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Review

# Advances in modulating the *in vivo* fate and therapeutic efficacy of mesenchymal stem cells with natural products

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## ABSTRACT

Mesenchymal stem cells (MSCs) are widely utilized in disease treatment and regenerative medicine due to their potent immunomodulatory properties and capacity for tissue repair. However, limitations—including insufficient migratory capacity, suboptimal survival, proliferation, differentiation potential, and variable immunomodulatory responses—significantly hinder their clinical translation and therapeutic impact. Natural products have been shown to enhance MSC homing, stress resilience, immune regulation, and lineage-specific differentiation through multi-target mechanisms, thereby emerging as promising, safe, and practical strategies to improve the *in vivo* performance of MSC-based therapies. This review examines the key translational challenges associated with MSCs, elucidates the mechanistic basis by which natural products regulate the *in vivo* fate of MSCs, and explores the potential of integrating natural product adjuvants with MSC therapy for enhanced clinical outcomes.

## 1. Introduction

Mesenchymal stem cells (MSCs), which can be isolated from various tissues such as bone marrow, umbilical cord, adipose tissue, and dental pulp, possess the capacity for self-renewal and multilineage differentiation, with low tumorigenic potential and immunogenicity [1, 2]. In 1995, the first Phase I trial confirmed the feasibility of *ex vivo* culture expansion and intravenous infusion of autologous MSCs [3]. Since then, numerous clinical trials have demonstrated that MSCs exert therapeutic effects through homing, paracrine signaling, cell-cell interactions, and differentiation into target tissue lineages in regenerative medicine and disease treatment. However, most registered MSC-related clinical trials worldwide remain in Phase I or Phase II. Factors limiting the safety and efficacy of MSCs in clinical applications include, but are not limited to, inadequate *in vivo* homing capacity, suboptimal survival, high cellular heterogeneity, and inconsistent immune responses, which collectively challenge clinical translation [4, 5].

Natural products, widely distributed in nature, refer to bioactive chemical compounds and their derivatives extracted from animals, plants, microbes, or endogenous constituents in humans and animals—such as phenols, flavonoids, quinones, terpenoids, alkaloids, glycosides, and steroids—many of which exhibit anti-oxidant, anti-inflammatory, anti-apoptotic, and antiviral properties [6–9]. Numerous studies indicate that these compounds can enhance MSC proliferation and differentiation, inhibit senescence, and improve *in vivo* homing, damage tolerance, and immunomodulatory functions. Furthermore, recent years have seen increasing application of natural products such as trehalose, betaine, hyaluronic acid, and chitosan in MSC cryopreservation and *in vivo* delivery. Additionally, clinical exploration of MSCs combined with natural herbal formulations has revealed substantial potential in diverse areas, including inflammation suppression, aging mitigation, cardiac and cerebrovascular protection, and tissue regeneration.

Compared with existing engineering or priming strategies, natural products offer a novel approach to enhancing the *in vivo* therapeutic efficacy of MSCs, leveraging their intrinsic biological activities and advantages of multi-target modulation, cost-effectiveness, and safety.

## 2. Status of MSC products development

Owing to their potent immunosuppressive and regenerative properties, MSC-based therapies have become prominent in cell therapy [10, 11]. On December 18, 2024, Ryoncil was approved by the Food and Drug Administration (FDA) as the first universal MSC product in the United States, significantly motivating research groups and biotechnology companies to pursue standardized preclinical and clinical studies aimed at regulatory approval. According to the National Institutes of Health (https://clinicaltrials.gov/), 1914 clinical trials involving “mesenchymal stem cells” were registered globally as of December 1, 2024. These trials span multiple indications, including graft-versus-host disease (GvHD), autoimmune disorders such as rheumatoid arthritis and

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inflammatory bowel disease, neurodegenerative conditions like multiple sclerosis and amyotrophic lateral sclerosis (ALS), cardiovascular diseases such as ischemic heart disease, liver cirrhosis, and pulmonary disorders, including chronic obstructive pulmonary disease (COPD).

MSCs represent a promising therapeutic modality for refractory diseases and demonstrate considerable clinical potential. Nevertheless, research data reveal that only 5% of the 1914 trials have advanced to Phase III, and merely 1% have reached Phase IV (Fig. 1). Consequently, the therapeutic efficacy of MSCs requires further validation. For instance, in a study involving 62 patients with moderately severe COPD who received Prochymal infusion and were followed for two years, no significant difference in outcomes was observed between the Prochymal and placebo groups [12]. Moreover, post-marketing clinical trials of MSC products do not always succeed. Alofisel, approved by the European Medicines Agency (EMA) in 2018 for treating complex perianal fistulas in Crohn's disease patients, failed to meet its primary endpoint in a subsequent randomized, placebo-controlled trial and was withdrawn from the European Union on December 13, 2024 (ClinicalTrials.gov; No.: NCT03279081). These findings suggest that the underlying cellular and molecular mechanisms of MSC action in certain complex diseases remain poorly understood, necessitating further optimization of current therapeutic strategies.

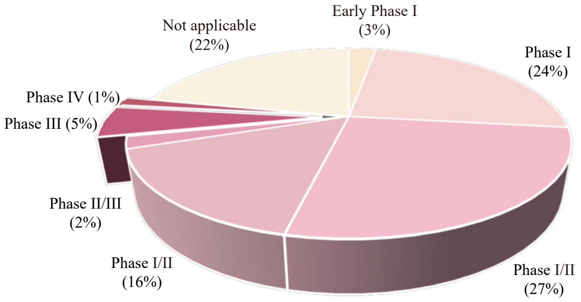

**Fig. 1** Clinical trials phases of MSCs. There have been 1914 registered studies globally on *clinicaltrials.gov* by searching keywords "mesenchymal stem cells" or "mesenchymal stromal cells" up to December 1, 2024, including 50 early phase Ⅰ, 465 Phase Ⅰ, 509 Phase Ⅰ/Ⅱ, 307 Phase Ⅱ, 39 Phase Ⅱ/Ⅲ, 101 Phase Ⅲ, 28 Phase Ⅳ, and 415 not applicable trials.

### 2.1. Problems to be solved in the clinical application of MSCs

Research indicates that clinical trial success is closely associated with donor source, tissue origin, production and preparation methods, formulation types, and *in vivo* fate of MSCs (Fig. 2) [5, 13]. MSCs derived from different donors and tissues exhibit considerable heterogeneity in differentiation potential and functional characteristics [14]. Moreover, MSCs are typically expanded *in vitro* to meet industrial-scale and clinical demands, a process that may induce cellular senescence and downregulate genes associated with proliferation and differentiation, such as PCNA and CDK1 [15]. Senescent MSCs not only display diminished regenerative capacity but also impair physiological functions in healthy mice, including locomotor activity and grip strength [16].

Following transplantation, MSCs encounter challenges posed by the complex pathological microenvironment, resulting in low homing efficiency and limited survival, thereby impeding effective inflammation regulation and tissue repair. For example, intravenously administered $^{111}$In-oxine-labeled MSCs in patients with decompensated cirrhosis are initially trapped in the lungs [17]. In children with osteogenesis imperfecta, the homing efficiency of MSCs in bone, bone marrow, and skin was found to be less than 1% [18]. Additionally, MSCs are susceptible to oxidative stress, leading to autologous apoptosis [19]. A randomized controlled Phase IIa clinical trial on MSC therapy for acute respiratory distress syndrome identified poor MSC survival as a key factor contributing to suboptimal therapeutic outcomes [20].

Furthermore, the immunomodulatory function of MSCs in innate and adaptive immune responses depends on their responsiveness to the inflammatory microenvironment. Variability in this responsiveness significantly limits therapeutic consistency [21]. Li et al. [22] demonstrated that MSCs effectively suppress T cell proliferation when strongly activated by inflammatory stimuli. Conversely, under attenuated responsiveness, MSCs secrete chemokines that recruit lymphocytes and exacerbate inflammation, indicating that the immunomodulatory behavior of MSCs is highly dependent on the disease stage and inflammatory context of the host.

In conclusion, while MSCs hold significant potential for disease treatment and regenerative medicine, addressing the aforementioned challenges through rigorous research and methodological innovation is essential for successful clinical translation.

### 2.2. Unique advantages of natural products in regulating MSCs

Cell modification strategies, including genetic engineering, hypoxic preconditioning, small-molecule priming, and biomaterial-based delivery systems, have emerged as key approaches to enhance the *in vivo* therapeutic efficacy of MSCs [23, 24]. However, significant challenges hinder their clinical translation. Genetic modification poses risks of insertional mutagenesis, off-target effects, and immune rejection [25, 26]; hypoxic and pharmacological priming yield inconsistent outcomes, with prolonged hypoxia potentially inducing senescence or apoptosis in MSCs [27, 28], and biomaterial applications face limitations due to biocompatibility concerns, technical complexity, and high costs [29, 30]. Therefore, safer and more feasible strategies are urgently needed to overcome

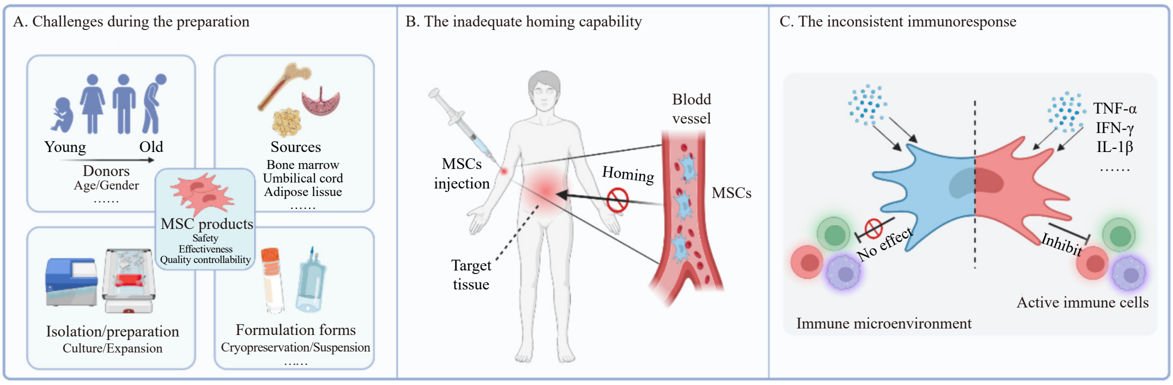

**Fig. 2** Problems to be solved in the clinical application of MSCs. (A) The influence of donors, source, production and preparation processes, and formulation forms on MSCs. (B) The *in vivo* homing capability of MSCs is relatively weak. (C) The immune response ability of MSCs within the disease microenvironment shows inconsistency.

these limitations and advance the clinical application of MSC-based therapies.

Natural products—including phenols, flavonoids, quinones, terpenoids, alkaloids, glycosides, and steroids—are widely available in nature and generally exhibit high biocompatibility along with anti-oxidant, anti-inflammatory, anti-apoptotic, and anti-viral properties, enabling multi-target therapeutic effects through diverse signaling pathways [31]. Accumulating evidence indicates that natural compounds can safely regulate the *in vivo* fate of MSCs by inhibiting cellular senescence, enhancing homing and engraftment, improving immunomodulatory capacity, promoting lineage-specific differentiation, and facilitating tissue regeneration, thereby augmenting MSC efficacy in treating refractory diseases. For instance, ferulic acid preserves MSC self-renewal capacity [32] and enhances their ability to ameliorate liver fibrosis [33], naringin promotes osteogenic differentiation by modulating the immune microenvironment [34]; dendrobium officinale polysaccharides (DOP) mitigate oxidative stress to balance osteogenic and adipogenic differentiation of MSCs [35]; and salidroside strengthens MSC-mediated repair of brain tissue injury [36], with biomaterials incorporating this compound shown to promote osteogenic differentiation [37]. Collectively, natural products offer a promising approach to MSC modulation, combining multi-target regulation, safety, cost-effectiveness, and operational simplicity to improve *in vivo* therapeutic performance.

## 3. The *in vivo* fate modulation of MSCs with natural products and the underlying mechanisms

The modulation of MSC *in vivo* fate by natural products—primarily herbal extracts and traditional formulae—is characterized by synergistic actions across multiple molecular targets and signaling pathways. These compounds not only enhance MSC migration and homing but also reduce senescence during manufacturing and protect against *in vivo* stressors, thereby improving colonization at target tissues. Furthermore, natural products activate MSCs to modulate the local immune microenvironment, attenuate inflammation, and amplify their regenerative potential through differentiation into functional cell types and secretion of trophic factors that support damaged tissue repair (Table 1, Fig. 3).

### 3.1. Enhance the migrating and homing capability of MSCs

Directional homing of MSCs is a key prerequisite for regulating inflammation and facilitating tissue repair at injury sites; thus, limited homing efficiency significantly restricts their *in vivo* therapeutic efficacy [68, 69]. Natural herbal extracts, such as salidroside [38] and icariin [39], enhance MSC migration by inducing actin polymerization. Additionally, the stromal cell-derived factor-1 (SDF-1)/C-X-C chemokine receptor type 4 (CXCR4) axis is a well-established signaling pathway mediating MSC homing [70–72]. Studies indicate that natural products enhance MSC homing through a dual regulatory mechanism: upregulation of CXCR4 expression on MSCs and stimulation of SDF-1 secretion in injured tissues. Notably, various herbal extracts significantly elevate CXCR4 levels in MSCs. For instance, cyasterone enhances bone MSC (BMSC) migration *in vitro* by upregulating CXCR4 expression [40]. Pretreatment with a tanshinone IIA-astragaloside IV combination promotes MSC homing to the ischemic myocardium in rats with acute myocardial infarction (AMI) by increasing CXCR4 expression, potentially supporting synergistic pretreatment strategies [41].

Compared to single-component extracts, traditional herbal formulations that promote blood circulation—such as Bushen Huoxue recipe and Guanxin Danshen formulation—exhibit more comprehensive regulatory effects. The Bushen Huoxue recipe enhances BMSC migration by upregulating CXCR4 expression and increasing SDF-1 levels in the ovaries of mice with premature ovarian insufficiency, thereby promoting endogenous BMSC homing [42]. Similarly, Guanxin Danshen formulation increases MSC homing by elevating SDF-1 levels in the ischemic myocardium of AMI rats, leading to improved angiogenesis and cardiac function [43]. This “homing-repair” synergy may underlie its superior efficacy compared to CXCR4 agonists, as multicomponent formulations may better adapt to dynamically changing microenvironments in complex diseases.

In summary, natural products significantly enhance MSC homing to damaged tissues—an essential factor for *in vivo* therapeutic success. However, current research remains predominantly focused on the SDF-1/CXCR4 axis, despite evidence of disease-specific chemokine involvement. For example, recent studies have highlighted the critical role of the C-X-C motif chemokine ligand 10 (CXCL10)/CXCR3 axis in MSC homing to kidneys in lupus nephritis [73]. Our laboratory is currently investigating how natural products modulate the CXCL10/CXCR3 axis, aiming to inform strategies for improving MSC homing across diverse pathological conditions.

### 3.2. Improve the colonizing ability of MSCs

Senescent MSCs resulting from production, preparation, or exposure to hostile *in vivo* microenvironments exhibit reduced therapeutic efficacy [16, 19]. Senescent or damaged MSCs are characterized by cell cycle arrest, impaired autophagy, accumulation of $\beta$-galactosidase ($\beta$-gal), and elevated reactive oxygen species (ROS) [74, 75]; collectively, these factors compromise MSC colonization potential.

Natural herbal extracts mitigate senescence by reducing $\beta$-gal activity and downregulating p53, p21, and p16 expression. Autophagy plays a crucial role in maintaining intracellular homeostasis by enabling the degradation and recycling of cellular components [76, 77]. Curcumin activates autophagy to alleviate BMSC senescence and suppresses messenger ribonucleic acid (mRNA) expression of *interleukin-6* (*IL-6*) and *tumor necrosis factor α* (*TNF-α*), thereby inhibiting the senescence-associated secretory phenotype (SASP) [44]. Excessive ROS induce oxidative stress, including telomere shortening in MSCs [78]. Jujuboside A [45] and DOP [35] activate the nuclear factor erythroid 2-related factor 2 (Nrf2)/heme oxygenase-1 (HO-1) pathway to counteract oxidative damage in BMSCs. Licochalcone A reduces ROS levels and extends telomeres, supporting sustained MSC proliferation [46]. These extracts also inhibit apoptosis: myricetin [47] and baicalin [48] attenuate drug-induced MSC apoptosis. *In vivo* experiments show that salidroside pretreatment reduces hyperglycemia-induced ROS accumulation and MSC apoptosis, significantly accelerating wound healing in diabetic mice [38].

Collectively, natural herbal extracts demonstrate strong antioxidant and anti-apoptotic properties. Moreover, herbal formulations also improve MSC colonization. A novel formulation containing *Artemisia argyi*, *Ohwia caudate*, and *Ophiopogon japonicas* ameliorates cell cycle arrest in adipose-derived mesenchymal stem cells (AD-MSCs) [49]. Tongxinluo formulation priming improves MSC survival under hypoxia by upregulating *hypoxia-inducible factor-1α* (*HIF-1α*) mRNA expression, reducing infarct size, and promoting cardiac recovery in AMI rats [50].

Given that senescence during preparation and oxidative stress upon transplantation are unavoidable challenges, integrating natural products into clinical protocols may enhance MSC engraftment and therapeutic outcomes.

### 3.3. Promote the immunomodulation of MSCs

The responsiveness of MSCs to inflammatory cues in the dis-

**Table 1** Mechanisms in modulating the *in vivo* fate of MSCs with natural products.

| Effect | Natural products | Category | MSCs source | Mechanism | Result | Ref. |
|---|---|---|---|---|---|---|
| Enhance homing capability | Salidroside | Natural herbal extract | Mouse | Promote F-actin polymerization and upregulate HGF and FGF2 | Improve the migration potential impaired by hyperglycemia of MSCs | 38 |
| | Icariin | Natural herbal extract | Rabbit bone marrow | Promote actin polymerization through the MAPK pathway | Promote the homing of MSCs to the knees in cartilage-defect rabbits | 39 |
| | Cyasterone | Natural herbal extract | Mouse bone marrow | Upregulate CXCR4, SDF-1, ROCK2 | Promote the *in vitro* migration of MSCs | 40 |
| | Tanshinone IIA and Astragaloside IV | Natural herbal extract | Mouse bone marrow | Upregulate CXCR4 expression | Promote the homing of MSCs to ischemic myocardium in rats with acute myocardial infarction | 41 |
| | Bushen Huoxue recipe | Natural herbal formulation | Mouse bone marrow | Upregulate CXCR4 expression | Promote the homing of endogenous MSCs to the ovary in mice with premature ovarian failure | 42 |
| | Guanxin Danshen Formulation | Natural herbal formulation | Rat bone marrow | Upregulate SDF-1 expression in ischemic myocardium | Promote the homing of MSCs to ischemic myocardium in rats with acute myocardial infarction | 43 |
| Inhibit senescence and apoptosis | Curcumin | Natural herbal extract | Dog bone marrow | Upregulate ATG7, ATG12, LC3-Ⅱ/LC3-Ⅰ, SOX-2 and Nanog, downregulate p62, $\beta$-gal, p16, p21, IL-6 and TNF-α | Activate the autophagy to inhibit the senescence of MSCs | 44 |
| | Jujuboside A | Natural herbal extract | Human umbilical cord | Activate the Nrf2/HO-1 pathway to upregulate Bcl-2 and downregulate Bax, Caspase3 expression | Alleviate oxidative stress damage of MSCs | 45 |
| | Dendrobium officinale polysaccharide | Natural herbal extract | Mouse bone marrow | Activate the Nrf2/HO-1 pathway | | 35 |
| | Licochalcone A | Natural herbal extract | Human adipose | Downregulate $\beta$-gal, p53, p21, p16, and ROS, lengthen telomere, promote MSCs to enter S phase, and regulate the osteogenic and adipogenic differentiation | Alleviate the DNA damage of MSCs | 46 |
| | Myricetin | Natural herbal extract | Rat nucleus pulposus | Upregulate Bcl-2, downregulate Bax, Caspase3, $\beta$-gal, p53, p21, p16, IL-6 and ROS | Inhibit senescence and apoptosis of MSCs | 47 |
| | Baicalin | Natural herbal extract | Human bone marrow | Activate the hedgehog pathway to upregulate Bcl-2 and downregulate Bax, Caspase3 | Inhibit the apoptosis of MSCs | 48 |
| | Salidroside | Natural herbal extract | Mouse | Downregulate the ROS level | | 38 |
| | Jing Si formulation | Natural herbal formulation | Human adipose | Upregulate TERT, Klotho, CD90, Nanog, SOX2, downregulate $\gamma$-H2AX | Ameliorate cell cycle arrest in MSCs | 49 |
| | Tongxinluo | Natural herbal formulation | / | Upregulate *HIF-1α* mRNA expression and downregulate Caspase3 | Inhibit the apoptosis of MSCs | 50 |
| Strengthen immune-modulation | Wogonin | Natural herbal extract | Umbilical cord | Activate higher cellular glycolysis through the AKT pathway, upregulate *IL-10*, *IDO1*, *VEGF*, *Arg1*, *HIF-1α* mRNA expression | Ameliorate intestinal inflammation in IBD mice | 51 |
| | Triptolide | Natural herbal extract | Human umbilical cord | Upregulate IL-10, TGF-β, SOD1, PD-L1, PD-L2 | Inhibit CD4$^{+}$ and CD8$^{+}$ T cells proliferation *in vitro* | 52 |
| | Asarinin | Natural herbal extract | Human umbilical cord | Inhibit CD4$^{+}$ and CD8$^{+}$ T cells proliferation and regulate the production of Th1/Th2 cytokines | Ameliorate lung, liver, and small intestine injury in GvHD mice | 53 |
| | Jujuboside A | Natural herbal extract | Human umbilical cord | Upregulate IDO expression | Inhibit Th1 and Th17 cells in PBMC and promote the differentiation of Treg cells | 45 |
| | Curcumin | Natural herbal extract | Mouse bone marrow | Inhibit Th1 immune reaction and promote M2 macrophage polarization | Promote skin reconstruction in mice | 54 |
| | Quercetin | Natural herbal extract | Mouse bone marrow | Inhibit the Mincle/Syk pathway to downregulate TNF-α and IL-6 in the mouse brain tissues | Improve the neurologic deficits and brain edema in mice with intracerebral hemorrhage | 55 |
| | Qi-fang-bi-min-tang | Natural herbal formulation | / | Inhibit Th1, Th17 cells, downregulate IFN-γ, IL-17, IgE | Inhibit the symptoms and reduce the pathological changes of the nasal mucosa in rats with allergic rhinitis | 56 |

Continued

| Effect | Natural products | Category | MSCs source | Mechanism | Result | Ref. |
|---|---|---|---|---|---|---|
| Promote tissue repair | Codonopsis pilosula polysaccharides | Natural herbal extract | Rat bone marrow | Activate the Wnt/*β*-catenin pathway to upregulate RUNX2, COL1A1, ALP, OPN | Promote osteogenic differentiation of MSCs | 57 |
| | 1-Methoxy-2-hydroxyanthracene-9,10-dione | Natural herbal extract | Mouse bone marrow | Activate the Wnt/*β*-catenin pathway to upregulate RUNX2, OPN | | 58 |
| | Icariin | Natural herbal extract | Rat bone marrow | Activate the Wnt/*β*-catenin pathway | | 59 |
| | Wedelolactone | Natural herbal extract | Mouse bone marrow | Activate METTL3-mediated m6A RNA methylation to upregulate HIF-1α, VEGF-A and RASSF1 | | 60 |
| | Total flavonoids from Rhizoma Drynariae | Natural herbal extract | Rat bone marrow | Activate the TGF-β/Smad pathway to upregulate RUNX2, COL1A1, ALP, OPN | Promote osteogenesis of MSCs in rats with cranial defects | 61 |
| | Levistolide A | Natural herbal extract | Rat bone marrow | Promote the Smad pathway by inhibiting Skp-1 | | 62 |
| | Dendrobium officinale polysaccharide | Natural herbal extract | Rat bone marrow | Upregulate *Nestin*, *MAP2*, *VEGF-A* mRNA expression | Promote MSCs to differentiate into neuron-like cells | 63 |
| | Asperosaponin VI | Natural herbal extract | Human | Upregulate SOX9, KRT19, PAX1 and Collagen Ⅱ expression | Promote MSCs to differentiate into nucleus pulposus-like cells | 64 |
| | GuiLu-ErXian Glue | Natural herbal formulation | Human umbilical cord | Upregulate SOX9, ACAN, Collagen Ⅱ and X expression | Repair cartilage defects in osteoarthritic rats | 65 |
| | Icariin | Natural herbal extract | Rat bone marrow | Activate the PI3K and ERK1/2 pathway, upregulate VEGF, BDNF, and doublecortin in the ischemic frontal cortex and hippocampus | Promote angiogenesis and neurogenesis in rats with middle cerebral artery occlusion | 66 |
| | Resveratrol | Natural herbal extract | Human umbilical cord | Upregulate *BDNF, NGF, and NT-3* mRNA expression, activate the SIRT1 pathway to downregulate p53, p21, and p16 expression in the hippocampus | Attenuate neural apoptosis and enhance neurogenesis in the hippocampus to improve cognition in AD mice | 67 |
| | Salidroside | Natural herbal extract | Rat bone marrow | Decrease astrocyte | Inhibit neuroinflammation and enhance neurogenesis of the ischemic hippocampus in rats with middle cerebral artery occlusion | 36 |

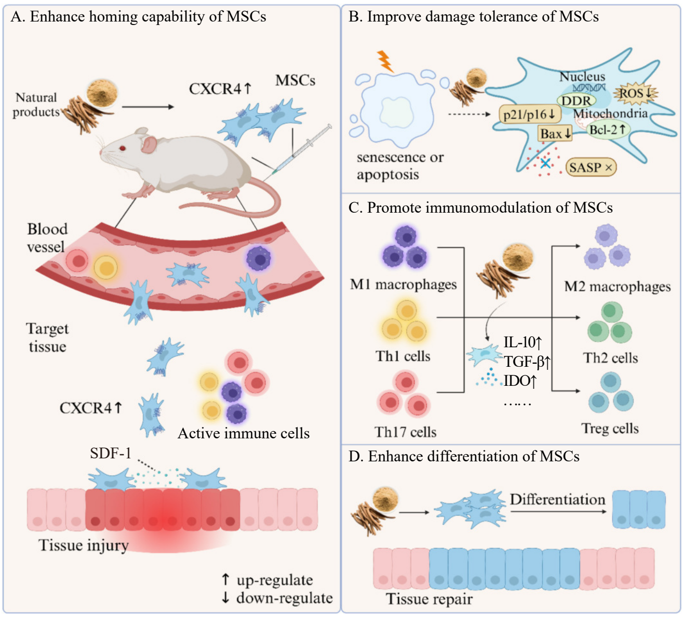

**Fig. 3** The modulation of MSCs with natural products. (A) Natural products can increase the CXCR4 expression of MSCs to enable MSCs to better respond to SDF-1 at the lesion sites, enhancing their homing ability. (B) Natural products facilitate DNA damage response and inhibit senescence and apoptosis of MSCs. (C) Natural products can activate the paracrine effects of MSCs to robust their immunomodulation. (D) Natural products promote MSCs to differentiate into specific functional cells to replace damaged cells. CXCR4: C-X-C chemokine receptor 4; SDF-1: stromal cell-derived factor-1; ROS: reactive oxygen species; DDR: DNA-damage response; Bcl-2, Bax: apoptosis-associated proteins; SASP: senescence-associated secretory phenotype; IL-10: Interleukin-10; TGF-β: transforming growth factor-β; IDO: indoleamine-2,3-dioxygenase.

ease microenvironment critically influences their immunomodulatory capacity [22]. Evidence shows that natural herbal extracts can act as immune primers, inducing MSCs to express and secrete anti-inflammatory cytokines and growth factors. For example, wogonin-pretreated MSCs show increased mRNA expression of *IL-10*, *2,3-dioxygenase 1* (*IDO1*), *vascular endothelial growth factor (VEGF)*, *Arg1*, and *HIF-1α* [51]. Triptolide-primed human umbilical cord mesenchymal stem cells (hUC-MSCs) exhibit elevated protein levels of IL-10, TGF-β, SOD1, programmed cell death ligand 1 (PD-L1), and PD-L2 [52], indicating pre-activation of immunomodulatory functions.

Natural extracts also enhance the ability of MSCs to regulate immune cells, such as T cells and macrophages, thereby mitigating inflammation. Imbalances in T helper type 17 (Th17)/Treg and Th1/Th2 subsets disrupt cellular and humoral immunity [79, 80]. Jujuboside A upregulates IDO expression in hUC-MSCs, suppressing Th17 cells and promoting Treg differentiation [45]. Asarinin enhances MSC-mediated inhibition of cluster of differentiation 4 (CD4)$^+$ and CD8$^+$ T cell proliferation and modulates Th1/Th2 cytokine production in the serum of GvHD mice, markedly reducing organ damage in lungs, liver, and small intestine [53]. M2 macrophages, which possess anti-inflammatory properties, contribute to tissue repair and wound healing [81]. For instance, curcumin-treated BMSCs promote M2 polarization in mouse skin wounds, accelerating tissue regeneration [54]. Furthermore, natural products improve the inflammatory milieu, enabling MSCs to more effectively repair damaged tissues. BMSCs combined with an iron-quercetin complex inhibit the Mincle/Syk pathway, downregulating TNF-α and IL-6 in brain tissues of intracerebral hemorrhage mice, thereby enhancing neural functional recovery [55]. Additionally, the anti-inflammatory herbal formula Qi-fang-bi-min-tang—used clinically for allergic rhinitis (AR)—augments MSC-mediated suppression of Th1 and Th17 cells in AR mice, reducing IFN-γ and IL-17 secretion and lowering IgE levels associated with nasal mucosal injury [56].

These findings suggest that natural products can pre-activate MSCs to enhance immunomodulation and improve the *in vivo* inflammatory environment. Future studies should explore their effects on other immune cells such as B cells and NK cells, which remain under-investigated.

### *3.4. Enhance the tissue repair ability of MSCs*

Natural products promote MSC differentiation into functional cell types to replace damaged cells and stimulate resident functional cells to self-renew, facilitating tissue regeneration. Signaling pathways, including Wnt/*β*-catenin, m6A RNA methylation, and Smad, are involved in MSC osteogenic differentiation. Codonopsis pilosula polysaccharides [57], 1-methoxy-2-hydroxyanthracene-9,10-dione from Morinda officinalis [58], icariin [59], wedelolactone [60], total flavonoids from Rhizoma Drynariae (emodin, apigenin, and naringenin) [61], and levistilide A [62] promote osteogenic differentiation by modulating one or more of these pathways, supporting bone regeneration. DOP may induce neuronal differentiation of MSCs, reducing infarct volume in middle cerebral artery occlusion (MCAO) rats [63]. Asperosaponin VI promotes MSC differentiation into nucleus pulposus-like cells, alleviating intervertebral disc degeneration (IVDD) [64]. The GuiLu-ErXian Glue, a traditional formulation used to relieve joint pain in osteoarthritis patients, enhances chondrogenic differentiation of MSCs and repairs cartilage defects in osteoarthritis rat models [65, 82].

Moreover, combinations of natural extracts and MSCs enhance tissue repair. Icariin promotes MSC migration to injured brain regions in MCAO rats and increases VEGF and brain-derived neurotrophic factor (BDNF) secretion and *doublecortin* mRNA expression in the ischemic frontal cortex and hippocampus *via* activation of PI3K and ERK1/2 pathways, thereby stimulating angiogenesis and neural repair [66]. Resveratrol enhances hUC-MSC homing to the hippocampus in AD mice, upregulates *BDNF*, *NGF*, and *NT-3* mRNA expression to promote neurogenesis, and downregulates p53, p21, and p16 *via* the SIRT1 pathway to inhibit neuronal senescence and apoptosis, ultimately restoring cognitive function [67]. Salidroside improves MSC survival in hypoxic-ischemic environments, reduces astrogliosis, and mitigates brain injury in MCAO rats [36].

These results indicate that natural products significantly enhance MSC differentiation, and their synergistic application further supports the self-renewal of functional cells—both of which are essential for *in vivo* tissue repair.

Overall, natural products—predominantly herbal extracts—play multifaceted roles in regulating the *in vivo* fate of MSCs. However, most evidence derives from *in vitro* and animal studies. Further investigation is needed to evaluate the clinical potential of natural product-pretreated MSCs.

## 4. Application of natural compounds in the preparation of MSCs

MSCs are typically cryopreserved during manufacturing to support immediate clinical use. Recently, natural compounds such as trehalose and betaine have been explored for MSC cryopreservation due to their non-toxic and effective cryoprotective properties. Trehalose protects biomembranes and macromolecules from cold-induced damage when present intra- and extracellularly. Fuenteslópez et al. demonstrated that MSCs cryopreserved for four weeks using ultrasonic microbubble-mediated trehalose delivery recovered viability and retained pluripotency to differentiate into adipocytes, osteoblasts, and chondroblasts by day 5 post-thaw [83]. However, ultrasonic microbubbles may cause mechanical damage; gentler delivery methods (e.g., nanocarriers) warrant exploration. Betaine, a zwitterionic compound with trimethylammonium and carboxyl groups, binds water molecules and inhibits ice crystal formation during freezing. When delivered intracellularly *via* electroporation, betaine protects UC-MSCs from osmotic stress, maintains viability and function, and reduces intracellular ROS levels [84], offering a promising strategy for MSC cryopreservation.

In addition, natural compounds are widely incorporated into tissue engineering scaffolds for MSC delivery due to their excellent biocompatibility. Hyaluronic acid is favored in cartilage tissue engineering for its lubricating, water-retaining, and anti-inflammatory properties [85]. Cartistem, a Korean MSC product, combines *in vitro*-expanded allogeneic UC-MSCs with hyaluronic acid hydrogel. A multicenter, randomized, controlled phase III trial involving 114 elderly patients with full-thickness cartilage defects showed significantly better cartilage restoration and histological scores in the Cartistem group at 48 weeks. A five-year follow-up study of 73 participants confirmed greater improvements in pain and function among treated patients [86]. Chitosan, a natural polysaccharide, exhibits high mucoadhesion and enhanced drug penetration, making it suitable for drug delivery systems [87]. Composite chitosan hydrogels protect UC-MSCs from high glucose and inflammatory conditions, improving glucose tolerance and restoring islet morphology in type Ⅱ diabetic mice [88]. Chitosan-based cardiogel patches also enhance MSC survival at myocardial injury sites, significantly repairing damaged cardiac tissue [89]. These advances highlight the potential for targeted delivery and enhanced efficacy of MSC therapies.

In conclusion, natural compounds offer unique advantages for the cryopreservation and delivery of MSCs, though challenges in process optimization and regulatory compliance remain. Future research should prioritize rational design to ensure safety and standardization.

## 5. Clinical treatment exploration of MSCs combined with natural products

Given the substantial therapeutic potential of both natural products and MSCs, supported by extensive *in vitro* and animal studies, researchers are actively advancing clinical investigations of their combined use. A clinical trial evaluating Cervus and Cucumis peptides (LG) in conjunction with UC-MSCs for rheumatoid arthritis demonstrated that, in addition to standard oral antirheumatic therapy, all 59 patients receiving the combination achieved ACR20 remission, with 14 reaching ACR50 remission after three months —without serious adverse events. These findings support the feasibility of integrating natural products with MSCs in clinical treatment [90].

Furthermore, three clinical research initiatives combining MSCs with natural herbal formulations have been approved by the National Health Commission of the PRC as of December 2024, targeting psoriasis, ALS, and diabetic foot. Following successful outcomes using AD-MSCs and PSORI-CM01 in psoriasis patients [91, 92], Guangdong Hospital of Traditional Chinese Medicine implemented a regimen in 2017 involving AD-MSC injection, oral PSORI-CM01, and topical calcipotriene for moderately severe psoriasis vulgaris. In 2021, Hebei Yiling Hospital initiated two trials: “Clinical research on the efficacy and safety of umbilical cord mesenchymal stem cells combined with traditional Chinese medicine in the treatment of amyotrophic lateral sclerosis” and “Clinical research on the efficacy and safety of umbilical cord mesenchymal stem cells alone or combined with Tongxinluo capsules in the treatment of diabetic foot.” Notably, the novel TCM formulation Shenrong granules has advanced to phase Ⅱ clinical testing (No.: ChiCTR2400083114) for ALS, while Tongxinluo capsules have already been integrated into clinical practice for diabetic foot within combined traditional Chinese and Western medicine frameworks [93], thereby promoting synergistic applications of natural products and MSCs in treating these refractory conditions.

Currently, clinical trials combining natural products with MSCs remain limited. With more robust preclinical evidence, however, broader clinical translation of such combinations is anticipated.

## 6. Summary and outlook

MSCs are widely regarded as promising agents in cell therapy. Nevertheless, certain clinical trials have failed to achieve expected therapeutic outcomes across various diseases. Enhancing MSC efficacy through engineered modifications is, therefore, a major research focus. Compared to conventional approaches such as genetic engineering or hypoxic preconditioning, pretreatment or co-administration of natural products with MSCs offers advantages including high safety, low cost, and operational simplicity. Natural products can modulate multiple cellular targets, inhibit MSC senescence, enhance *in vivo* homing, and improve engraftment at injury sites. They also potentiate MSC immunomodulatory functions, regulate inflammatory microenvironments, and create favorable conditions for tissue repair. Moreover, they promote site-specific differentiation of MSCs into functional cell types, facilitating effective tissue regeneration. Due to their excellent biocompatibility and safety profile, natural products hold strong potential for use in MSC cryoprotectants, delivery systems, and tissue engineering scaffolds. Continued exploration of their role in regulating the *in vivo* fate of MSCs—leveraging modern biotechnologies—may enable clinically effective combinatorial therapies.

Despite these prospects, several challenges persist in the regulation of MSCs by natural products. Their effects may be influenced by MSC heterogeneity and variable microenvironmental conditions. Additionally, the precise mechanisms and molecular targets underlying natural product actions on MSCs remain incompletely understood, complicating their precise deployment across different pathologies. Furthermore, the safety and efficacy of combining natural products with MSCs require rigorous validation through systematic preclinical and clinical studies. To address these translational barriers, three strategic approaches are proposed:

1. Modulation effect stabilization by natural products

Establish certified protocols for MSC isolation, expansion, and quality-controlled culture systems, and incorporate 3D biomimetic platforms and patient-derived organoids to improve batch-to-batch consistency and functional stability.

2. Mechanistic deconvolution of natural product actions

Implement integrated multi-omics platforms (transcriptomic-proteomic-metabolomic cascades) coupled with AI-driven molecular docking to systematically map natural product-MSC interactomes and identify master regulators governing MSC homing, survival efficiency, differentiation, and paracrine reprogramming.

3. Advancing clinical translation of natural product-MSC therapies

Develop species-relevant pharmacokinetic/pharmacodynamic (PK/PD) models using quantitative systems pharmacology (QSP) to define therapeutic indices and exposure-response relationships. Concurrently, execute multicenter adaptive trial designs incorporating mechanism-informed biomarkers to validate clinical efficacy while minimizing off-target effects of natural product-MSC combinatorial regimens.

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## Declaration of competing interest

These authors declare no conflict of interest.

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