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Natural bioactive compounds modified with mesenchymal stem cells: new hope for regenerative medicine

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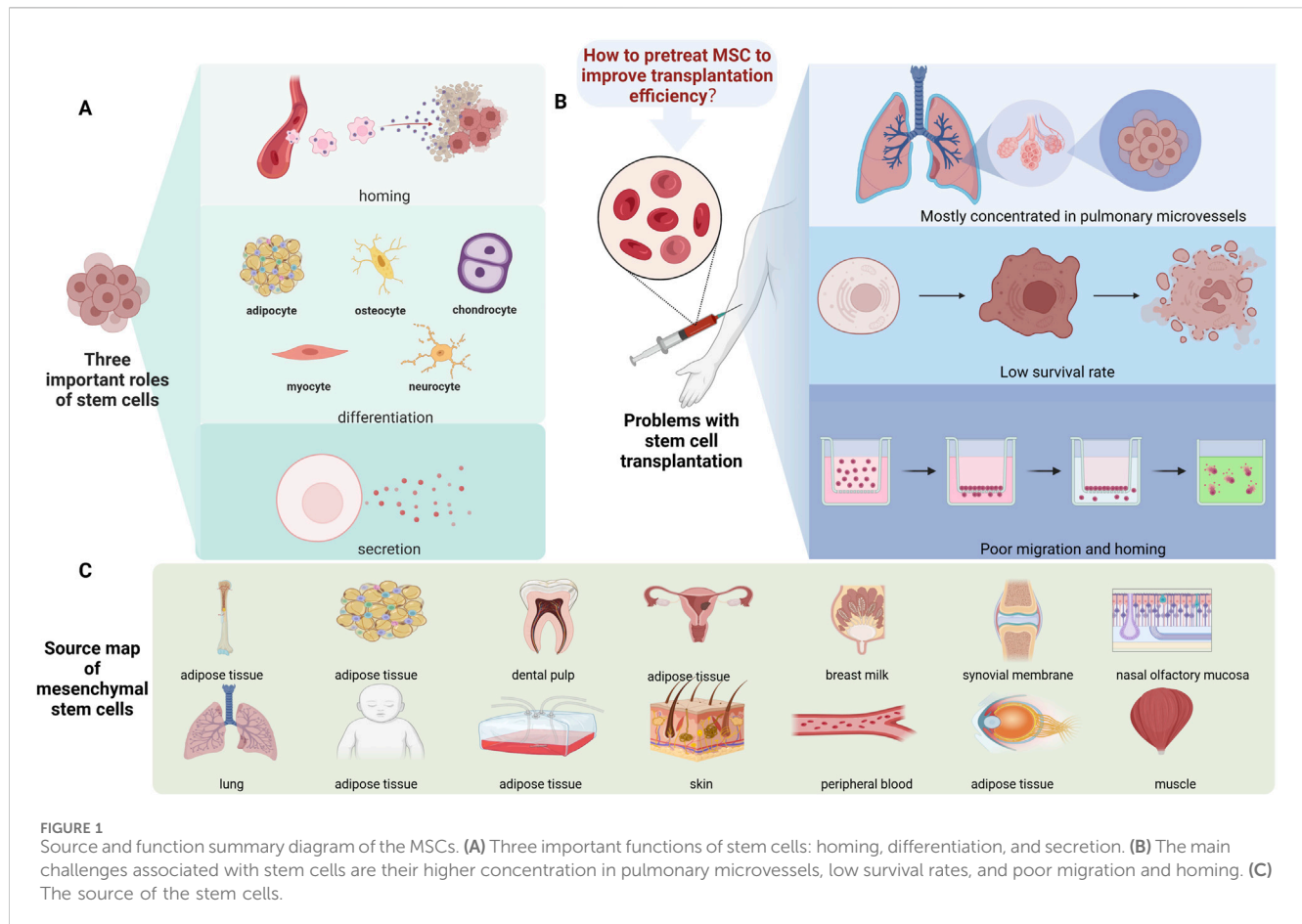
Mesenchymal stem cells (MSCs) have the potential to differentiate into various cell types, providing important sources of cells for the development of regenerative medicine. Although MSCs have various advantages, there are also various problems, such as the low survival rate of transplanted cells and poor migration and homing; therefore, determining how to reform MSCs to improve their utilization is particularly important. Although many natural bioactive compounds have shown great potential for improving MSCs, many mechanisms and pathways are involved; however, in the final analysis, natural bioactive compounds promoted MSC proliferation, migration and homing and promoted differentiation and antiaging. This article reviews the regulatory effects of natural bioactive compounds on MSCs to provide new ideas for the therapeutic effects of modified MSCs on diseases.

KEYWORDS

mesenchymal stem cells, natural bioactive compounds, resveratrol, icariin, Ginkgo biloba extract, tanshinone IIA, astragaloside IV, curcumin

1 Introduction

There are many types of stem cells that can be divided into three categories: embryonic stem cells derived from early embryos, induced pluripotent stem cells, and adult stem cells, including haematopoietic stem cells, neural stem cells, and mesenchymal stem cells (MSCs) (Tian et al., 2023). MSCs were first discovered from bone marrow in 1976 (Lan et al., 2021) and have been found in almost all tissues in the human body. Compared with unipotent stem cells, stem cells have high self-renewal ability and good differentiation ability. The pluripotency of MSCs manifests in their ability to differentiate into bone cells, chondrocytes, fat cells, and other cell lines. Bone marrow and subcutaneous fat are the preferred sources of MSCs (Zhou and Shi, 2023; Eirin et al., 2024). MSCs can also be isolated from various adult tissues, such as adipose tissue (Gou et al., 2024), synovial membrane (Li et al., 2020), dental pulp (Yang et al., 2025), skin (Rendra et al., 2023), peripheral blood (Chen et al., 2023), nasal olfactory mucosa (Valipour et al., 2024), lung (Rangasamy et al., 2021), breast milk (Rahmani-Moghadam et al., 2022), muscle (Serteayn et al., 2024), periosteum (Ye et al., 2024), corneal limbus (Santra et al., 2024), endometrial and



menstrual blood (Song et al., 2024), cervix (Eiro et al., 2024), and foetal/neonatal tissue (Thiruvengataramani et al., 2024). MSCs are good candidates for future experimental or clinical applications and have received increasing attention (Matsuzaka and Yashiro, 2024; Pharoun et al., 2024; Shan et al., 2024). Stem cells have three important functions that make them potentially useful. The first is homing, which is the chemotactic effect of stem cells when damage occurs in the body (Han et al., 2022). The second is differentiation, whereby stem cells can differentiate into a variety of cell types by means of transplantation and by adding or replacing damaged tissue to enhance functional recovery (Nie et al., 2023). The third is the secretion of bioactive factors, which may influence local and systemic physiological processes (Daneshmandi et al., 2020). The most important function of stem cells is self-renewal (Wilkinson et al., 2020).

The contribution of stem cells to modern medicine is crucial. Not only because they can be widely used in basic research but also because they offer more and better opportunities to develop new treatment strategies (Pharoun et al., 2024). Their properties make them valuable for a wide range of applications in the biological and medical sciences (Lu et al., 2025). MSCs play a wide range of physiological roles, including maintaining tissue homeostasis and regeneration (Zhidu et al., 2024), as well as modulating immune effects (Hazrati et al., 2024). As a result, indications for MSCs have expanded to include graft-versus-host disease, multiple sclerosis, Crohn's disease, amyotrophic lateral sclerosis, myocardial

infarction, and acute respiratory distress syndrome (ARDS) (Han et al., 2022; Pharoun et al., 2024). Over the past decade, several preclinical studies and more than 5,000 clinical trials involving MSCs have been registered, with more than 1,500 completed (Al-Azab et al., 2023). In addition, more than 100 clinical trials have tested stem cells for regenerative medicine, and MSCs have great potential in treating Parkinson's disease, among other conditions (Abbott, 2025). Although the clinical application of stem cells is promising, there are still some challenges that warrant consideration in cell therapy and regenerative medicine. Studies have shown that most MSCs lose their biological activity within a week, even after the orthotopic transplantation of MSCs (Preda et al., 2021). Moreover, most transplanted MSCs are concentrated in pulmonary microvessels, and the amount of targeted tissues is limited (Shan et al., 2024). Therefore, even though MSCs have various advantages, there are also various challenges, such as the low survival rate of transplanted cells and poor migration and homing of MSCs; thus, the function of MSCs is limited. Currently, various studies have shown that they can increase the survival, migration, proliferation and differentiation of stem cells; promote homing; and induce the release of nutrient factors in various ways to further promote the recovery of neural function (Han et al., 2024). Some studies have been conducted to pretreat stem cells before injection to change some of the characteristics of the cells, thereby improving the efficacy of stem cell transplantation (Huang et al., 2018; Yu et al., 2023) (Figure 1).

According to the World Health Organization (WHO), two-thirds of the world's population has access to herbal medicines. Therefore, the WHO encourages the inclusion of plants in treatment regimens for various diseases to improve their effectiveness and reduce potential costs (Mekhemar et al., 2020). Natural bioactive compounds are defined as chemical substances derived from natural sources (such as plants, animals, or microorganisms) that have biological effects on living organisms, tissues, or cells. Plants constitute one of their main sources (Li et al., 2024). Since ancient times, plant-derived natural compounds have been widely used to treat various diseases (Gugliandolo et al., 2020; Huang et al., 2024). In recent years, increasing attention has been given to natural bioactive compounds, and the modification of stem cells is a new research direction. They are able to modulate stem cell self-renewal and differentiation potential and target a wide range of types of intracellular signal transduction (Feng et al., 2022; Li et al., 2023; Li et al., 2024). An increasing amount of data show that natural bioactive compounds may have different protective mechanisms through their antioxidants, free radical scavengers, harmful metal ion chelators, regulation of cell survival genes and signals, and antiapoptotic activity, so they have a wide range of applications in the treatment of many diseases (Huang et al., 2023; Pacyga et al., 2024; Wang et al., 2024). In addition to treating diseases, some natural bioactive compounds can also play an antioxidant role by activating the proliferation of lymphocytes to enhance immune function, increasing the number of natural killer (NK) cells and scavenging free radicals (Kim et al., 2022; Mahmoudi et al., 2024). Studies have shown that natural bioactive compounds may be able to effectively regulate the proliferation and differentiation of stem cells (Lakshminarayanan et al., 2025). Therefore, natural bioactive compounds have the potential to be a new source for improving stem cells, increasing their proliferation and improving their function. In this work, the regulatory effects of natural bioactive compounds on MSCs were reviewed to provide better theoretical support for the improvement of stem cells and enhance their application in clinical and basic research.

2 Overview of MSCs

MSCs are pluripotent stem cells that can self-renew and differentiate into multilineage cells (Lin et al., 2022). These cells have the ability to differentiate into osteoblasts, chondrocytes, and adipocytes, and the cell phenotypes CD73, CD90, and CD105 are positive, while the major histocompatibility complex class II (MHC-II), CD11b, CD14, CD31, CD34, and CD45 are negative (Zhou and Shi, 2023; Cao et al., 2024). The quality and criteria of MSCs should include cell surface markers, differentiation potential and other necessary parameters. These parameters include cell surface labelling profiles, bone formation capacity in the model, as well as cell and particle sizes, telomere length, state of ageing, secretion of trophic factors (secretomes), and immune regulation (Trivanović et al., 2015; Samsonraj et al., 2017). Because MSCs are easy to extract from foetal and adult tissues and do not require overly demanding cell culture conditions, they are promising research targets. Many studies have confirmed their anti-inflammatory components, multilineage potential, tissue regeneration ability and immunomodulatory effects, so they have been widely studied in

the treatment of many diseases (Al-Azab et al., 2022; Gopalarethinam et al., 2023).

2.1 Bone marrow mesenchymal stem cells (BMSCs)

BMSCs are the most widely used stem cells in regenerative medicine and tissue engineering. They are nonhematopoietic stem cells that exist in the bone marrow and have pluripotent differentiation potential (Zhang et al., 2023). However, the mobilization of BMSCs from the bone marrow and their migration to damaged tissue during healing are key issues. The migration of BMSCs to target tissues is a complex biological process. This transport process is affected by many factors, such as chemical factors (e.g., chemokines, cytokines, and growth factors) and mechanical factors (e.g., shear stress and vascular circulation) (Fu et al., 2019). At present, several methods are used to evaluate the migration of BMSCs, the most common methods are the Transwell method and the scratch test (Sun and Fan, 2025). Moreover, BMSCs can also be labelled with fluorescence to track their location (Yun et al., 2023). The therapeutic use of BMSCs also has certain limitations, such as cell rejection, poor immune response, toxicity, tumorigenicity, potential contamination by viruses and problems with cell transport and storage prior to transplantation (Tayebi et al., 2022; Zhang et al., 2022).

2.2 Human umbilical cord mesenchymal stem cells (HUCMSCs)

The human umbilical cord is a promising source of mesenchymal stem cells (HUCMSCs). Unlike that for BMSCs, the process of HUCMSC collection is painless, and HUCMSCs exhibit faster self-renewal. HUCMSCs are a better source than commonly used embryonic stem cells. They can differentiate into three types of germ layers that promote tissue repair, regulate the immune response, and have anticancer properties (Rodríguez-Eguren et al., 2022). However, HUCMSCs also have certain limitations, such as maintaining biological activity and quantifying bioactive substances (Ding et al., 2018).

2.3 Adipose-derived mesenchymal stem cells (ASCs)

ASCs are generally isolated from heterogeneous cell populations produced in the stromal vascular fraction (SVF) of adipose tissue. The SVF is obtained from subcutaneous fat tissue from individuals who undergo surgical procedures such as liposuction to remove excess, unwanted fat, so easy access to sources is one reason for its widespread use (Yaylaci et al., 2023). ASCs can self-renew and differentiate into multiple cell lines. ASCs have been proven to have anti-inflammatory, antifibrotic, antiapoptotic and proangiogenic effects both *in vitro* and *in vivo*. Therefore, they have been widely used in cell therapy and regenerative medicine (Al-Ghadban et al., 2022; Zeng et al., 2022; Barone et al., 2023). ASCs are widely used in many diseases, such as multiple sclerosis, diabetes,

Crohn's disease, SLE, and graft-versus-host disease (Al-Ghadban et al., 2022). Unlike BMSCs, ASCs differ in that their fatty acid translocase marker CD36 and cell adhesion marker CD106 are not expressed (Poon et al., 2020). Previous reports have shed new light on the ability of ASCs to differentiate. ASCs can differentiate into various types of epithelial cells, such as renal tubular epithelial cells and retinal pigment epithelial cells (Cawthorn et al., 2012). However, other researchers have demonstrated that these cells may have less potential for bone formation and cartilage formation than BMSCs. The importance of adipose tissue-derived stem cells has been questioned (Al-Sammarraie et al., 2024).

2.4 Other types of mesenchymal stem cells

Other well-known sources of adult MSCs include the cervix, placenta, amniotic fluid, dental pulp, breast milk, and synovial membrane. Compared with other methods used to obtain other MSCs (such as bone marrow or adipose tissue), human cervical stem cells (hUCESCs) are also a type of MSC that can be obtained via cervical smears, are easy to separate, have a high proliferation rate, and can yield a greater number of hUCESCs or exosomes and other derivatives, which is conducive to basic research and clinical applications (Vizoso et al., 2017; Ge et al., 2024). Compared with MSCs from other sources, human placental mesenchymal stem cells (hPMSCs) have the advantages of stable proliferation and low immunogenicity. These properties make hPMSCs ideal materials for stimulating tissue repair (Lu et al., 2021; Yu et al., 2024). Amniotic fluid MSCs are a type of MSC produced during the perinatal period. Compared with adult MSCs such as BMSCs, their advantages include a minimally invasive separation process, more primitive cell characteristics, nontumorigenicity, and low immunogenicity. Currently, they have received increasing attention (Doktor et al., 2025). On the basis of the clinical diagnosis of nonfunctional or pathogenic tissues in the mouth, oral MSCs can be obtained through minimally invasive surgery. In addition, they are often discarded as medical waste after they are removed from the mouth. Therefore, compared with the use of MSCs from other tissues, this is a unique advantage of dental MSCs in research (Masuda et al., 2021).

3 Effects of different types of natural bioactive compounds on MSCs

Because MSCs are good candidates for clinical and basic research, it is especially important to obtain adequate numbers of these cells. They are usually cultured *in vitro* with animal serum and various growth factors. However, repeated freeze–thaw cycles, *in vitro* culture conditions and continuous passages during the culture process have adverse effects on the proliferation of MSCs, such as reduced self-renewal, increased cell senescence, increased apoptosis and premature differentiation, and these cells are very susceptible to the influence of the microenvironment (Yang et al., 2018; Preda et al., 2021). A variety of natural bioactive compounds are used worldwide to treat and prevent various diseases, and they have multitarget, multilevel and multipathway characteristics (Huang et al., 2023). The bioactive compounds naturally present

in seaweed, herbs, fruits, and vegetables have the ability to regulate the self-renewal and differentiation potential of adult stem cells. They mainly target a wide range of intracellular signal transduction pathways (Li et al., 2022). Natural plant compounds can improve the rate of tissue regeneration, which has certain advantages in the tissue engineering of stem cell therapy and alternative therapy. Although bioactive ingredients have not been widely used in the clinic because of their variability and complexity, a growing number of studies have focused on the modified effects of natural compounds on MSCs (Table 1) (Figure 2).

3.1 Resveratrol

Resveratrol (RSVL) is a natural polyphenol plant antitoxin (Huang et al., 2020; Huang et al., 2023) and is a natural polyphenolic phytoestrogen. It was first found in the root extract of white mustard (*Veratrum grandiflorum*) and was found in the roots of knotweed in 1963 (Vauzour, 2012). RSVL has two configurations, cis-type or trans-type structures, among which trans-RSVL is the main form existing in nature and the most widely studied form (Huang et al., 2020). RSVL has a wide range of biological activities, including antioxidant, antiviral, anti-inflammatory, antiaging and anticancer properties (Khattar et al., 2022). It has great potential to prevent a variety of acute and chronic diseases. Recent studies have shown that it can play a reliable rejuvenating role in various animal models, tissues and organs, especially in the modification of stem cells. Studies have shown that RSVL can improve the therapeutic effect of MSCs by increasing their survival rate, self-renewal ability and antiaging effects (Hu and Li, 2019). RSVL is also involved in the regulation of bone formation and fat, as well as nerve regeneration, in MSCs (Joe et al., 2015).

In terms of the antiaging effects of MSCs on BMSCs, studies have shown that RSVL can activate Sirtuin 1 (SIRT1), reduce β -catenin activity, increase extracellular signal-regulated kinase (ERK) phosphorylation and glycogen synthase kinase-3 beta (GSK-3 β) phosphorylation, improve the self-renewal potential of early-passage MSCs and improve their pluripotency (Yoon et al., 2015). Different concentrations of RSVL had different antiaging effects on HUCMSCs. At 0.1, 1 and 2.5 μ M, RSVL promoted cell viability and slowed the ageing of MSCs by increasing SIRT1 expression and inhibiting p53 and p16 expression. At concentrations of 5 and 10 μ M, RSVL can increase the degree of senescence and apoptosis of MSCs by inhibiting SIRT1 and PCNA and stimulating the expression of p53 and p16 (Wang et al., 2016). Therefore, not all concentrations of RSVL are beneficial for the growth of MSCs.

RSVL is involved in the differentiation of MSCs. Studies have shown that RSVL can enhance the osteogenic differentiation ability of BMSCs by increasing NO production and the cGMP content, activating ERK1/2 and p38 mitogen-activated protein kinase (MAPK), and upregulating the expression of mitogens (Song et al., 2006; Dai et al., 2007; Lv et al., 2018). RSVL can also replace insulin in lipid-forming medium, increase the phosphorylation of cyclic AMP response element binding protein (CREB), and induce lipid differentiation in MSCs (Caldarelli et al., 2015).

TABLE 1 Effect of natural bioactive compounds modified mesenchymal stem cells.

Compounds	Sources of MSC	Function	Mechanism of action	Ref
Icariin	BMSC	1.Promote proliferation and osteogenic differentiation of BMSC, inhibit lipogenic differentiation 2.Promote migration of BMSCs	1.Upregulated Runx2, ALP and I collagen promote bone formation, the expression of PPAR γ , adipsin, CCAAT/C/EBP α and FABP4 mRNA was inhibited to inhibit the differentiation of BMSC into adipocytes 2.Activation of STAT-3 increases the activity and expression of cysteine (C)-X-C motif chemokine receptor 4 (CXCR4) 3. Stimulate the MAPK signaling pathway 4.Stimulation of Wnt/ β -catenin signaling pathway	Sheng et al. (2013), Huang et al. (2017), Liu et al. (2017), Wu et al. (2017), Lim et al. (2018)
	ASCs	Promote osteogenic differentiation	The mRNA expression of ALP, Col-1 and OC, Dlx5 and Runx2, BMP-2, -4 and -7 genes was stimulated. Improve Runx2, bmp and OC levels	Yang et al. (2019), Sharifi et al. (2020)
Resveratrol	BMSC	Promote proliferation and osteogenic differentiation of BMSC, inhibit lipogenic differentiation. Promote homing of MSC.	Runx2 gene expression on the SIRT1/FOXO3A axis can also be upregulated through ERK1/2 and MAPK signaling pathways	Dai et al. (2007), Tseng et al. (2011), Okay et al. (2015)
	HUCMSCs	Increase cell vitality, slow down aging and aging	Increase SIRT1 level, inhibiting the expression of p53 and p16	Wang et al. (2016)
	ASCs	Enhance the epithelial and osteogenic differentiation of MSCs	ASC differentiation was induced on collagen scaffolds	Wang et al. (2018)
Ginkgo biloba extract	BMSC	Promote proliferation and osteogenic differentiation of BMSC	1.Promotes osteogenesis by up-regulating BMP and Wnt/ β -catenin signaling pathways 2. Upregulated PAX6 expression in cells	Gu et al. (2015)
Tanshinone IIA	BMSC	1.Better anti-neuroinflammatory effects 2.Promote the differentiation of neuron cells Promote hBMSCs proliferation	1.Downregulated BACE1 expression 2.It may improve the survival rate of transplanted BMSCs, increase the level of nutrient factors secreted by BMSCs to the lesion area, and reduce inflammatory cytokines 3.Increase the release of fibroblast growth factor 2 (FGF2)	Zhang et al. (2018), Huang et al. (2019), Yuan et al. (2022)
	Human periodontal ligament stem cells (hPDLSC)	It promotes this differentiation and hPDLSC maturation	Osteogenesis of hPDLSC was induced by the ERK1/2-Runx2 axis	Liu et al. (2019)
	MSC	Regulate the migration ability of MSC.	Regulate the expression of CXCR4	Xie et al. (2013)
Curcumin	BMSC	1.Delay the aging 2.Promote osteogenic differentiation. Inhibition of lipogenic differentiation	1.Activated autophagy 2.It is associated with HO-1 expression The expression of Kruppel-like factor 15 was inhibited	Gu et al. (2012), Wang et al. (2019), Chen et al. (2021), Deng et al. (2021)
	ASCs	Delay the aging	1.Increase the expression of TERT gene 2.Increased tolerance to oxidative stress damage	Liu et al. (2015),Pirmoradi et al. (2018)
	hDP-MSC	Enhance immune regulation and regeneration		Ayadilord et al. (2022)

(Continued on following page)

TABLE 1 (Continued) Effect of natural bioactive compounds modified mesenchymal stem cells.

Compounds	Sources of MSC	Function	Mechanism of action	Ref
Astragaloside	MSC	Promotes angiogenesis of endothelium-like cells	Upregulated expression of Cx37, Cx40 and Cx43	Li et al. (2018)
	ASCs	1.Enhance its ability to proliferate 2.Promote migration and homing	1.Decreased PC-I secretion and increased MMP-1 release were induced in fibroblasts 2.FAK phosphorylation induced by CXCR2	Niu et al. (2020), Wang et al. (2022)
	hBMSCs	Ability to promote proliferation and differentiation	Regulated by the miR-124-3p.1/STAT3 axis	Cao et al. (2021)
Ginsenoside Rg1	BMSCs	1.Delay the aging 2.Promote osteogenic differentiation	1.Inhibition of phosphorylation of GSK-3 β 2.Activation of AKT or NRF2 3.Example Activate the GR/BMP-2 signal path	Gu et al. (2016), Wang et al. (2020), Wang et al. (2021)
Thymoquinone	G-MSCs	Promotes cell transformation into an immunocompetent differentiated phenotype	Increase the expression of TLR3	Mekhemar et al. (2022)
	Breast CSCs	Wnt/PI3K signaling pathway	Altered angiogenesis capacity and mesenchymal to epithelial transformation	(Haiaty et al., 2021b; a)
	MSCs	Promote differentiation	Triggers inhibition of NF- κ B signaling	Rahmani-Moghadam et al. (2021), Banu (2022), Ishaque et al. (2022)
Ptychotis verticillate		1. Promote migration 2. Immunomodulation	PI3K and MAPK signaling pathways	Maeda, 2020; Najjar et al. (2024)

RSVL has also been shown to improve the regulation of nerve regeneration. In BMSCs, RSVL can upregulate AMPK/SIRT1 signal transduction, thereby increasing the level of neural progenitor cell markers in MSCs isolated from ALS patients (Yun et al., 2019). In dental pulp stem cells, RSVL can increase the expression of the neuron-specific marker genes *Nestin*, *Musashi* and *NF-M*, thereby promoting the differentiation of dental pulp stem cells into neuronal cells (Geng et al., 2017). RSVL can activate the phosphatidylinositol 3-kinase (PI3K) signalling pathway or increase the levels of protein kinase A, GSK-3 β , and ERK1/2 in HUCMSCs, thereby increasing the expression of neural markers and promoting neural repair (Jahan et al., 2018a; Jahan et al., 2018b). Moreover, RSVL can play a positive role in the treatment of periodontitis by promoting the proliferation, osteogenic differentiation and immune regulation of MSCs (Jiang et al., 2023).

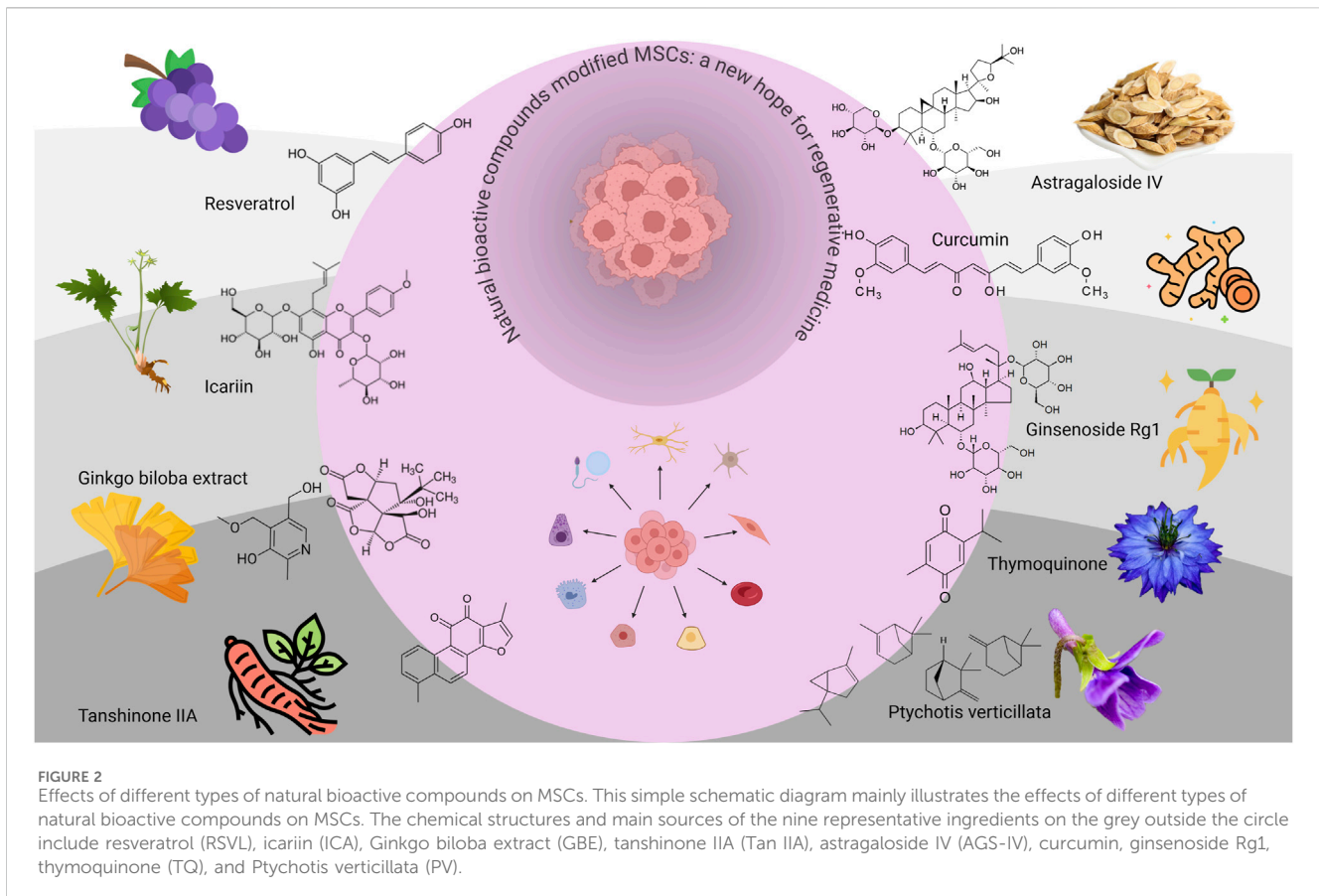
Thus, although RSVL can regulate the survival of MSCs, it can promote their self-renewal and maintain their pluripotency. However, to some extent, the concentration of RSVL, the time of administration and the method and time of pretreatment all affect the effect of RSVL on MSCs. Moreover, although many studies have focused on RSVL, few studies have investigated RSVL derivatives. Perhaps related studies can be conducted in the future, which will contribute to further exploration of the improvement effect of RSVL on MSCs in regenerative medicine. There are also several contradictory conclusions in the research. For example, some studies have shown that RSVL can help MSCs maintain

pluripotency (Yoon et al., 2015), but other studies have shown that RSVL can lead to the production of neural markers in HUCMSCs (Jahan et al., 2018a; Jahan et al., 2018b). This may be related to the different types of MSCs, doses and intervention methods used.

3.2 Icariin (ICA)

ICA is the main bioactive compound of *Epimedium brevicornum Maxim* (Hsieh et al., 2011). The composition of ICA includes a C-3 glucose group, a C-4 methoxy group, a C-8 isoprene group and a C-7 rhamnosyl group, and it is a class of isoprene flavonoid compounds. The molecular formula of ICA is C₃₃H₄₀O₁₅, and its molecular weight is 676.67 g/mol (Sharifi et al., 2020). ICA has a variety of pharmacological activities, including hormone-like, antitumour, immunomodulatory and antioxidant effects (Bi et al., 2022; Seyedi et al., 2023). ICA has been used to treat many diseases, such as preventing osteoporosis, improving sexual dysfunction, regulating immune system function and improving cardiovascular function (He et al., 2020).

As mentioned earlier, while the use of MSCs has many advantages, many methods have been developed, which limits their application. Therefore, new drugs have been developed to promote the proliferation and differentiation of MSCs. The effects of ICA have been extensively studied in animal and *in vitro* models, and its ability to modify MSCs has attracted much attention. The



beneficial effect of ICA on MSCs involves promoting osteogenic differentiation and inhibiting lipogenic differentiation. Some studies suggest that this effect is achieved by inactivating GSK-3 β and inhibiting the expression of PPAR γ (Sheng et al., 2013). Some studies suggest that this effect is related to the BMP (BMP-2, BMP-4, BMP-7) and MAPK/ERK pathways (Wu et al., 2017). Some studies suggest that it promotes osteogenesis through the upregulation of Runx2, ALP and I collagen and the Notch signalling pathway and inhibits PPAR γ , *adipsin* gene expression, and CCAAT/enhancer binding protein α (C/EBP α) and fatty acid binding protein 4 (FABP4) mRNAs (Huang et al., 2017; Liu et al., 2017). EGB 761 may be associated with findings in other studies that have shown that ICA can activate STAT-3 and increase the activity and expression of cysteine (C)-X-C motif chemokine receptor 4 (CXCR4) (Lim et al., 2018), thus promoting the proliferation and osteogenic differentiation of MSCs. Moreover, ICA can promote BMSC migration by stimulating the MAPK signalling pathway (Jiao et al., 2018).

In addition to BMSCs, hADSCs can effectively promote osteogenic differentiation by stimulating the mRNA expression of bone matrix protein (ALP, Col-1, and OC), bone transcription factor (*Dlx5* and *Runx2*), and bone morphogenetic protein (BMP-2, -4, and -7) genes (Yang et al., 2019; Sharifi et al., 2020). The beneficial effect of ICA on MSCs involves mainly promoting osteogenic differentiation and inhibiting lipogenic differentiation, and studies on whether ICA can promote proliferation, survival, homing and migration are limited, which also provides ideas for future studies.

3.3 Ginkgo biloba extract (GBE)

GBE is a bioactive component of *Ginkgo biloba* L. with various pharmacological activities (Hu et al., 2023). Its two main extracts have similar compositions: EGB 761, which has 24% ginkgo flavonoid glycosides and 6% terpenoids, and LI1370, which is composed of 25% ginkgo flavonoid glycosides and 6% terpenoids. GBE has been widely used to treat cerebrovascular insufficiency, peripheral vascular insufficiency, and cognitive impairment associated with ageing and neurodegenerative diseases (such as Alzheimer's disease) because of its ability to improve high blood pressure, antithrombosis, inflammation, oxidative stress, and infection (Mousavi et al., 2022; Xie et al., 2022). Specifically, GBE can reduce oxidative stress and inhibit the expression of inflammatory cytokines. In addition, studies have confirmed that GBE can promote the growth and proliferation of different cell types, such as neural stem cells, endothelial progenitor cells, and cochlear hair cells (Gu et al., 2015).

Studies have reported that GBE can promote the growth and differentiation of a variety of cells, including neural stem cells and endothelial progenitor cells (Zheng et al., 2018). Studies have shown that when GBE is in the range of 25–75 mg/L, GBE can promote the proliferation and osteogenesis of human BMSCs by upregulating the BMP and Wnt/ β -catenin signalling pathways. When the concentration of GBE was 100 mg/L or above, the ability of GBE to promote the proliferation of BMSCs weakened or disappeared (Gu et al., 2015). The concentration of GBE is particularly important for the modification of BMSCs, which directly determines whether the growth of MSCs is promoted or inhibited; thus, special attention should be given to GBE

concentrations in future studies. In rat models of myocardial infarction, EGb 761 may mediate the protective effect of EGb on myocardial infarction by increasing the implantation rate of MSCs, thereby improving the viability and differentiation of cardiomyocytes (Liu et al., 2014). Other studies have shown that MSCs modified with GBE may have good applications in the treatment of local inflammation and the oxidative microenvironment (Gu et al., 2015). Hence, these findings underscore the concentration-dependent therapeutic potential of GBE in stem cell-based neuroregeneration.

3.4 Tanshinone IIA (Tan IIA)

Tan IIA, a bioactive ingredient isolated from the herb *Salvia miltiorrhiza* Bge, is an antioxidant and anti-inflammatory agent that inhibits the cytotoxicity of damaged tissues, significantly improves blood circulation and delays tumour progression (Zeng et al., 2021; Ng et al., 2022). Studies have shown that Tan IIA has the potential to reduce oxidative stress by regulating the levels of antioxidant enzymes, including glutathione peroxidase (GPx), superoxide dismutase (SOD), and catalase. The anti-inflammatory effect of Tan IIA may be mediated by weakened inflammatory mediators in RAW264.7 macrophages, namely, interleukin (IL)-1 β , IL-6 and tumour necrosis factor (TNF)- α (Ansari et al., 2021).

With respect to the modification effect of Tan IIA on MSCs, Tan IIA can regulate the migration ability of MSCs. Studies have shown that Tan IIA is at least partially regulated by regulating CXCR4 expression (Xie et al., 2013). Tan IIA can improve the survival rate of MSCs, and some researchers have reported that Tan IIA can promote the differentiation of transplanted BMSCs into neurocell-like cells in SCI models. The hypothesized mechanism is that TIIA can improve the survival rate of transplanted BMSCs, increase the level of nutrient factors secreted by BMSCs to the lesion area, and reduce the secretion of inflammatory cytokines (Zhang et al., 2018). Tan IIA may better induce the osteogenic ability of MSCs. Studies have confirmed that Tan IIA can induce hPDLSC osteogenesis through the ERK1/2-Runx2 axis, which provides a choice in regenerative medicine approaches for the treatment of periodontitis (Liu et al., 2019). However, Tan IIA-modified MSCs can play a better role; for example, researchers have reported that Tan IIA-pretreated stem cells can reduce neuronal death by increasing the levels of anti-inflammatory cytokines (such as IL-4, -6, -8, and -13) and reducing inflammation through the PI3K/Akt/mTOR and/or TREM2 signalling pathways (Dai et al., 2017; Huang et al., 2022; Kaiser et al., 2022; Wu et al., 2024). Studies have also shown that TIIA-MSCs can significantly improve the learning and memory ability of A β ₂₅₋₃₅ model rats and are more effective than MSCs. The protective mechanism may involve promoting the survival of hippocampal neurons by downregulating BACE1 expression and regulating neuroinflammation-related cytokines (Huang et al., 2019). In general, many studies have investigated the modification effect of Tan IIA on MSCs, but the specific mechanism of action of Tan IIA on MSC modification still needs further study.

3.5 Astragaloside IV (AGS-IV)

AGS-IV is one of the main compounds of *Astragalus membranaceus* water extract and is a cycloartemisan-type

triterpenoid glycoside chemical. Several studies have shown that AGS-IV has a strong protective effect on cardiovascular, lung, kidney, and brain-related diseases (Zhang et al., 2020). The pharmacological effects of AGS-IV are multifactorial and include anti-inflammatory effects via the inhibition of inflammatory factors, increased proliferation of T and B lymphocytes, and the inhibition of neutrophil adhesion-related molecules. Moreover, it has neuroprotective, antifibrotic and antitumour effects (Liang et al., 2023).

The ability of AGS-IV to modify MSCs is first reflected in the increased proliferative and paracrine activities of these cells. AGS-IV-treated ADSCs can significantly reverse the UV-B-induced decrease in PC-I secretion and increase MMP-1 release in fibroblasts. In addition, ASI-treated ADSCs significantly increased dermal thickness, collagen content, and microvascular density in the photoaged skin of nude mice (Niu et al., 2020). Second, AGS-IV has a positive effect on the cell cycle and osteogenic differentiation of MSCs. Studies have shown that AGS-IV can promote the activity of hBMSCs, the cell cycle, ALP activity and osteogenic differentiation through the miR-124-3p.1/STAT3 axis while increasing the expression of osteoblast marker molecules (Cao et al., 2021). Furthermore, AS-IV improved ADSC migration, angiogenesis, and endothelial recruitment. *In vivo*, AS-IV-pretreated ADSCs have greater angiogenesis potential and better therapeutic efficacy in ischaemic hindlimb models. The molecular mechanism may be related to the upregulation of CXCR2 to promote the phosphorylation of FAK (Wang et al., 2022). In contrast to other biological compounds, some studies have combined the modification effect of AGS-IV on MSCs with other biological compounds to explore the modification effect on MSCs. Studies have shown that the combination of tanshinone IIA and astragaloside IV can promote the proliferation and differentiation of MSCs. The mechanism may involve regulating the mobilization of MSCs by regulating the expression of CXCR4. Similarly, studies have shown that they can promote angiogenesis of endothelium-like cells by upregulating the expression of Cx37, Cx40 and Cx43 and enhancing the function of intercellular communication (Xie et al., 2013; Li et al., 2018).

3.6 Curcumin

Curcumin (1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione) is a phenolic natural product isolated from the roots of *Curcuma longa* L. Curcumin is reported to be a nutritional compound with a wide range of therapeutic effects and great medicinal potential. Curcumin has a variety of pharmacological effects, including anti-inflammatory, antioxidant, antiproliferative and antiangiogenic effects. It has been extensively studied in a variety of diseases, including cancer, cardiovascular disease, diabetes, arthritis, neurological diseases, and Crohn's disease (Genchi et al., 2024; Moon, 2024).

In terms of the ability of curcumin to modify MSCs, first, curcumin can slow the ageing of MSCs. Some studies have shown that curcumin can delay ageing by activating autophagy (Deng et al., 2021), and some studies have reported that its antiaging effect is related to its concentration. Curcumin at concentrations of 1 and 5 μ M is a good antioxidant that can improve the lifespan of

ASCs. The mechanism involves increasing the expression of the *TERT* gene (Pirmoradi et al., 2018). Second, curcumin can promote the osteogenic differentiation of BMSCs and inhibit the formation of adipocytes, which may be related to the expression of HO-1 (Gu et al., 2012). It has also been confirmed that curcumin can inhibit the expression of Kruppel-like Factor 15 (KLF15), which may bind to the PPAR γ promoter, resulting in the downregulation of PPAR γ expression to inhibit the lipid-forming differentiation of hMSCs. In addition, it can also protect the mitochondrial function of BMSCs. Moreover, it can improve the tolerance of ASCs to oxidative stress damage (Wang et al., 2019). The dual effects of curcumin on stem cell survival and proliferation are related to its concentration, treatment period and type of stem cells. Therefore, these results should be applied reasonably to aid in understanding the role of curcumin in the transformation of stem cells (Attari et al., 2015).

3.7 Ginsenoside Rg1

Ginsenoside Rg1 belongs to the B-panaxtriol group of ginsenosides and is one of the main natural bioactive compounds of *Panax ginseng*. In traditional Chinese medicine, roots and rhizomes are the main medicinal parts of the plant. Rg1 ginsenosides are present in the stems, leaves and buds of *P. ginseng* and *Panax notoginseng* (Wu et al., 2022). In recent years, the pharmacological activity and bioavailability of ginsenoside Rg1 have been studied, and some new insights have been obtained (Gao et al., 2020; Lu et al., 2022). Ginsenoside Rg1 is a natural *ginseng* extract that has a variety of pharmacological effects, including anti-inflammatory, antioxidant and antiaging properties (Wang et al., 2021). The antiaging and antioxidant effects of Rg1 are related to the activation of the nuclear Factor E2-related Factor 2 (Nrf2) signalling pathway. Rg1 may activate the Nrf2 pathway by upregulating P62 and activating Akt to increase the interaction between P62 and KEAP1. Therefore, the activation of Akt or Nrf2 may be an important target for preventing BMSC ageing (Wang et al., 2021). In addition, studies have shown that Rg1 can reduce overactivation of the Wnt pathway in ageing cells by inhibiting the phosphorylation of GSK-3 β and regulating the differentiation ability of MSCs (Wang et al., 2020). Rg1 can also promote the osteogenic differentiation of MSCs. Studies have shown that Rg1 can promote the osteogenic differentiation of BMSCs by activating the GR/BMP-2 signalling pathway (Gu et al., 2016). Other studies have shown that Rg1 can also induce the expression of cellular neurons, such as cells. The researchers cultured rat MSCs with the serum-free ginsenoside Rg1 (10 μ mol/L) for 3 days. Some of the cells expressed NSE, but GFAP staining was negative. The *NGF* mRNA level in the ginsenoside Rg1 treatment group was significantly greater than that in the control group, suggesting that ginsenoside Rg1 induced neuron-like cells to express *NGF* mRNA (Si et al., 2014).

3.8 Thymoquinone (TQ)

Nigella damascena L. is an annual herb in the *Ranunculaceae* family. TQ is the key active component of *N. damascena* L., with a molecular formula of C₁₀H₁₂O₂ and a molar mass of 164.20 g/mol (Mekhemar et al., 2020). Its anti-inflammatory, antioxidant,

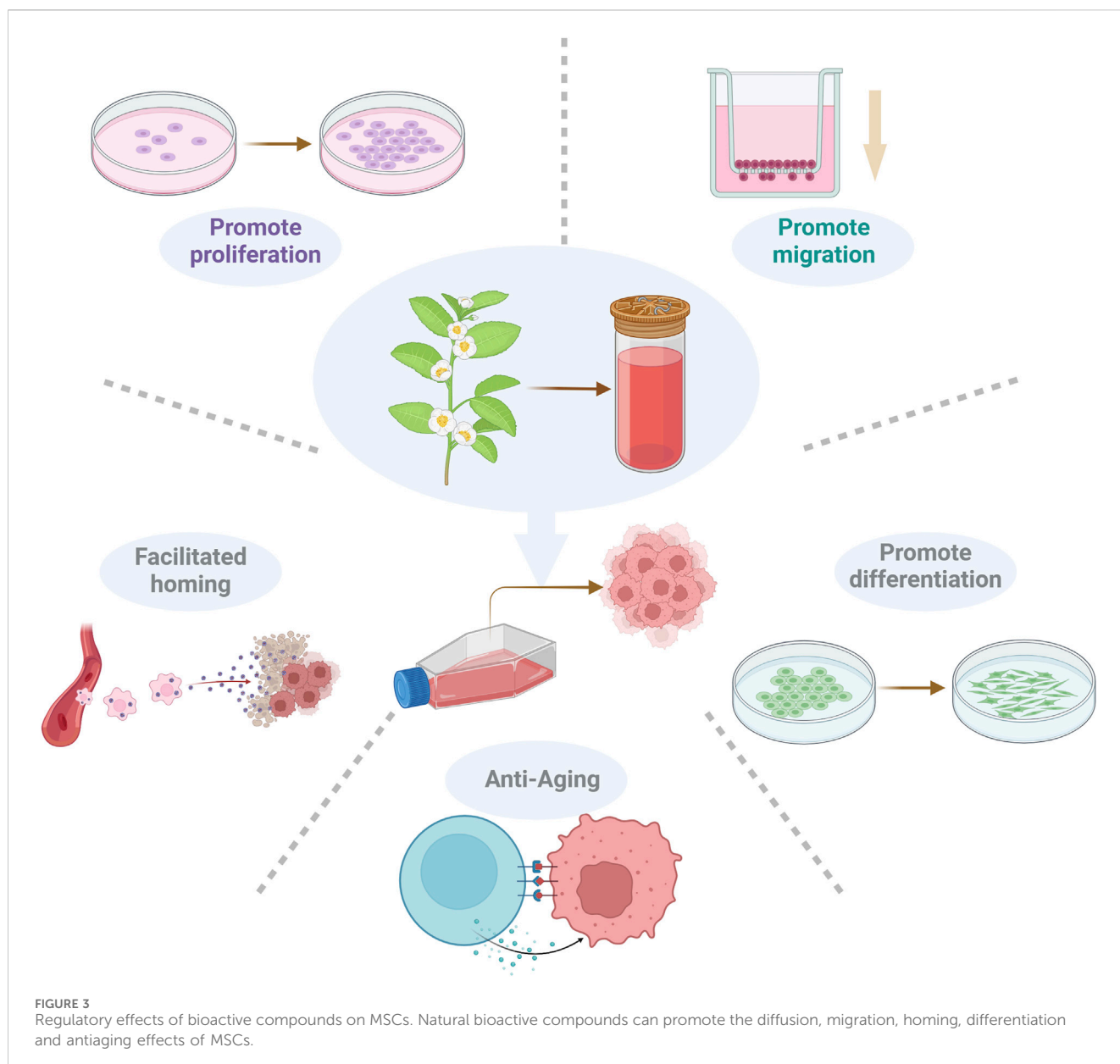
antibacterial and anticancer properties have broad application prospects in biomedicine. TQ-mediated stimulation preserves the pluripotency of gingival mesenchymal stem cells/progenitors (G-MSCs) and promotes the transformation of these cells into immunocompetent differentiated phenotypes by increasing TLR3 expression. This characteristic may influence the potential therapeutic application of G-MSCs (Mekhemar et al., 2022). TQ can alter angiogenesis and the mesenchymal to epithelial transformation of human breast CSCs *in vitro*. Therefore, TQ, together with antiangiogenic therapy, may be a novel therapeutic agent to inhibit breast cancer angiogenesis (Haiaty et al., 2021a; Haiaty et al., 2021b).

Acute neurodegeneration due to stroke or trauma, for example, can lead to local cell damage in the injured area, whereas chronic neurodegeneration can lead to damage to specific subtypes of neurons and widespread loss of specific groups of neurons (Qin et al., 2007). Regenerating neurons by using stem cells seems to be a useful approach, as these cells can differentiate into multiple lineages (Lunn et al., 2011). The potential of stem cells to differentiate into neuronal lineages can be enhanced by the use of various compounds. TQ is a bioactive compound with neuroprotective properties (Ishaque et al., 2022). TQ was found to induce the differentiation of MSCs and promote significant gene expression of neuronal markers, including neuronal-specific enolase (NSE), nestin, microtubule-associated protein 2 (MAP2), neurofilament light chain (Nefl), and tau, as well as astrocyte markers, Glial fibrillary acidic protein (GFAP) (Ishaque et al., 2022). Similarly, studies have shown that TQ promotes the acceleration of stem cell differentiation into osteoblasts, the mechanism of which may be related to the inhibition of NF- κ B signalling (Banu, 2022), and has been shown to not alter the physical and mechanical properties of the scaffold (Rahmani-Moghadam et al., 2021).

3.9 Ptychotis verticillata (PV)

Ptychotis verticillata L. is an aromatic plant, and PV and its phytochemical components (thymol and carvacrol) have been reported as valuable medicinal candidates (El Ouariachi et al., 2011; Seo et al., 2019). Some studies have explored the effects of PV and its compounds on the immunological characteristics of MSCs. It was first emphasized that PV extracts can maintain low immunogenicity and enhance the immunomodulatory function of MSCs. The positive effects of the essential oils thymol and carvacrol on the immune properties of MSCs will open a new field for the use of natural compounds in cell therapy (Najar et al., 2024). Like many of the compounds mentioned earlier, thymol is also concentration dependent, and in the presence of thymol (3 and 6 μ g/mL), MSCs show an increased ability to inhibit T-cell responses during direct coculture. High concentrations of thymol were more effective at reducing MSC-activated T-cell responses. The incubation time also affected the inhibitory properties of MSCs pretreated with thymol, as a small reduction was observed after 5 days. Based on this evidence, we aimed to study the effects of the characteristics of the MSC immune system, PV and its compounds (Najar et al., 2024). In addition, carvacrol and thymol have been shown to alter the maturation and function of dendritic cells, as well as the T-cell response and activation.

Different plant-derived components have been shown to promote MSC migration and homing to damaged sites to enhance tissue repair and healing. The activation of the PI3K



and MAPK signalling pathways and the CXCL12/CXCR4 axis and the increased expression of matrix metalloproteinases (MMPs) may stimulate extracellular matrix remodelling, thereby promoting the migration of MSCs (Maeda, 2020). Other studies have shown that thymol and carvacrol increase osteogenesis and adipogenesis in a time- and dose-dependent manner and stimulate tissue regeneration and the repair function of MSCs, and further optimization of PV compound extraction and characterization and cell processing conditions should increase their therapeutic value in combination with MSCs (Bouhtit et al., 2022).

4 Regulatory effects of natural bioactive compounds on MSCs

Although many natural bioactive compounds have shown great potential for improving MSCs, they involve many mechanisms and

pathways, making related research complicated and confusing. In fact, we found that natural bioactive compounds promote MSC proliferation, migration and homing and promote MSC differentiation and antiaging effects (Figure 3). However, their effects can be guaranteed only under certain conditions. For example, although resveratrol can increase the self-renewal potential and pluripotency of early-passage MSCs, it also accelerates the senescence of late-passage MSCs. Therefore, cell passage and SIRT1 expression must be considered before resveratrol is used for late-passage MSCs (Yoon et al., 2015). In addition, the amount of naturally active compounds is also an important influencing factor; for example, 250 mg/kg/day is the most effective dose under the conditions where ICA has been shown to be beneficial to OP rats. However, ICA may inhibit the differentiation of MSCs into adipocytes by inhibiting the expression of *PPAR γ* , *C/EBP α* , and *FABP4* mRNAs. ICA can also inhibit *Notch2* mRNA expression by inhibiting *NIICD* expression. Therefore, further preclinical studies are needed to better define the pharmacological

targets of ICA and to determine the associations between different signalling pathways (Liu et al., 2017). In the modification of MSCs by GBE, the key role of drug concentration was clearly proposed, and it was proposed that GBE improved the proliferation and osteogenesis of human BM-MSCs in a dose-dependent manner in the range of 25–75 mg/L. However, this effect was weakened or inhibited at 100 mg/L or higher (Gu et al., 2015). In summary, natural bioactive compounds have complex and context-dependent effects on MSCs.

4.1 Promotion of proliferation, migration and homing

Although MSCs have various advantages and good applications in regenerative medicine, they are limited in the amount of tissue they target and have challenges associated with poor migration and homing. Therefore, it is worth exploring how to promote the proliferation, migration and homing of MSCs to play a better role in clinical practice (Galipeau and Sensébé, 2018; Ullah et al., 2019). RSVL can play a positive role in the treatment of periodontitis by promoting the proliferation of MSCs (Jiang et al., 2023). Furthermore, AS-IV improved ADSC migration (Wang et al., 2022). *In vivo* animal experiments have confirmed that Rg1 promotes the homing of rabbit BMSCs to myocardial tissue (Wang et al., 2005). These changes reduced the myocardial infarct size and improved cardiac function. Some of them are obviously related to their concentration, so special attention should be given to this point when they are used (Gu et al., 2015).

4.2 Promotion of differentiation

In some pathological conditions, such as ageing, osteoporosis and some bone defects, the osteogenic ability of BMSCs is significantly inhibited. Therefore, methods that can modulate the osteogenic differentiation of BMSCs to manage and treat these diseases are needed (Houdek et al., 2016; Zhang et al., 2021). In addition to RSVL, GBE, Tan IIA, and AGS-IV can promote the osteogenic differentiation of MSCs, as mentioned above, and studies have shown that walnut leaf extract regulates the osteogenic differentiation and autophagy of hBMSCs through the BMP2/Smad/Runx2 and Wnt/ β -catenin pathways (Pang et al., 2022). Unlike the concentration dependence mentioned earlier, this study confirmed that different concentrations of walnut leaf extract did not have a significant effect on cell proliferation, indicating a reliable safety profile of hBMSCs treated with walnut leaf extract (Pang et al., 2022). Quercetin can activate the Wnt/ β -catenin pathway through the H19/miR-625-5p axis and promote the osteogenic differentiation of BMSCs (Bian et al., 2021). In summary, various natural bioactive compounds have been demonstrated to enhance the differentiation of MSCs through distinct signalling pathways.

4.3 Anti-aging

Cellular senescence is the result of cumulative changes in cellular structure and function. Its function manifests as reduced oxidative phosphorylation, a slowed respiratory rate, and reduced enzyme activity

and receptor protein levels, resulting in decreased cell function and inhibited cell proliferation (Young et al., 2019). Studies have shown that senescent cells and the VDR gene expression interference system can reduce cell viability, proliferation and bone differentiation ability. MSCs inevitably encounter the problem of ageing, but studies have shown that after the addition of Astragalus, the viability and osteogenic ability of BMSCs are significantly increased. Among them, the expression levels of FGF23, Klotho and CYP24A1 decreased, whereas the expression level of CYP27B1 increased, and the effect became more obvious with increasing Astragalus concentration. It has been confirmed that astragalus can inhibit the ageing of BMSCs and improve their osteogenic ability by regulating the VD-FGF23-Klotho pathway (Pu et al., 2020). As mentioned earlier, curcumin can alleviate the ageing of BMSCs by activating autophagy, and curcumin is also a good antioxidant that can increase the lifespan of ASCs (Liu et al., 2015; Ayadilord et al., 2022). In summary, regulating ageing-related pathways and promoting autophagy are key to improving the effects of natural bioactive compounds on MSCs. The effects of natural bioactive compounds themselves, such as antioxidation, are the potential basis for these effects.

5 Discussion

With the continuous development of cell therapy, researchers are striving to achieve the goal of effective repair and regeneration after tissue damage. The application of allogeneic human stem cells benefits from the immune tolerance of specific types of stem cells. In this context, the use of MSCs as promising tools for cellular immunotherapy is being explored for the treatment of a variety of diseases (Hussen et al., 2024). However, the clinical application of MSCs also faces many challenges. In the process of preparing MSC products, the main challenges include the following: 1) the heterogeneity of MSCs is caused by donor differences such as health status, genetics, gender and age. 2) The dry stability and differentiation ability of MSCs isolated from different sources (such as bone marrow, adipose tissue, the umbilical cord, or muscle) differ. 3) The amplification ability was different under different culture conditions. In stem cell applications, the application of MSCs may be limited for the following reasons: 1) Challenges remain regarding the influence of the homing or migration ability of MSCs under different administration routes (local/systemic), injection sites, infusion times, and cell carrier materials. 2) Immunocompatibility between donors and recipients is key to reducing the risk of rejection. 3) The complex active components released by MSCs depend on the host microenvironment (inflammatory state, hypoxia, and ECM), which can lead to highly variable factors shaping the different functions of MSCs (Zhou et al., 2021). Therefore, improving the treatment efficiency of MSCs on the premise of ensuring safety, which has been discussed in the relevant literature (Seo et al., 2019), is imperative.

Natural bioactive compounds such as RSVL, GBE and curcumin can regulate the survival and proliferation of MSCs, but their effects on proliferation are closely related to their concentration, so caution should be taken. ICA and RSVL can promote osteogenic differentiation and inhibit lipid differentiation via different mechanisms, and research on nonbone tissue differentiation is insufficient. Tan IIA and AGS-IV can promote MSC migration

and homing, but few relevant studies exist. Curcumin and Rg1 can inhibit MSC ageing, but such studies are scarce. These compounds have multitarget and multilevel effects, have different effects on the improvement of MSCs, and may receive more attention in the future.

Although the effects of many bioactive compounds on MSCs have been discussed above, several issues warrant attention. For example, not all concentrations of bioactive compounds can positively modify MSCs, and they are not all concentration dependent; each has its own characteristics. In addition, relatively few *in vivo* experiments have investigated the effects of natural bioactive compounds on MSCs, which may be the direction of our attention in the future. Moreover, another challenge is that most of the natural bioactive compounds mentioned in the literature are only 98% or 99% pure. However, their application in the field of stem cell research is promising, and we hope to further identify their purity, remove impurities, and achieve better promotion and application of these compounds in the future (Li et al., 2024).

6 Conclusion

Different types of natural bioactive compounds have different effects on the improvement of MSCs, such as promoting their proliferation and differentiation, migration and homing, and antiaging effects. It is expected that improved MSCs can provide new ideas for disease treatment and regenerative medicine in the future.

Author contributions

JW: Funding acquisition, Writing – original draft, Writing – review and editing. YG: Writing – review and editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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