	HSYA	Safflower	MSC	NF-κB↑, TNF-α↓, IL-1β↓	96
	Ginsenoside Rg1	Terpenoids	hAD-MSC	IGF-I↑	82
Exosome	GLEXG	Chinese medicine	MSC	Type II/X collagen II, SOX9	74

genetic modifications. Additionally, herbal medicines directly decrease ROS levels through enhanced antioxidant enzyme activity, thereby reducing oxidative damage and improving MSC senescence. The review also analyzed current limitations in research regarding herbal medicines and their compounds against MSC senescence, proposed corresponding improvement strategies,

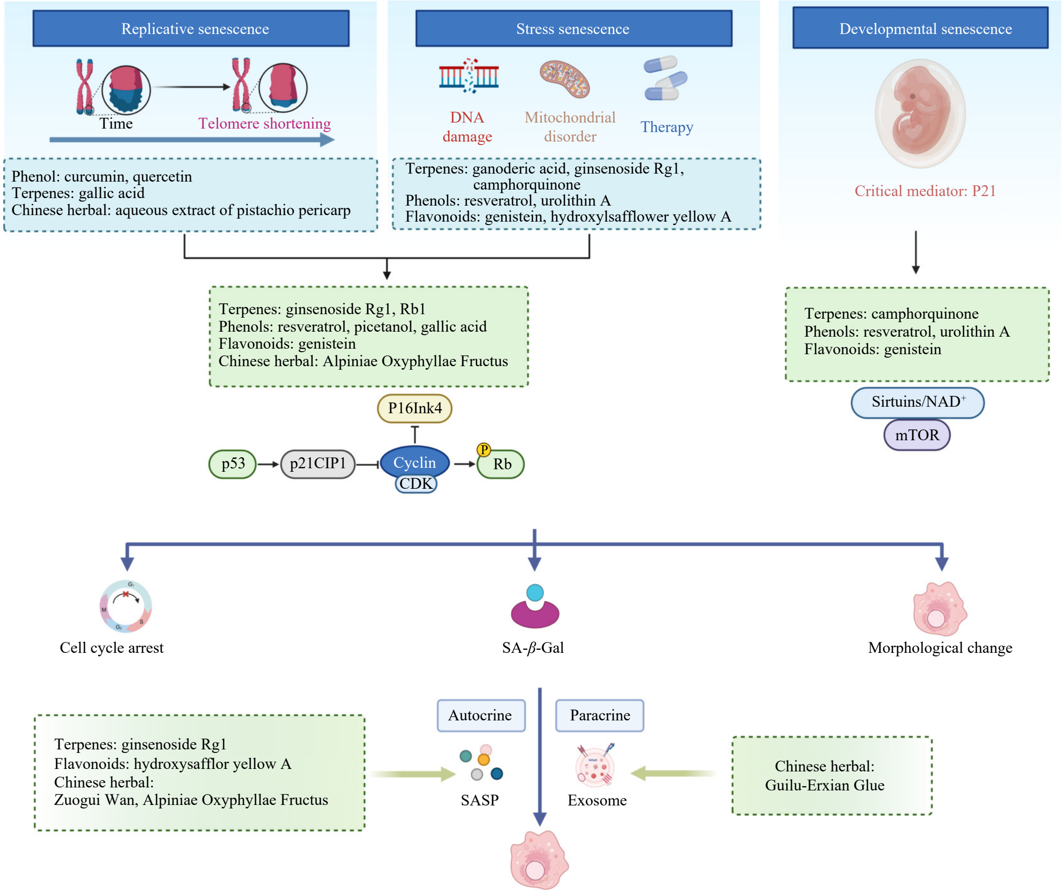

Fig. 5 Effect and mechanism of traditional Chinese medicine on inhibiting senescence of MSCs. The detailed molecular mechanism of inhibition of MSC senescence by herbal medicine is mainly realized through cell cycle arrest mediated by p16, p53 and sirtuins/NAD$^+$, as well as secretion of SASP and exosomes.

and provided perspectives on the future development of anti-MSC senescence therapeutics.

Funding

This research was supported by Zhejiang Provincial Natural Science Foundation of China (No. LQ23H290006), the National Natural Science Foundation of China (No. 82204781), the Key Laboratory of Clinical Cancer Pharmacology and Toxicology Research of Zhejiang Province (No. 2020E10021), Zhejiang Provincial Program for the Cultivation of High-level Innovative Health Talents (No. ZWB-2020-18), and Zhejiang Provincial Traditional Chinese Medicine Science and Technology Project (No. 2023ZR119).

Declaration of competing interest

The authors declare no conflict of interest.

References

1 Potten CS, Loeffler M. Stem cells: attributes, cycles, spirals, pitfalls and uncertainties. Lessons for and from the Crypt. *Development*. 1990;110(4):1001-1020. https://doi.org/10.1242/dev.110.4.1001.

2 Caplan AI. Mesenchymal stem cells. *J Orthop Res*. 1991;9(5):641-650. https://doi.org/10.1002/jor.1100090504.

3 Short B, Brouard N, Occhiodoro-Scott T, et al. Mesenchymal stem cells. *Arch Med Res*. 2003;34(6):565-571. https://doi.org/10.1016/j.arcmed.2003.09.007.

4 Dominici M, Le Blanc K, Mueller I, et al. Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy Position Statement. *Cytotherapy*. 2006;8(4):315-317. https://doi.org/10.1080/14653240600855905.

5 Prager P, Kunz M, Ebert R, et al. Mesenchymal stem cells isolated from the anterior cruciate ligament: characterization and comparison of cells from young and old donors. *Knee Surg Relat Res*. 2018;30(3):193-205. https://doi.org/10.5792/ksrr.17.067.

6 Beane OS, Fonseca VC, Cooper LL, et al. Impact of aging on the regenerative properties of bone marrow, muscle, and adipose-derived mesenchymal stem/stromal cells. *PLoS One*. 2014;9(12):e115963. https://doi.org/10.1371/journal.pone.0115963.

7 Bonab MM, Alimoghaddam K, Talebian F, et al. Aging of mesenchymal stem cell *in vitro*. *BMC Cell Biol*. 2006;7(1):14. https://doi.org/10.1186/1471-2121-7-14.

8 Fossett E, Khan WS. Optimising human mesenchymal stem cell numbers for clinical application: a literature review. *Stem Cells Int*. 2012;2012:465259. https://doi.org/10.1155/2012/465259.

9 Wang Y, Han ZB, Song YP, et al. Safety of mesenchymal stem cells for clinical application. *Stem Cells Int*. 2012;2012:652034. https://doi.org/10.1155/2012/652034.

10 Zhou T, Yuan Z, Weng J, et al. Challenges and advances in clinical applications of mesenchymal stromal cells. *J Hematol Oncol*. 2021;14(1):24. https://doi.org/10.1186/s13045-021-01037-x.

11 Li SH, Guo PD, Wang WJ. Research progress of bone marrow mesenchymal stem cells differentiation into nerve-like cells induced by traditional Chinese medicine. *Chin J Orthop Traumatol*. 2010;23(3):233-235. https://doi.org/10.3969/j.issn.1003-0034.2010.03.029.

12 Chen M, Feng W, Cao H, et al. A traditional Chinese medicine formula extracts stimulate proliferation and inhibit mineralization of human mesenchymal stem cells *in vitro*. *J Ethnopharmacol*. 2009;125(1):75-82. https://doi.org/10.1016/j.jep.2009.06.013.

13 Dong S, Su SB. Advances in mesenchymal stem cells combined with traditional Chinese medicine therapy for liver fibrosis. *J Integr Med*. 2014;12(3):147-155. https://doi.org/10.1016/S2095-4964(14)60022-4.

14 Sun S, Liu F, Fan F, et al. Exploring the mechanism of atherosclerosis and the intervention of traditional Chinese medicine combined with mesenchymal stem cells based on inflammatory targets. *Heliyon*. 2023;9(11):e22005. https://doi.org/10.1016/j.heliyon.2023.e22005.

15 Fu Y, Kong Y, Li J, et al. Mesenchymal stem cells combined with traditional Chinese medicine (Qi-Fang-Bi-Min-Tang) alleviates rodent allergic rhinitis. *J Cell Biochem*. 2020;121(2):1541-1551. https://doi.org/10.1002/jcb.29389.

16 He H, Yang T, Li F, et al. A novel study on the immunomodulatory effect of umbilical cord derived mesenchymal stem cells pretreated with traditional Chinese medicine asarinin. *Int Immunopharmacol*. 2021;100:108054. https://doi.org/10.1016/j.intimp.2021.108054.

17 Zhao H, Luo Y. Traditional Chinese medicine and aging intervention. *Aging Dis*. 2017;8(6):688-690. https://doi.org/10.14336/AD.2017.1002.

18 Su J, Su Q, Hu S, et al. Research progress on the anti-aging potential of the active components of ginseng. *Nutrients*. 2023;15(15):3286. https://doi.org/10.3390/nu15153286.

19 Wang J, Cao B, Zhao H, et al. Emerging roles of *Ganoderma lucidum* in anti-aging. *Aging Dis*. 2017;8(6):691-707. https://doi.org/10.14336/AD.2017.0410.

20 Berezutsky MA, Durnova NA, Vlasova IA. Experimental and clinical studies of mechanisms of the anti-aging effects of chemical compounds in *Astragalus membranaceus*. *Adv Gerontol*. 2019;32(5):702-710. https://doi.org/10.1134/S2079057020020046.

21 Chen G, Huang C, Shi P, et al. Mechanism of Chinese yam for the treatment of aging-related diseases based on network pharmacology. *Eur J Integr Med*. 2021;41:101254. https://doi.org/10.1016/j.eujim.2020.101254.

22 Liu BH, Gu YH, Tu Y, et al. Molecular regulative mechanisms of aging and interventional effects of Chinese herbal medicine. *Chin J Chin Mater Med*. 2017;42(16):3065-3071. https://doi.org/10.19540/j.cnki.cjcmm.20170731.001.

23 Yang YHK, Ogando CR, Wang SC, et al. Changes in phenotype and differentiation potential of human mesenchymal stem cells aging *in vitro*. *Stem Cell Res Ther*. 2018;9(1):131. https://doi.org/10.1186/s13287-018-0876-3.

24 Stolzing A, Jones E, McGonagle D, et al. Age-related changes in human bone marrow-derived mesenchymal stem cells: consequences for cell therapies. *Mech Ageing Dev*. 2008;129(3):163-173. https://doi.org/10.1016/j.mad.2007.12.002.

25 Dimri GP, Lee X, Basile G, et al. A biomarker that identifies senescent human cells in culture and in aging skin *in vivo*. *Proc Natl Acad Sci U S A*. 1995;92(20):9363-9367. https://doi.org/10.1073/pnas.92.20.9363.

26 Brenner AJ, Stampfer MR, Aldaz CM. Increased p16 expression with first senescence arrest in human mammary epithelial cells and extended growth capacity with p16 inactivation. *Oncogene*. 1998;17(2):199-205. https://doi.org/10.1038/sj.onc.1201919.

27 Özcan S, Alessio N, Acar MB, et al. Unbiased analysis of senescence associated secretory phenotype (SASP) to identify common components following different genotoxic stresses. *Aging (Albany NY)*. 2016;8(7):1316-1329. https://doi.org/10.18632/aging.100971.

28 Coussens M, Maresh JG, Yanagimachi R, et al. Sirt1 deficiency attenuates spermatogenesis and germ cell function. *PLoS One*. 2008;3(2):e1571. https://doi.org/10.1371/journal.pone.0001571.

29 Pérez-Garijo A, Steller H. The benefits of aging: cellular senescence in normal development. *EMBO J*. 2014;33(2):99-100. https://doi.org/10.1002/embj.201387401.

30 Schellenberg A, Lin Q, Schüler H, et al. Replicative senescence of mesenchymal stem cells causes DNA-methylation changes which correlate with repressive histone marks. *Aging (Albany NY)*. 2011;3(9):873-888. https://doi.org/10.18632/aging.100391.

31 Zhao Q, Wang XY, Yu XX, et al. Expression of human telomerase reverse transcriptase mediates the senescence of mesenchymal stem cells through the PI3K/AKT signaling pathway. *Int J Mol Med*. 2015;36(3):857-864. https://doi.org/10.3892/ijmm.2015.2284.

32 Larsson LG. Oncogene and tumor suppressor gene-mediated suppression of cellular senescence. *Semin Cancer Biol*. 2011;21(6):367-376. https://doi.org/10.1016/j.semcancer.2011.10.005.

33 Vono R, Garcia EJ, Gaia Spinetti, et al. Oxidative stress in mesenchymal stem cell senescence: regulation by coding and noncoding RNAs. *Antioxid Redox Signal*. 2018;29(9):864-879. https://doi.org/10.1089/ars.2017.7294.

34 Demaria M, O'Leary MN, Chang J, et al. Cellular senescence promotes adverse effects of chemotherapy and cancer relapse. *Cancer Discov*. 2017;7(2):165-176. https://doi.org/10.1158/2159-8290.CD-16-0241.

35 d'Adda di FF. Living on a break: cellular senescence as a DNA-damage response. *Nat Rev Cancer*. 2008;8(7):512-522. https://doi.org/10.1038/nrc2440.

36 Reinhardt HC, Schumacher B. The p53 network: cellular and systemic DNA damage responses in aging and cancer. *Trends Genet*. 2012;28(3):128-136. https://doi.org/10.1016/j.tig.2011.12.002.

37 Zhou L, Chen X, Liu T, et al. Melatonin reverses H_2O_2-induced premature senescence in mesenchymal stem cells *via* the SIRT1-dependent pathway. *J Pineal Res*. 2015;59(2):190-205. https://doi.org/10.1111/jpi.12250.

38 Wang Z, Wang L, Jiang R, et al. Ginsenoside Rg1 prevents bone marrow mesenchymal stem cell senescence *via* NRF2 and PI3K/Akt signaling. *Free Radic Biol Med*. 2021;174:182-194. https://doi.org/10.1016/j.freeradbiomed.2021.08.007.

39 Racz LZ, Racz CP, Pop LC, et al. Strategies for improving bioavailability, bioactivity, and physical-chemical behavior of curcumin. *Molecules*. 2022;27(20):6854. https://doi.org/10.3390/molecules27206854.

40 Fathi E, Charoudeh HN, Sanaat Z, et al. Telomere shortening as a hallmark of stem cell senescence. *Stem Cell Investig*. 2019;6:7. https://doi.org/10.21037/sci.2019.02.04.

41 Cheung HH, Liu X, Canterel-Thouennon L, et al. Telomerase protects werner syndrome lineage-specific stem cells from premature aging. *Stem Cell Rep*. 2014;2(4):534-546. https://doi.org/10.1016/j.stemcr.2014.02.006.

42 Deng J, Ouyang P, Li W, et al. Curcumin alleviates the senescence of canine bone marrow mesenchymal stem cells during *in vitro* expansion by activating the autophagy pathway. *Int J Mol Sci*. 2021;22(21):11356. https://doi.org/10.3390/ijms222111356.

43 Chen K, Ling J, Zhou X, et al. Deciphering the anti-senescence immune paradigm: kidney yin-yang equilibrium in traditional Chinese medicine. *J Holist Integr Pharm*. 2024;5(2):77-89. https://doi.org/10.1016/j.jhip.2024.05.001.

44 Ho TJ, Tsai BCK, Debakshee G, et al. *Ohwia caudata* aqueous extract attenuates senescence in aging adipose-derived mesenchymal stem cells. *Heliyon*. 2024;10(9):e29729. https://doi.org/10.1016/j.heliyon.2024.e29729.

45 Sun Y, Zhang H, Qiu T, et al. Epigenetic regulation of mesenchymal stem cell aging through histone modifications. *Genes Dis*. 2022;10(6):2443-2456. https://doi.org/10.1016/j.gendis.2022.10.030.

46 Bork S, Pfister S, Witt H, et al. DNA methylation pattern changes upon long-term culture and aging of human mesenchymal stromal cells. *Aging Cell*. 2010;9(1):54-63. https://doi.org/10.1111/j.1474-9726.2009.00535.x.

47 Li Z, Liu C, Xie Z, et al. Epigenetic dysregulation in mesenchymal stem cell aging and spontaneous differentiation. *PLoS One*. 2011;6(6):e20526. https://doi.org/10.1371/journal.pone.0020526.

48 Wang J, Liu L, Ding Z, et al. Exogenous NAD^+ postpones the D-Gal-induced senescence of bone marrow-derived mesenchymal stem cells *via* sirt1 signaling. *Antioxidants*. 2021;10(2):254. https://doi.org/10.3390/antiox10020254.

49 Qi J, Xue Q, Kuang L, et al. Berberine alleviates cisplatin-induced acute kidney injury by regulating mitophagy *via* PINK1/Parkin pathway. *Transl Androl Urol*. 2020;9(4):1712-1724. https://doi.org/10.21037/tau-20-1129.

50 Shin JH, Jeon HJ, Park J, et al. Epigallocatechin-3-gallate prevents oxidative stress-induced cellular senescence in human mesenchymal stem cells *via* Nrf2. *Int J Mol Med*. 2016;38(4):1075-1082. https://doi.org/10.3892/ijmm.2016.2694.

51 Maharajan N, Cho GW. Camphorquinone promotes the antisenescence effect *via* activating AMPK/SIRT1 in stem cells and D-galactose-induced aging mice. *Antioxidants*. 2021;10(12):1916. https://doi.org/10.3390/antiox10121916.

52 Hu C, Zhao L, Peng C, et al. Regulation of the mitochondrial reactive oxygen species: strategies to control mesenchymal stem cell fates *ex vivo* and *in vivo*. *J Cell Mol Med*. 2018;22(11):5196-5207. https://doi.org/10.1111/jcmm.13835.

53 Stab BR, Martinez L, Grismaldo A, et al. Mitochondrial functional changes characterization in young and senescent human adipose derived MSCs. *Front Aging Neurosci*. 2016;8:299. https://doi.org/10.3389/fnagi.2016.00299.

54 Ren L, Chen X, Chen X, *et al*. Mitochondrial dynamics: fission and fusion in fate determination of mesenchymal stem cells. *Front Cell Dev Biol*. 2020;8:580070. https://doi.org/10.3389/fcell.2020.580070.

55 Branco A, Moniz I, Ramalho-Santos J. Mitochondria as biological targets for stem cell and organismal senescence. *Eur J Cell Biol*. 2023;102(2):151289. https://doi.org/10.1016/j.ejcb.2023.151289.

56 Yan W, Diao S, Fan Z. The role and mechanism of mitochondrial functions and energy metabolism in the function regulation of the mesenchymal stem cells. *Stem Cell Res Ther*. 2021;12(1):140. https://doi.org/10.1186/s13287-021-02194-z.

57 Ashrafi G, Schwarz TL. The pathways of mitophagy for quality control and clearance of mitochondria. *Cell Death Differ*. 2013;20(1):31-42. https://doi.org/10.1038/cdd.2012.81.

58 Wang Y, Liu Y, Chen E, et al. The role of mitochondrial dysfunction in mesenchymal stem cell senescence. *Cell Tissue Res*. 2020;382(3):457-462. https://doi.org/10.1007/s00441-020-03272-z.

59 Poole AC, Thomas RE, Andrews LA, et al. The PINK1/Parkin pathway regulates mitochondrial morphology. *Proc Natl Acad Sci U S A*. 2008;105(5):1638-1643. https://doi.org/10.1073/pnas.0709336105.

60 Lin Q, Chen J, Gu L, et al. New insights into mitophagy and stem cells. *Stem Cell Res Ther*. 2021;12(1):452. https://doi.org/10.1186/s13287-021-02520-5.

61 Maharajan N, Ganesan CD, Moon C, et al. Licochalcone D ameliorates oxidative stress-induced senescence *via* AMPK activation. *Int J Mol Sci*. 2021;22(14):7324. https://doi.org/10.3390/ijms22147324.

62 Ashrafizadeh M, Ahmadi Z, Mohammadinejad R, et al. Curcumin activates the Nrf2 pathway and induces cellular protection against oxidative injury. *Curr Mol Med*. 2020;20(2):116-133. https://doi.org/10.2174/1566524019666191016150757.

63 Revuelta M, Matheu A. Autophagy in stem cell aging. *Aging Cell*. 2017;16(5):912-915. https://doi.org/10.1111/acel.12655.

64 Zhang D, Chen Y, Xu X, et al. Autophagy inhibits the mesenchymal stem cell aging induced by D-galactose through ROS/JNK/p38 signalling. *Clin Exper Pharmacol Physiol*. 2020;47(3):466-477. https://doi.org/10.1111/1440-1681.13207.

65 Ma Y, Qi M, An Y, et al. Autophagy controls mesenchymal stem cell properties and senescence during bone aging. *Aging Cell*. 2018;17(1):e12709. https://doi.org/10.1111/acel.12709.

66 Rastaldo R, Vitale E, Giachino C. Dual role of autophagy in regulation of mesenchymal stem cell senescence. *Front Cell Dev Biol*. 2020;8:276. https://doi.org/10.3389/fcell.2020.00276.

67 Zhang D, Lin J, Wang Y, et al. Effects of resveratrol on aging of mesenchymal stem cells and its mechanism. *J Zhejiang Univer (Med Sci)*. 2019;48(6):617-624. https://doi.org/10.3785/j.issn.1008-9292.2019.12.05.

68 Chang YM, Chang HH, Kuo WW, et al. Anti-apoptotic and pro-survival effect of Alpinate Oxyphyllae Fructus (AOF) in a D-galactose-induced aging heart. *Int J Mol Sci*. 2016;17(4):466. https://doi.org/10.3390/ijms17040466.

69 Lin HJ, Ramesh S, Chang YM, et al. D-galactose-induced toxicity associated senescence mitigated by alpinate oxyphyllae fructus fortified adipose-derived mesenchymal stem cells. *Environ Toxicol*. 2021;36(1):86-94. https://doi.org/10.1002/tox.23014.

70 Chang YM, Asokan SM, Tsai CT, et al. *Alpinate oxyphyllae* extracts enhance the longevity and homing of mesenchymal stem cells and augment their protection against senescence in H9c2 cells. *J Cell Physiol*. 2019;234(7):12042-12050. https://doi.org/10.1002/jcp.27867.

71 Lu PH, Tseng CW, Lee JL, et al. Jing Si Herbal Drink as a prospective adjunctive therapy for COVID-19 treatment: molecular evidence and mechanisms. *Pharmacol Res Modern Chin Med*. 2022;2:100024. https://doi.org/10.1016/j.prmcm.2021.100024.

72 Shibu MA, Lin YJ, Chiang CY, et al. Novel anti-aging herbal formulation Jing Si displays pleiotropic effects against aging associated disorders. *Biomed Pharmacother*. 2022;146:112427. https://doi.org/10.1016/j.biopha.2021.112427.

73 Kang X, Chen L, Yang S, et al. Zuogui Wan slowed senescence of bone marrow mesenchymal stem cells by suppressing Wnt/*β*-catenin signaling. *J Ethnopharmacol*. 2022;294:115323. https://doi.org/10.1016/j.jep.2022.115323.

74 Yang YH, Wen CS, Kuo YL, et al. GuiLu-ErXian Glue extract promotes mesenchymal stem cells (MSC)-induced chondrogenesis *via* exosomes release and delays aging in the MSC senescence process. *J Ethnopharmacol*. 2023;317:116784. https://doi.org/10.1016/j.jep.2023.116784.

75 Gershenzon J, Dudareva N. The function of terpene natural products in the natural world. *Nat Chem Biol*. 2007;3(7):408-414. https://doi.org/10.1038/nchembio.2007.5.

76 Leung KW, Wong AST. Pharmacology of ginsenosides: a literature review. *Chin Med*. 2010;5:20. https://doi.org/10.1186/1749-8546-5-20.

77 Li X, Chu S, Lin M, et al. Anticancer property of ginsenoside Rh2 from ginseng. *Eur J Med Chem*. 2020;203:112627. https://doi.org/10.1016/j.ejmech.2020.112627.

78 Sun Y, Liu Y, Chen K. Roles and mechanisms of ginsenoside in cardiovascular diseases: progress and perspectives. *Sci Chin Life Sci*. 2016;59(3):292-298. https://doi.org/10.1007/s11427-016-5007-8.

79 Tian T, Ko CN, Li D, et al. The anti-aging mechanism of ginsenosides with medicine and food homology. *Food Funct*. 2023;14(20):9123-9136. https://doi.org/10.1039/d3fo02580b.

80 Lou T, Huang Q, Su H, et al. Targeting sirtuin 1 signaling pathway by ginsenosides. *J Ethnopharmacol*. 2021;268:113657. https://doi.org/10.1016/j.jep.2020.113657.

81 Wang Z, Jiang R, Wang L, et al. Ginsenoside Rg1 improves differentiation by inhibiting senescence of human bone marrow mesenchymal stem cell *via* GSK-3β and *β*-catenin. *Stem Cells Int*. 2020;2020:2365814. https://doi.org/10.1155/2020/2365814.

82 Ling L, Shu H, Huang Y, et al. Effects of ginsenoside Rg1 on the biological behavior of human amnion-derived mesenchymal stem/stromal cells (hAD-MSCs). *Stem Cells Int*. 2023;2023:7074703. https://doi.org/10.1155/2023/7074703.

83 Che L, Zhu C, Huang L, et al. Ginsenoside Rg2 promotes the proliferation and stemness maintenance of porcine mesenchymal stem cells through autophagy induction. *Foods*. 2023;12(5):1075. https://doi.org/10.3390/foods12051075.

84 Xu Y, Yuan H, Luo Y, et al. Ganoderic acid D protects human amniotic mesenchymal stem cells against oxidative stress-induced senescence through the PERK/NRF2 signaling pathway. *Oxid Med Cell Longev*. 2020;2020:8291413. https://doi.org/10.1155/2020/8291413.

85 Yuan H, Xu Y, Luo Y, et al. Ganoderic acid D prevents oxidative stress-induced senescence by targeting 14-3-3ε to activate CaM/CaMKII/NRF2 signaling pathway in mesenchymal stem cells. *Aging Cell*. 2022;21(9):e13686. https://doi.org/10.1111/acel.13686.

86 Ertani A, Pizzeghello D, Francioso O, et al. Biological activity of vegetal extracts containing phenols on plant metabolism. *Molecules*. 2016;21(2):205. https://doi.org/10.3390/molecules21020205.

87 Ali D, Chen L, Kowal JM, et al. Resveratrol inhibits adipocyte differentiation and cellular senescence of human bone marrow stromal stem cells. *Bone*. 2020;133:115252. https://doi.org/10.1016/j.bone.2020.115252.

88 Alessio N, Squillaro T, Lettiero I, et al. Biomolecular evaluation of piceatannol's effects in counteracting the senescence of mesenchymal stromal cells: a new candidate for senotherapeutics? *Int J Mol Sci*. 2021;22(21):11619. https://doi.org/10.3390/ijms222111619.

89 Lei L, Chen J, Zhao Y, et al. Resveratrol attenuates senescence of adipose-derived mesenchymal stem cells and restores their paracrine effects on promoting insulin secretion of INS-1 cells through Pim-1. *Eur Rev Med Pharmacol Sci*. 2016;20(6):1203-1213.

90 Pirmoradi S, Fathi E, Farahzadi R, et al. Curcumin affects adipose tissue-derived mesenchymal stem cell aging through *TERT* gene expression. *Drug Res*. 2018;68(4):213-221. https://doi.org/10.1055/s-0043-119635.

91 Shi PZ, Wang JW, Wang PC, et al. Urolithin a alleviates oxidative stress-induced senescence in nucleus pulposus-derived mesenchymal stem cells through SIRT1/PGC-1α pathway. *World J Stem Cells*. 2021;13(12):1928. https://doi.org/10.4252/wjsc.v13.i12.1928.

92 Shan H, Geng L, Jiang X, et al. Large-scale chemical screen identifies gallic acid as a geroprotector for human stem cells. *Protein Cell*. 2022;13(7):532-539. https://doi.org/10.1007/s13238-021-00872-5.

93 Martens S, Mithöfer A. Flavones and flavone synthases. *Phytochemistry*. 2005;66(20):2399-2407. https://doi.org/10.1016/j.phytochem.2005.07.013.

94 Geng L, Liu Z, Zhang W, et al. Chemical screen identifies a geroprotective role of quercetin in premature aging. *Protein Cell*. 2019;10(6):417-435. https://doi.org/10.1007/s13238-018-0567-y.

95 Li M, Yu Y, Xue K, et al. Genistein mitigates senescence of bone marrow mesenchymal stem cells *via* ERRα-mediated mitochondrial biogenesis and mitophagy in ovariectomized rats. *Redox Biol*. 2023;61:102649. https://doi.org/10.1016/j.redox.2023.102649.

96 Song X, Wang J, Zhang Y, et al. Protective effect of hydroxysafflor yellow A on MSCs against senescence induced by D-galactose. *Chin Herb Med*. 2023;15(1):86-93. https://doi.org/10.1016/j.chmed.2022.06.011.

97 Sasidharan S, Chen Y, Saravanan D, *et al*. Extraction, isolation and characterization of bioactive compounds from plants' extracts. *Afr J Tradit Complement Altern Med*, 2011;8(1):1-10. https://doi.org/10.4314/ajtcam.v8i1.60483.

98 Opara EI, White KN, Uvere PO. Chemical analyses and therapeutic properties of plant extracts. *Molecules*. 2025;30(3):610. https://doi.org/10.3390/molecules30030610.

99 Jeong SG, Oh YS, Joe IS, et al. Functional restoration of replicative senescent mesenchymal stem cells by the brown alga *Undaria pinnatifida*. *Anim Cells Syst*. 2017;21(2):108-114. https://doi.org/10.1080/19768354.2017.1292951.

100 Askari N, Asadi F, Nazer A, et al. Anti-aging effects of the pistachio extract on mesenchymal stem cells proliferation and telomerase activity. *Arch Gerontol Geriatr*. 2023;111:105016. https://doi.org/10.1016/j.archger.2023.105016.

101 Weng Z, Wang Y, Ouchi T, et al. Mesenchymal stem/stromal cell senescence: hallmarks, mechanisms, and combating strategies. *Stem Cells Transl Med*. 2022;11(4):356-371. https://doi.org/10.1093/stcltm/szac004.

102 Liu R, Li X, Huang N, Fan M,et al. Toxicity of traditional Chinese medicine herbal and mineral products. *Adv Pharmacol*. 2020;87:301-346. https://doi.org/10.1016/bs.apha.2019.08.001.

103 Muralikumar M, Manoj JS, Ganesan H, et al. Current understanding of the mesenchymal stem cell-derived exosomes in cancer and aging. *Biotechnol Rep*. 2021;31:e00658. https://doi.org/10.1016/j.btre.2021.e00658.

104 Li X, Liu Z, Liao J, et al. Network pharmacology approaches for research of traditional Chinese medicines. *Chin J Nat Med*. 2023;21(5):323-332. https://doi.org/10.1016/S1875-5364(23)60429-7.

105 Qiu Z, Li S, Luo M, et al. Detection of differentially expressed genes in spatial transcriptomics data by spatial analysis of spatial transcriptomics: a novel method based on spatial statistics. *Front Neurosci*. 2022;16:1086168. https://doi.org/10.3389/fnins.2022.1086168.