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Stem Cell

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Stem Cell Research Literatures (4)

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Abstract: Stem cells are derived from embryonic and non-embryonic tissues. Most stem cell studies are for animal stem cells and plants have also stem cell. Stem cells were discovered in 1981 from early mouse embryos. Stem cells have the potential to develop into all different cell types in the living body. Stem cell is a body repair system. When a stem cell divides it can be still a stem cell or become adult cell, such as a brain cell. Stem cells are unspecialized cells and can renew themselves by cell division, and stem cells can also differentiate to adult cells with special functions. Stem cells replace the old cells and repair the damaged tissues. Embryonic stem cells can become all cell types of the body because they are pluripotent. Adult stem cells are thought to be limited to differentiating into different cell types of their tissue of origin. This article introduces recent research reports as references in the related studies.
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Key words: stem cell; life; research; literature

Introduction

The stem cell is the origin of an organism's life that has the potential to develop into many different types of cells in life bodies. In many tissues stem cells serve as a sort of internal repair system, dividing essentially without limit to replenish other cells as long as the person or animal is still alive. When a stem cell divides, each new cell has the potential either to remain a stem cell or become another type of cell with a more specialized function, such as a red blood cell or a brain cell. This article introduces recent research reports as references in the related studies.

The following introduces recent reports as references in the related studies.

Chen, C. H., et al. (2005). "Green tea catechin enhances osteogenesis in a bone marrow mesenchymal stem cell line." Osteoporos Int **16**(12): 2039-2045.

Green tea has been reported to possess antioxidant, antitumorigenic, and antibacterial qualities that regulate the endocrine system. Previous epidemiological studies found that the bone mineral density (BMD) of postmenopausal women with a habit of tea drinking was higher than that of women without habitual tea consumption. However, the effects of green tea catechins on osteogenic function have rarely been investigated. In this study, we tested (-)-epigallocatechin-3-gallate (EGCG), one of the green tea catechins, on cell proliferation, the mRNA expressions of relevant osteogenic markers, alkaline phosphatase (ALP) activity and mineralization. In a murine bone marrow mesenchymal stem cell line, D1, the mRNA expressions of core binding factors a1 (Cbfa1/Runx2), osterix, osteocalcin, ALP increased after 48 h of EGCG treatment. ALP activity was also significantly augmented upon EGCG treatment for 4 days, 7 days and 14 days. Furthermore, mineralizations assayed by Alizarin Red S and von Kossa stain were enhanced after EGCG treatment for 2-4 weeks in D1 cell cultures. However, a 24-h treatment of EGCG inhibited thymidine incorporation of D1 cells. These results demonstrated that long-term treatment of EGCG increases the expressions of osteogenic genes, elevates ALP activity and eventually stimulates mineralization, in spite of its inhibitory effect on proliferation. This finding suggests that the stimulatory effects of EGCG on osteogenesis of mesenchymal stem cells may be one of the mechanisms that allow tea drinkers to possess higher BMD.

Chen, Y. B., et al. (2015). "Mesenchymal stem cell-based HSP70 promoter-driven VEGFA induction by resveratrol alleviates elastase-induced emphysema in a mouse model." Cell Stress Chaperones **20**(6): 979-989.

Chronic obstructive pulmonary disease (COPD) is a sustained blockage of the airways due to lung inflammation occurring with chronic bronchitis and/or emphysema. Progression of emphysema may be slowed by vascular endothelial growth factor A (VEGFA), which reduces apoptotic tissue depletion. Previously, authors of the present report demonstrated that cis-resveratrol (c-RSV)-induced heat-shock protein 70 (HSP70) promoter-regulated VEGFA expression promoted neovascularization of genetically modified mesenchymal stem cells (HSP-VEGFA-MSC) in a mouse model of ischemic disease. Here, this same stem

cell line was evaluated for its protective capacity to alleviate elastase-induced pulmonary emphysema in mice. Results of this study showed that c-RSV-treatment of HSP-VEGFA-MSC exhibited synergy between HSP70 transcription activity and induced expression of anti-oxidant-related genes when challenged by cigarette smoke extracts. Eight weeks after jugular vein injection of HSP-VEGFA-MSC into mice with elastase-induced pulmonary emphysema followed by c-RSV treatment to induce transgene expression, significant improvement was observed in respiratory functions. Expression of VEGFA, endogenous nuclear factor erythroid 2-related factor (Nrf 2), and manganese superoxide dismutase (MnSOD) was significantly increased in the lung tissues of the c-RSV-treated mice. Histopathologic examination of treated mice revealed gradual but significant abatement of emphysema and restoration of airspace volume. In conclusion, the present investigation demonstrates that c-RSV-regulated VEGFA expression in HSP-VEGFA-MSC significantly improved the therapeutic effects on the treatment of COPD in the mouse, possibly avoiding side effects associated with constitutive VEGFA expression.

Gao, P., et al. (2015). "Salvianolic acid B improves bone marrow-derived mesenchymal stem cell differentiation into alveolar epithelial cells type I via Wnt signaling." Mol Med Rep **12**(2): 1971-1976.

Acute lung injury (ALI) is among the most common causes of mortality in intensive care units. Previous studies have suggested that bone marrow-derived mesenchymal stem cells (BMSCs) may attenuate pulmonary edema. In addition, alveolar epithelial cells type I (ATI) are involved in reducing the alveolar edema in response to ALI. However, the mechanism involved in improving the efficiency of differentiation of MSCs into ATI remains to be elucidated. In the present study, the effect of salvianolic acid B (Sal B) on the differentiation of BMSCs into ATI and the activities of the Wnt signaling pathways were investigated. The BMSCs were supplemented with conditioned medium (CM). The groups were as follows: i) CM group: BMSCs were supplemented with CM; ii) lithium chloride (LiCl) group: BMSCs were supplemented with CM and 5 mM LiCl; iii) Sal B group: BMSCs were supplemented with CM and 10 mM Sal B. The samples were collected and assessed on days 7 and 14. It was revealed that aquaporin (AQP)-5 and T1alpha were expressed in BMSCs, and induction with LiCl or Sal B increased the expression of AQP-5 and T1alpha. Furthermore, the Wnt-1 and Wnt-3a signaling pathways were activated during the differentiation of BMSCs into ATI. In conclusion, it was suggested that the promotive effects of Sal B on the differentiation of BMSCs into ATI occurred through the activation of Wnt signaling pathways.

Gong, X. (2016). "PROTECTIVE EFFECT OF Ailanthus excelsa ROXB IN MYOCARDIAL INFARCTION POST MESENCHYMAL STEM CELL TRANSPLANTATION: STUDY IN CHRONIC ISCHEMIC RAT MODEL." Afr J Tradit Complement Altern Med **13**(6): 155-162.

BACKGROUND: Thia study evaluates the effects of Ailanthus excelsa Roxb methanolic extract (AER-ME) in rats induced with Myocardial Infarction (MI) followed by transplantation of MSCs. MATERIAL AND METHODS: Rats were induced with MI by ligation technique of left coronary artery. The sham-operated the control and AER-ME treated group of rats received transplantation of PKH-26 and marked MSCs followed by normal saline and AER-ME treatment (200mg/kg/day of AER-ME extract) respectively for 30 days. Parameters such as cardiac function, inflammation, oxidative stress, apoptosis and differentiation of MSCs (angiogenesis) were evaluated. Histological studies of infracted myocardium reveled anti-inflammatory activity of AER-ME treatment. RESULT AND DISCUSSION: Oxidative stress parameters revealed decrease in levels of malondialdehyde (MDA) and increase in superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GSHpx) activity significantly indicating antioxidant activity of the extract. There was a reduction in cell death rate of treated rats due to the decrease in apoptotic index with prolongation of MI when compared to both control and sham-operated groups. The expression of Fas protein was parallel to apoptotic index. The vascular density increased significantly in extract treated group. The treatment showed improved cardiac activity with decreased left ventricular end diastolic (LVEDP) and arterial pressure while the left ventricular end systolic pressure (LVEP) and dp/dtmax increased significantly when compared to both control and sham-operated groups respectively showing the protective effect of the extract as necessitated by the transplantation of MSCs. The study marked the protective outcomes of AER-ME treatment for MSCs in microenvironment of infracted myocardium by improving their viability and increasing differentiation into cardiomyocytes.

Harrell, C. R., et al. (2018). "Therapeutic Potential of Mesenchymal Stem Cell-Derived Exosomes in the Treatment of Eye Diseases." Adv Exp Med Biol.

Mesenchymal stem cells (MSCs) were, due to their immunomodulatory and pro-angiogenic characteristics, extensively explored as new therapeutic agents in cell-based therapy of uveitis, glaucoma, retinal and ocular surface diseases.Since it was recently

revealed that exosomes play an important role in biological functions of MSCs, herewith we summarized current knowledge about the morphology, structure, phenotype and functional characteristics of MSC-derived exosomes emphasizing their therapeutic potential in the treatment of eye diseases.MSC-derived exosomes were as efficient as transplanted MSCs in limiting the extent of eye injury and inflammation. Immediately after intravitreal injection, MSC-derived exosomes, due to nano-dimension, diffused rapidly throughout the retina and significantly attenuated retinal damage and inflammation. MSC-derived exosomes successfully delivered trophic and immunomodulatory factors to the inner retina and efficiently promoted survival and neuritogenesis of injured retinal ganglion cells. MSC-derived exosomes efficiently suppressed migration of inflammatory cells, attenuated detrimental Th1 and Th17 cell-driven immune response and ameliorated experimental autoimmune uveitis. MSC-derived exosomes were able to fuse with the lysosomes within corneal cells, enabling delivering of MSC-derived active beta-glucuronidase and consequent catabolism of accumulated glycosaminoglycans, indicating their therapeutic potential in the treatment of Mucopolysaccharidosis VII (Sly Syndrome). Importantly, beneficent effects were noticed only in animals that received MSC-derived exosomes and were not seen after therapy with fibroblasts-derived exosomes confirming specific therapeutic potential of MSCs and their products in the treatment of eye diseases.In conclusion, MSC-derived exosomes represent potentially new therapeutic agents in the therapy of degenerative and inflammatory ocular diseases.

He, W., et al. (2010). "[Effect of ginsenoside Rg1 on the microenvironment dependent differentiation of human bone marrow mesenchymal stem cell to vaso-endothelioid formative cells in vitro]." Zhongguo Zhong Xi Yi Jie He Za Zhi **30**(11): 1201-1205.

OBJECTIVE: To investigate the effect of ginsenoside Rg1 on the microenvironment dependent differentiation of human mesenchymal stem cells (hMSCs) to vaso-endothelioid cells (VECs) in vitro. METHODS: The in vitro differentiation of hMSCs to VECs were established adopting the in vivo environment simulated semi-permeable membrane separated non-contact co-culturing method. The mRNA expressions of endothelial markers, such as platelet endothelial adhesive factor-1 (CD31), vascular hemophillia factor (vWF) and vascular endothelial cadherin (VE-cadherin) were analyzed by RT-PCR; the protein expressions of CD31 and vascular endothelial adhesive factor-1 (VCAM1) were detected by fluorescence immunohistochemistry; structural identification for the endothelial characteristics of differentiated hMSCs were made under electron microscopy; and the percentage of CD31 expression in differentiated hMSCs was determined by flow cytometry to explore the effect of ginsenoside Rg1 on the differentiation. RESULTS: The bone marrow mesenchymal stem cells co-cultured with mature endothelial membrane showed a microenvironment dependent capacity for differentiating to endothelium, with the morphological changes revealed starting from the 2nd week, showing cell body contraction, polygonal-shaped change; and at the 3rd week, the markedly speedily cell proliferation with elliptic or slabstone-like change of cells. High levels of classic endothelial cell markers, such as mRNA expressions of CD31, vWF, VE-cadherin, and protein expressions of CD31 and VCAM1, were shown; the typical weibel-palade body of endothelial cell was found in the differentiated cells. Moreover, percentage of CD31 expression in the differentiated hMSCs was increased after Rg1 treatment dose-dependently. CONCLUSION: Under the microenvironment of co-culture, hMSCs could differentiate into cells presenting the characteristics of endothelial cell in aspects of the morphology and ultrastructure of cells, as well as the gene and protein expressions of cell markers; ginsenoside Rg1 can promote the microenvironment dependent differentiation of hMSCs to VECs system in vitro.

Jakovljevic, J., et al. (2018). "Modulation of autophagy as new approach in mesenchymal stem cell-based therapy." Biomed Pharmacother **104**: 404-410.

Due to their trophic and immunoregulatory characteristics mesenchymal stem cells (MSCs) have tremendous potential for use in a variety of clinical applications. Challenges in MSCs' clinical applications include low survival of transplanted cells and low grafting efficiency requiring use of a high number of MSCs to achieve therapeutic benefits. Accordingly, new approaches are urgently needed in order to overcome these limitations. Recent evidence indicates that modulation of autophagy in MSCs prior to their transplantation enhances survival and viability of engrafted MSCs and promotes their pro-angiogenic and immunomodulatory characteristics. Here, we review the current literature describing mechanisms by which modulation of autophagy strengthens pro-angiogenic and immunosuppressive characteristics of MSCs in animal models of multiple sclerosis, osteoporosis, diabetic limb ischemia, myocardial infarction, acute graft-versus-host disease, kidney and liver diseases. Obtained results suggest that modulation of autophagy in MSCs may represent a new therapeutic approach that could enhance efficacy of MSCs in the treatment of ischemic and autoimmune diseases.

Jezierska-Wozniak, K., et al. (2018). "Migration of human mesenchymal stem cells stimulated with pulsed electric field and the dynamics of the cell surface glycosylation." Adv Clin Exp Med **27**(9): 1181-1193.

BACKGROUND: The analysis of the stem cells' glycome dynamics at different stages of differentiation and migration makes possible the exploration of the cell surface glycans as markers of the stem cell functional status, and, in the future, compatibility between transplanted cell and host environment. OBJECTIVES: The objective of our study was to develop novel techniques of investigating cell motility and to assess whether the electric field of the therapeutic spinal cord stimulation system used in vivo contributes to the migration of human mesenchymal stem cells (hMSCs) in vitro. MATERIAL AND METHODS: We have investigated the electrotaxis of bone marrow-derived MSCs using pulsed electric field (PEF) in the range of 16-80 mV/mm and the frequency of 130 Hz and 240 Hz. The PEF-related dynamics of the cell surface glycosylation was evaluated using 6 plant lectins recognizing individual glycans. RESULTS: Pulsed electric field at physiological levels (10 mV/mm; 130 Hz) did not influence cellular motility in vitro, which may correspond to the maintenance of the transplanted cells at the lesion site in vivo. An increase of the PEF intensity and the frequency exceeding physiological levels resulted in an increase in the cellular migration rate in vitro. Pulsed electric field elevated above physiological intensity and frequency (40-80 mV/mm; 240 Hz), but not at physiological levels, resulted in changes of the cell surface glycosylation. CONCLUSIONS: We found the described approach convenient for investigations and for the in vitro modeling of the cellular systems intended for the regenerative cell transplantations in vivo. Probing cell surface glycomes may provide valuable biomarkers to assess the competence of transplanted cells.

Jin, Z., et al. (2015). "[Effects and possible mechanisms of mesenchymal stem cell transplantation on emphysema in rats]." Zhonghua Yi Xue Za Zhi **95**(22): 1731-1735.

OBJECTIVE: To explore the effects of transplanting bone marrow mesenehymal stem cells (MSCs) on emphysema in rats and elucidate the possible mechanisms. METHODS: A total of 24 female Sprague-Dawley rats were randomly divided randomly into 3 groups of control, emphysema and MSCs transplantation (n=8 each). The rat model of emphysema was established by 14-week exposure to cigarette smoking and then MSCs labeled with 4, 6-diamidino-2-phenylindole (DAPI) were injected into recipient rats of MSCs transplantation group via tail veins. At 2 and 4 weeks post-transplantation, engraftment and differentiation of MSCs was determined. At 8 weeks post-transplantation, lung fissure sections were prepared for examining the morphological alterations. The apoptosis of alveolar septal cells was assessed. And the levels of oxidative stress in sera and lung were detected. RESULTS: At 2 and 4 weeks post-transplantation, MSCs labeled with DAPI could be found in recipient lungs, some of which differentiated into type II alveolar epithelial cells. Mean linear intercept was higher in emphysema and MSCs transplantation groups than control group [(111 +/- 23) and (90 +/- 15) vs (74 +/- 10) microm], mean alveolar numbers were lower than control group [(94 +/- 22) and (125 +/- 15) vs (159 +/- 22)/mm(2)] (all $P<0.05$); mean linear intercept was higher and mean alveolar numbers were lower in emphysema group than MSCs transplantation group (both $P<0.05$). The apoptotic index of alveolar wall cells in emphysema group was higher than MSCs transplantation group [(13.5 +/- 2.5)% vs (4.8 +/- 0.7)%, $P<0.05$]. Malondialdehyde of sera and lung in emphysema and MSCs transplantation groups was higher than control group [(4.3 +/- 0.8), (3.7 +/- 0.4) vs (3.0 +/- 0.4) nmol/ml, (5.4 +/- 0.5), (4.8 +/- 0.4) vs (4.2 +/- 0.6) nmol/mg, all $P<0.05$]; malondialdehyde of sera and lung in emphysema group was higher than MSCs transplantation group (both $P<0.05$). Superoxide dismutase (SOD) of sera and lung in emphysema and MSCs transplantation groups was lower than control group [(8.7 +/- 0.8), (9.6 +/- 0.7) vs (10.5 +/- 0.9) U/ml and (56.3 +/- 13.4), (70.2 +/- 11.0) vs (84.9 +/- 13.0) U/mg, all $P<0.05$]; SOD of sera and lung in emphysema group was lower than MSCs transplantation group (both $P<0.05$). CONCLUSION: MSCs transplantation via tail vein may arrest the progression of emphysema in a cigarette-smoke-induced rat model of emphysema through a differentiation of injected MSCs into type II alveolar epithelial cells and down-regulations of apoptosis and oxidative stress.

Kim, D. S., et al. (2017). "Cell culture density affects the stemness gene expression of adipose tissue-derived mesenchymal stem cells." Biomed Rep **6**(3): 300-306.

The results of clinical trials using mesenchymal stem cells (MSCs) are controversial due to the heterogeneity of human MSCs and differences in culture conditions. In this regard, it is important to identify gene expression patterns according to culture conditions, and to determine how the cells are expanded and when they should be clinically used. In the current study, stemness gene expression was investigated in adipose tissue-derived MSCs (AT-MSCs) harvested following culture at different densities. AT-MSCs were plated at a density of 200 or

5,000 cells/cm(2). After 7 days of culture, stemness gene expression was examined by reverse transcription-quantitative polymerase chain reaction (RT-qPCR) analysis. The proliferation rate of AT-MSCs harvested at a low density (~50% confluent) was higher than that of AT-MSCs harvested at a high density (~90% confluent). Although there were differences in the expression levels of stemness gene, such as octamer-binding transcription factor 4, nanog homeobox (Nanog), SRY-box 2, Kruppel like factor 4, v-myc avian myelocytomatosis viral oncogene homolog (c-Myc), and lin-28 homolog A, in the AT-MSCs obtained from different donors, RT-qPCR analysis demonstrated differential gene expression patterns according to the cell culture density. Expression levels of stemness genes, particularly Nanog and c-Myc, were upregulated in AT-MSCs harvested at a low density (~50% confluent) in comparison to AT-MSCs from the same donor harvested at a high density (~90% confluent). These results imply that culture conditions, such as the cell density at harvesting, modulate the stemness gene expression and proliferation of MSCs.

Kim, D. S., et al. (2014). "Gene expression profiles of human adipose tissue-derived mesenchymal stem cells are modified by cell culture density." PLoS One **9**(1): e83363.

Previous studies conducted cell expansion ex vivo using low initial plating densities for optimal expansion and subsequent differentiation of mesenchymal stem cells (MSCs). However, MSC populations are heterogeneous and culture conditions can affect the characteristics of MSCs. In this study, differences in gene expression profiles of adipose tissue (AT)-derived MSCs were examined after harvesting cells cultured at different densities. AT-MSCs from three different donors were plated at a density of 200 or 5,000 cells/cm(2). After 7 days in culture, detailed gene expression profiles were investigated using a DNA chip microarray, and subsequently validated using a reverse transcription polymerase chain reaction (RT-PCR) analysis. Gene expression profiles were influenced primarily by the level of cell confluence at harvest. In MSCs harvested at approximately 90% confluence, 177 genes were up-regulated and 102 genes down-regulated relative to cells harvested at approximately 50% confluence ($P<0.05$, $FC>2$). Proliferation-related genes were highly expressed in MSCs harvested at low density, while genes that were highly expressed in MSCs harvested at high density (approximately 90% confluent) were linked to immunity and defense, cell communication, signal transduction and cell motility. Several cytokine, chemokine and growth factor genes involved in immunosuppression, migration, and reconstitution of damaged tissues were up-regulated in MSCs harvested at high density compared with MSCs harvested at low density. These results imply that cell density at harvest is a critical factor for modulating the specific gene-expression patterns of heterogeneous MSCs.

Kim, S. Y., et al. (2012). "Mesenchymal stem cell-conditioned media recovers lung fibroblasts from cigarette smoke-induced damage." Am J Physiol Lung Cell Mol Physiol **302**(9): L891-908.

Cigarette smoking causes apoptotic death, senescence, and impairment of repair functions in lung fibroblasts, which maintain the integrity of alveolar structure by producing extracellular matrix (ECM) proteins. Therefore, recovery of lung fibroblasts from cigarette smoke-induced damage may be crucial in regeneration of emphysematous lung resulting from degradation of ECM proteins and subsequent loss of alveolar cells. Recently, we reported that bone marrow-derived mesenchymal stem cell-conditioned media (MSC-CM) led to angiogenesis and regeneration of lung damaged by cigarette smoke. In this study, to further investigate reparative mechanisms for MSC-CM-mediated lung repair, we attempted to determine whether MSC-CM can recover lung fibroblasts from cigarette smoke-induced damage. In lung fibroblasts exposed to cigarette smoke extract (CSE), MSC-CM, not only inhibited apoptotic death, but also induced cell proliferation and reversed CSE-induced changes in the levels of caspase-3, p53, p21, p27, Akt, and p-Akt. MSC-CM also restored expression of ECM proteins and collagen gel contraction while suppressing CSE-induced expression of cyclooxygenase-2 and microsomal PGE(2) synthase-2. The CSE-opposing effects of MSC-CM on cell fate, expression of ECM proteins, and collagen gel contraction were partially inhibited by LY294002, a phosphatidylinositol 3-kinase (PI3K) inhibitor. In rats, MSC-CM administration also resulted in elevation of p-Akt and restored proliferation of lung fibroblasts, which was suppressed by exposure to cigarette smoke. Taken together, these data suggest that MSC-CM may recover lung fibroblasts from cigarette smoke-induced damage, possibly through inhibition of apoptosis, induction of proliferation, and restoration of lung fibroblast repair function, which are mediated in part by the PI3K/Akt pathway.

Li, X., et al. (2014). "Mitochondrial transfer of induced pluripotent stem cell-derived mesenchymal stem cells to airway epithelial cells attenuates cigarette smoke-induced damage." Am J Respir Cell Mol Biol **51**(3): 455-465.

Transplantation of mesenchymal stem cells (MSCs) holds great promise in the repair of cigarette

smoke (CS)-induced lung damage in chronic obstructive pulmonary disease (COPD). Because CS leads to mitochondrial dysfunction, we aimed to investigate the potential benefit of mitochondrial transfer from human-induced pluripotent stem cell-derived MSCs (iPSC-MSCs) to CS-exposed airway epithelial cells in vitro and in vivo. Rats were exposed to 4% CS for 1 hour daily for 56 days. At Days 29 and, human iPSC-MSCs or adult bone marrow-derived MSCs (BM-MSCs) were administered intravenously to CS-exposed rats. CS-exposed rats exhibited severe alveolar destruction with a higher mean linear intercept (Lm) than sham air-exposed rats ($P < 0.001$) that was attenuated in the presence of iPSC-MSCs or BM-MSCs ($P < 0.01$). The attenuation of Lm value and the severity of fibrosis was greater in the iPSC-MSC-treated group than in the BM-MSC-treated group ($P < 0.05$). This might have contributed to the novel observation of mitochondrial transfer from MSCs to rat airway epithelial cells in lung sections exposed to CS. In vitro studies further revealed that transfer of mitochondria from iPSC-MSCs to bronchial epithelial cells (BEAS-2B) was more effective than from BM-MSCs, with preservation of adenosine triphosphate contents. This distinct mitochondrial transfer occurred via the formation of tunneling nanotubes. Inhibition of tunneling nanotube formation blocked mitochondrial transfer. Our findings indicate a higher mitochondrial transfer capacity of iPSC-MSCs than BM-MSCs to rescue CS-induced mitochondrial damage. iPSC-MSCs may thus hold promise for the development of cell therapy in COPD.

Lin, C. H., et al. (2012). "Epigallocathechin gallate, polyphenol present in green tea, inhibits stem-like characteristics and epithelial-mesenchymal transition in nasopharyngeal cancer cell lines." BMC Complement Altern Med **12**: 201.

BACKGROUND: Previous studies have demonstrated that the consumption of green tea inhibits the growth of various cancers. Most cancers are believed to be initiated from and maintained by a small population of cancer stem-like cells (CSC) or tumor-initiating cells (TIC) that are responsible for tumor relapse and chemotherapeutic resistance. Although epigallocathechin gallate (EGCG), the most abundant catechin in green tea, has been reported to induce growth inhibition and apoptosis in some cancer cells, its effect on CSC is undefined. In this study, we enriched CSC by the sphere formation, and provided an efficient model for further experiments. Using this method, we examined the effects of EGCG regulating the nasopharyngeal carcinoma (NPC) CSC and attempted to elucidate the possible mechanisms. METHODS: NPC TW01 and TW06 cell lines were enriched by sphere formation and characterized their phenotypical properties, such as invasion capacity, epithelial-mesenchymal transition (EMT) and gene expression were analyzed by quantitative real-time reverse transcription polymerase chain reaction (q-RT-PCR). EGCG-induced growth inhibition in the parental and sphere-derived cells was determined by MTT and bromodeoxyuridine (BrdU) assay. EGCG-induced apoptosis was analyzed by flow cytometry with Annexin V and PI staining. The effects of EGCG on sphere-derived cell tumorigenicity, migration and invasion were determined by soft agar assay, wound healing, and cell invasion assay. The alternation of protein expression regulated by EGCG on these sphere-derived cells was assessed by immunofluorescence staining and western blot. RESULTS: NPC sphere-derived cells grown in serum-free non-adherent culture showed increased expression of stem cell markers and EMT markers compared to parental cells grown in conventional culture. Although EGCG induced growth inhibition and apoptosis in the parental cells in a dose-dependent manner, it was not as effective against spheres. However, EGCG potently inhibited sphere formation and can eliminate the stem cell characteristics of NPC and inhibit the epithelial-mesenchymal transition (EMT) signatures. CONCLUSIONS: Overall, these findings show that NPC cells with sphere formations possess the properties of CSC. Using this model, we found that EGCG regulated NPC CSC, their self-renewal capacity, and inhibited their invasive characteristics. It supports the pivotal role of EGCG as a dietary compound targeting NPC and may decrease recurrence and metastasis in nasopharyngeal carcinoma cells.

Lin, T. C., et al. (2017). "Pueraria mirifica inhibits 17beta-estradiol-induced cell proliferation of human endometrial mesenchymal stem cells." Taiwan J Obstet Gynecol **56**(6): 765-769.

OBJECTIVE: The notion that the human endometrium may contain a population of stem cells has recently been proposed. The mesenchymal stem cells (MSCs) in the endometrium are believed to be responsible for the remarkable regenerative ability of endometrial cells. Estrogens influence the physiological and pathological processes of several hormone-dependent tissues, such as the endometrium. Pueraria mirifica (PM) is a herbal plant that contains several phytoestrogens, including isoflavones, lignans, and coumestans, and is known to exert an estrogenic effect on animal models. The present study investigated the effects of PM on the proliferation of human endometrial MSCs (hEN-MSCs). MATERIALS AND METHODS: The hEN-MSCs were isolated from human endometrial tissue. The surface markers of these hEN-MSCs were identified through reverse transcription-polymerase chain reaction analysis. The

proliferation potential of hEN-MSCs was measured through a cell proliferation assay. Multilineage differentiation ability was confirmed through Oil red O and von Kossa staining. RESULTS: This study demonstrated that 17beta-estradiol-responsive MSCs with Oct-4, CD90, and CD105 gene expression can be derived from the human endometrium and that PM exerts biological effects on hEN-MSCs, specifically, enhanced cell growth rate, through the estrogen receptor. Furthermore, PM at 1500 and 2000 mug/mL significantly increased cell proliferation compared with the vehicle control, and PM concentration at 1000 mug/mL significantly inhibited the enhanced cell growth rate induced by 17beta-estradiol in hEN-MSCs. CONCLUSION: This study provides new insights into the possible biological effects of PM on the proliferation of hEN-MSCs.

Lin, Y. H., et al. (2017). "Enhancement of Bone Marrow-Derived Mesenchymal Stem Cell Osteogenesis and New Bone Formation in Rats by Obtusilactone A." Int J Mol Sci **18**(11).

The natural pure compound obtusilactone A (OA) was identified in Cinnamomum kotoense Kanehira & Sasaki, and shows effective anti-cancer activity. We studied the effect of OA on osteogenesis of bone marrow-derived mesenchymal stem cells (BMSCs). OA possesses biocompatibility, stimulates Alkaline Phosphatase (ALP) activity and facilitates mineralization of BMSCs. Expression of osteogenesis markers BMP2, Runx2, Collagen I, and Osteocalcin was enhanced in OA-treated BMSCs. An in vivo rat model with local administration of OA via needle implantation to bone marrow-residing BMSCs revealed that OA increased the new bone formation and trabecular bone volume in tibias. Micro-CT images and H&E staining showed more trabecular bone at the needle-implanted site in the OA group than the normal saline group. Thus, OA confers an osteoinductive effect on BMSCs via induction of osteogenic marker gene expression, such as BMP2 and Runx2 expression and subsequently elevates ALP activity and mineralization, followed by enhanced trabecular bone formation in rat tibias. Therefore, OA is a potential osteoinductive drug to stimulate new bone formation by BMSCs.

Mao, X. Y., et al. (2012). "[Analysis of the osteogenetic effects exerted on mesenchymal stem cell strain C3H10T1/2 by icariin via MAPK signaling pathway in vitro]." Zhong Xi Yi Jie He Xue Bao **10**(11): 1272-1278.

OBJECTIVE: To investigate the effects of icariin, an effective extract from traditional Chinese medicine Epimedium pubescens with the function of tonifying kidney, in promoting osteogenesis of mesenchymal stem cell line C3H10T1/2, and to explore the underlying mechanism. METHODS: After culture with icariin (0, 10(-7), 10(-6), 10(-5), and 10(-4) mol/L) and osteogenic supplement for 26 d in vitro, osteogenic differentiation of C3H10T1/2 cells was detected by alkaline phosphatase (ALP) assay. The RNA was extracted from cells cultured with 10(-5) mol/L icariin for 2, 8, 24 and 48 hours, and mRNA expressions of p38, p42 and p44 were measured using real-time reverse transcription-polymerase chain reaction (PCR) method. Three main proteins of MAPK signaling pathway (p38, and extracellular signal-regulated protein kinase (ERK), also named p42/44) and c-Jun N-terminal kinase (JNK) and their phospho-products were examined using Western blotting after icariin treatments of 10, 30, 60 and 120 min. RESULTS: Icariin at a dose of 10(-5) mol/L, when combined with the osteogenic supplement, had the best ability to promote osteogenic differentiation on C3H10T1/2 cells. Based on real-time PCR, the authors found that after two-hour ICA treatment, the gene expression of p38 revealed a significant decline compared with the control group ($P<0.01$). The levels of p42 and p44 mRNAs were decreased greatly after two-hour ICA treatment, while increased after 48-hour ICA treatment ($P<0.05$, $P<0.01$). There was no significant difference at other time points ($P>0.05$). Phospho-p42 was decreased after 10-minute icariin treatment, while phospho-p38 expression displayed an increase after 10- and 30-minute of treatment with icariin. There was no notable difference in phospho-JNK expression at these four time points. CONCLUSION: Icariin promotes differentiation of the mesenchymal stem cells C3H10T1/2 into osteoblasts, and its effect is related to the restraining of ERK expression and activation of p38 expression in the MAPK signaling pathway.

Markovic, B. S., et al. (2018). "Molecular and Cellular Mechanisms Involved in Mesenchymal Stem Cell-Based Therapy of Inflammatory Bowel Diseases." Stem Cell Rev **14**(2): 153-165.

Mesenchymal stem cells (MSCs) are promising resource for the therapy of inflammatory bowel diseases (IBDs) on the grounds of their differentiation capabilities and immuno-modulatory characteristics. Results of clinical studies indicate that local application of MSCs is a secure and beneficial approach for the treatment of perianal fistulas while systemic application of MSCs leads to the attenuation or aggravation of IBDs. Herein, we emphasized molecular mechanisms and approaches that should improve efficacy of MSC-based therapy of IBDs.

Nallanthighal, S., et al. (2017). "Pomegranate Extract Alters Breast Cancer Stem Cell Properties in Association with Inhibition of Epithelial-to-

Mesenchymal Transition." Nutr Cancer **69**(7): 1088-1098.

Cancer stem cells (CSCs) have become an important target population in cancer therapy and prevention due to their ability to self-renew, initiate tumors, and resist therapy. We examined whether pomegranate extract (PE) alters characteristics of breast CSCs. Ability to grow as mammospheres is a hallmark of breast CSCs. PE inhibited mammosphere formation in two different cell lines, neoplastic mammary epithelial HMLER and breast cancer Hs578T. In addition, mammosphere-derived cells from PE treatment groups showed reduced mammosphere formation for at least two serial passages. These data indicate that PE inhibits CSC's ability to self-renew. In addition, incubation of mammospheres with PE reversed them into adherent cultures, indicating promotion of CSC differentiation. Epithelial-to-mesenchymal transition (EMT) is a key program in generating CSCs and maintaining their characteristics. Thus, we examined the effect of PE on EMT. PE reduced cell migration, a major feature of the EMT phenotype. In addition, PE downregulated genes involved in EMT, including the EMT-inducing transcription factor Twist family basic helix-loop-helix transcription factor 1 (TWIST1). This suggests that PE suppresses CSC characteristics in part due to inhibition of EMT. The ability of PE to suppress CSCs can be exploited in the prevention of breast cancer.

Ou, Y. F., et al. (2016). "[Inhibitory effect of total saponins of Panax notoginseng on rat bone marrow mesenchymal stem cell apoptosis]." Sheng Li Xue Bao **68**(3): 285-292.

The study was aimed to investigate the effects of total saponins of Panax notoginseng (tPNS) on cobalt chloride (CoCl2)-induced apoptosis of rat bone marrow mesenchymal stem cells (rBMSCs) and the underlying mechanism. rBMSCs were isolated by density gradient centrifugation from Sprague Dawley (SD) rats. After being incubated with different concentrations of tPNS (1, 10, 100 mug/mL) for 48 h, the rBMSCs were stained with EdU and PI for proliferation and cell cycle assay, respectively. CoCl2 group was treated with 300 mumol CoCl2 for 24 h, and different concentrations tPNS groups were treated with 300 mumol CoCl2 plus 1, 10 or 100 mug/mL tPNS. After Annexin V-FITC/PI staining, flow cytometry was applied to measure the cell apoptosis. For mitochondrial membrane potential assay, rhodamine123 and Hoechst33342 staining were used. qRT-PCR was applied to analyze gene expression of Bcl-2 family. The results showed that the proliferation rates of the three concentrations tPNS groups were all higher than that of the control group (all $P < 0.05$). Compared with control group, only 100 mug/mL tPNS group exhibited increased cell percentage of S and G2 phase. Compared with that in control group (without CoCl2), the apoptotic rate was increased by 14.2% in CoCl2 group. And the apoptotic rates were reduced by 14.4%, 12.8% and 13.9% in three concentrations tPNS groups, compared with that in CoCl2 group (all $P < 0.01$). CoCl2 could decrease the mitochondrial membrane potential, while different concentrations of tPNS reversed the inhibitory effect of CoCl2. Bcl-2 and Bcl-xl mRNA expressions in all tPNS groups were higher than those in CoCl2 group (all $P < 0.05$). Moreover, 10 and 100 mug/mL tPNS groups showed lower ratios of Bax/Bcl-2, compared with CoCl2 group. The results suggest that tPNS protects the rBMSCs against CoCl2-induced apoptosis through improving the cell mitochondrial membrane potential, up-regulating the expressions of anti-apoptosis genes Bcl-2 and Bcl-xl, and reducing the Bax/Bcl-2 gene expression ratio.

Park, M. J., et al. (2018). "Effects of three-dimensional spheroid culture on equine mesenchymal stem cell plasticity." Vet Res Commun **42**(3): 171-181.

Mesenchymal stem cells (MSCs) are useful candidates for tissue engineering and cell therapy fields. We optimize culture conditions of equine adipose tissue-derived MSCs (eAD-MSCs) for treatment of horse fractures. To investigate enhancing properties of three-dimensional (3D) culture system in eAD-MSCs, we performed various sized spheroid formation and determined changes in gene expression levels to obtain different sized spheroid for cell therapy. eAD-MSCs were successfully isolated from horse tailhead. Using hanging drop method, spheroid formation was generated for three days. Quantitative real-time PCR was performed to analyze gene expression. As results, expression levels of pluripotent markers were increased depending on spheroid size and the production of PGE2 was increased in spheroid formation compared to that in monolayer. Ki-67 showed a remarkable increase in the spheroid formed with 2.0 x 10(5) cells/drop as compared to that in the monolayer. Expression levels of angiogenesis-inducing factors such as VEGF, IL-6, IL-8, and IL-18 were significantly increased in spheroid formation compared to those in the monolayer. Expression levels of bone morphogenesis-inducing factors such as Cox-2 and TGF-beta1 were also significantly increased in spheroid formation compared to those in the monolayer. Expression levels of osteocyte-specific markers such as RUNX2, osteocalcin, and differentiation potential were also significantly increased in spheroid formation compared to those in the monolayer. Therefore, spheroid formation of eAD-MSCs through the hanging drop method can increases the expression of

angiogenesis-inducing and bone morphogenesis-inducing factors under optimal culture conditions.

Potu, B. K., et al. (2009). "Petroleum ether extract of Cissus quadrangularis (Linn.) enhances bone marrow mesenchymal stem cell proliferation and facilitates osteoblastogenesis." Clinics (Sao Paulo) **64**(10): 993-998.

OBJECTIVE: To evaluate the effects of the petroleum ether extract of Cissus quadrangularis on the proliferation rate of bone marrow mesenchymal stem cells, the differentiation of marrow mesenchymal stem cells into osteoblasts (osteoblastogenesis) and extracellular matrix calcification. This study also aimed to determine the additive effect of osteogenic media and Cissus quadrangularis on proliferation, differentiation and calcification. METHODS: MSCs were cultured in media with or without Cissus quadrangularis for 4 weeks and were then stained for alkaline phosphatase. Extracellular matrix calcification was confirmed by Von Kossa staining. marrow mesenchymal stem cells cultures in control media and osteogenic media supplemented with Cissus quadrangularis extract (100, 200, 300 microg/mL) were also subjected to a cell proliferation assay (MTT). RESULTS: Treatment with 100, 200 or 300 microg/mL petroleum ether extract of Cissus quadrangularis enhanced the differentiation of marrow mesenchymal stem cells into ALP-positive osteoblasts and increased extracellular matrix calcification. Treatment with 300 microg/mL petroleum ether extract of Cissus quadrangularis also enhanced the proliferation rate of the marrow mesenchymal stem cells. Cells grown in osteogenic media containing Cissus quadrangularis exhibited higher proliferation, differentiation and calcification rates than did control cells. CONCLUSION: The results suggest that Cissus quadrangularis stimulates osteoblastogenesis and can be used as preventive/ alternative natural medicine for bone diseases such as osteoporosis.

Singh, V. and M. Sherpa (2017). ""Neuronal-Like Differentiation of Murine Mesenchymal Stem Cell Line: Stimulation by Juglans regia L. Oil"." Appl Biochem Biotechnol **183**(1): 385-395.

Mesenchymal stem cells have been extensively used for cell-based therapies especially in neuronal diseases. Studies still continue to delineate mechanisms involved in differentiating mesenchymal stem cells into neuronal cells under experimental conditions as they have low mortality rate and hence, the number of cells available for experiments is much more limited. Culturing and differentiating of neuronal cell is more challenging as they do not undergo cell division thus, bringing them to differentiate proves to be a difficult task. Here, the aim of this study is to investigate whether Juglans regia L. (walnut oil) differentiates multipotent, C3H10T1/2 cells, a murine mesenchymal stem cell line, into neuronal cells. A simple treatment protocol induced C3H10T1/2 cells to exhibit a neuronal phenotype. With this optimal differentiation protocol, almost all cells exhibited neuronal morphology. The cell bodies extended long processes. C3H10T1/2 cells were plated and treated with walnut oil post 24 h of plating. The treatment was given (with walnut oil treated cultures with or without control cultures) at different concentrations. The cultured cells were then stained with cresyl violet acetate solution which was used to stain the Nissl substance in the cytoplasm of the induced neuronal culture. The results indicated that the C3H10T1/2 cells differentiated into neuronal-like cells with long outgrowths of axon-like structures able to take up the cresyl violet acetate stain indicating their preliminary differentiation into neuronal-like morphology with walnut oil treatment. Treating the mesenchymal stem cells can in future establish a cultured mesenchymal stem cell line as neuronal differentiating cell line model.

Song, C., et al. (2015). "Use of Ferritin Expression, Regulated by Neural Cell-Specific Promoters in Human Adipose Tissue-Derived Mesenchymal Stem Cells, to Monitor Differentiation with Magnetic Resonance Imaging In Vitro." PLoS One **10**(7): e0132480.

The purpose of this study was to establish a method for monitoring the neural differentiation of stem cells using ferritin transgene expression, under the control of a neural-differentiation-inducible promoter, and magnetic resonance imaging (MRI). Human adipose tissue-derived mesenchymal stem cells (hADMSCs) were transduced with a lentivirus containing the human ferritin heavy chain 1 (FTH1) gene coupled to one of three neural cell-specific promoters: human synapsin 1 promoter (SYN1p, for neurons), human glial fibrillary acidic protein promoter (GFAPp, for astrocytes), and human myelin basic protein promoter (MBPp, for oligodendrocytes). Three groups of neural-differentiation-inducible ferritin-expressing (NDIFE) hADMSCs were established: SYN1p-FTH1, GFAPp-FTH1, and MBPp-FTH1. The proliferation rate of the NDIFE hADMSCs was evaluated using a Cell Counting Kit-8 assay. Ferritin expression was assessed with western blotting and immunofluorescent staining before and after the induction of differentiation in NDIFE hADMSCs. The intracellular iron content was measured with Prussian blue iron staining and inductively coupled plasma mass spectrometry. R2 relaxation rates were measured with MRI in vitro. The proliferation rates of control and NDIFE hADMSCs did not differ significantly ($P > 0.05$). SYN1p-FTH1, GFAPp-FTH1, and MBPp-FTH1

hADMSCs expressed specific markers of neurons, astrocytes, and oligodendrocytes, respectively, after neural differentiation. Neural differentiation increased ferritin expression twofold, the intracellular iron content threefold, and the R2 relaxation rate two- to threefold in NDIFE hADMSCs, resulting in notable hypointensity in T2-weighted images ($P < 0.05$). These results were cross-validated. Thus, a link between neural differentiation and MRI signals (R2 relaxation rate) was established in hADMSCs. The use of MRI and neural-differentiation-inducible ferritin expression is a viable method for monitoring the neural differentiation of hADMSCs.

Stiller, D., et al. (1992). "Some characteristics of the mesenchymal stem cell of soft tissue tumors." In Vivo **6**(4): 477-480.

"Soft tissue tumors" is an unnatural term, used by clinicians and for convenience by pathologists, which unites the neoplasms of mesenchymal origin as opposed to those of the soft epithelial tissues. Not included are the reticuloendothelial system, glia and supporting tissues. The mesenchymal stem cell, the cell of the embryonal connective tissue, exhibits in man and mammals the most pronounced embryonal potential. A restricted comparison to the embryonal potential in larval and pupal cells of invertebrates, such as in hemi- or holometabolic insects and to meristematic cells in vascular plants is justified. The great embryonal potential may explain why the mesenchymal stem cell, at present a hypothetical unit, is able to transform and differentiate into the connective tissue as such, the muscular, supporting and hematogenic tissues. The musculature comprises the bulk of the mammal's body weight. The development of the normal ontogenetic specialization as well as especially those differentiations leading to soft tissue tumors are comparatively shown in this publication and placed in the framework of vertebrate and invertebrate animals with true tissues.

Subash-Babu, P. and A. A. Alshatwi (2012). "Aloe-emodin inhibits adipocyte differentiation and maturation during in vitro human mesenchymal stem cell adipogenesis." J Biochem Mol Toxicol **26**(8): 291-300.

In this study, we examined the effects of Aloe-emodin (AE) on the inhibition of adipocyte differentiation during 3-isobutyl-1-methylxanthine (IBMX)-induced adipocyte differentiation in human mesenchymal stem cells (hMSCs). AE treatment (5, 10, and 20 microM) of preadipocyte cells resulted in a significant ($p < 0.05$) decrease in glycerol phosphate dehydrogenase and triglyceride levels as well as an increase in lactate dehydrogenase activity and attenuated lipid accumulation compared with untreated differentiated adipocytes. Using quantitative reverse transcription polymerase chain reaction, we studied the mRNA expression levels of resistin, adiponectin, aP(2), lipoprotein lipase, PPARgamma, and tumor necrosis factor-alpha in hMSCs undergoing adipocyte differentiation; treatment with AE decreased the expression of these adipogenic genes and decreased adipocyte differentiation. In addition, AE suppresses the differentiation of hMSCs into adipocytes by downregulating PPARgamma and C/EBPalpha expressions. AE significantly inhibited hMSCs proliferation and preadipocyte differentiation within the first 2 days of treatment, indicating that the antiadipogenic effect.

Tong, Y., et al. (2011). "Tanshinone IIA increases recruitment of bone marrow mesenchymal stem cells to infarct region via up-regulating stromal cell-derived factor-1/CXC chemokine receptor 4 axis in a myocardial ischemia model." Phytomedicine **18**(6): 443-450.

Systemic administration with bone marrow mesenchymal stem cells (BMSCs) is a promising approach to cure myocardial ischemia (MI), while the efficacy of cell transplantation is limited by the low engraftment of BMSCs. Tanshinone IIA (Tan IIA) has been reported many times for the treatment of MI. Therefore, the present study was performed to investigate whether Tan IIA could increase the migration of BMSCs to ischemic region and its potential mechanisms. In our study, we found that combination treatment with Tan IIA and BMSCs significantly alleviated the infarct size when compared with control group (31.46 +/- 3.00% vs. 46.95 +/- 6.51%, $p<0.05$). Results of real-time PCR showed that Tanshinone IIA (Tan IIA) did increase the migration of BMSCs to ischemic region in vivo, which was correlated with cardiac function recovery after MI. Furthermore, 2 muM Tan IIA could enhance the migration capability of BMSCs in vitro (3.69-fold of control), and this enhancement could be blocked by AMD3100 (a CXC chemokine receptor 4 blocker). CXCR4, together with its specific receptor, stromal cell-derived factor-1 (SDF-1) plays a critical role in the stem cell recruitment. Our experiment indicated that Tan IIA could promote SDF-1alpha expression in the infarct area and enhance the CXCR4 expression of BMSCs in vitro. Therefore, we postulated that Tan IIA could increase the BMSCs migration via up-regulating SDF1/CXCR4 axis.

Udalamaththa, V. L., et al. (2016). "Potential role of herbal remedies in stem cell therapy: proliferation and differentiation of human mesenchymal stromal cells." Stem Cell Res Ther **7**(1): 110.

Stem cell therapy has revolutionized modern clinical therapy with the potential of stem cells to differentiate into many different cell types which may help to replace different cell lines of an organism. Innumerous trials are carried out to merge new scientific knowledge and techniques with traditional herbal extracts that may result in less toxic, affordable, and highly available natural alternative therapeutics. Currently, mesenchyamal stromal cell (MSC) lines are treated with individual and mixtures of crude herbal extracts, as well as with purified compounds from herbal extracts, to investigate the mechanisms and effects of these on stem cell growth and differentiation. Human MSCs (hMSCs) possess multilineage, i.e., osteogenic, neurogenic, adipogenic, chondrogenic, and myogenic, differentiation abilities. The proliferative and differentiation properties of hMSCs treated with herbal extracts have shown promise in diseases such as osteoporosis, neurodegenerative disorders, and other tissue degenerative disorders. Well characterized herbal extracts that result in increased rates of tissue regeneration may be used in both stem cell therapy and tissue engineering for replacement therapy, where the use of scaffolds and vesicles with enhanced attaching and proliferative properties could be highly advantageous in the latter. Although the clinical application of herbal extracts is still in progress due to the variability and complexity of bioactive constituents, standardized herbal preparations will strengthen their application in the clinical context. We have critically reviewed the proliferative and differentiation effects of individual herbal extracts on hMSCs mainly derived from bone marrow and elaborated on the plausible underlying mechanisms of action. To be fruitfully used in reparative and regenerative therapy, future directions in this area of study should (i) make use of hMSCs derived from different non-traditional sources, including medical waste material (umbilical cord, Wharton's jelly, and placenta), (ii) take account of the vast numbers of herbal extracts used in traditional medicine globally, and (iii) investigate the mechanisms and pathways of their effects on hMSCs.

Xue, W., et al. (2018). "Plants and Their Bioactive Constituents in Mesenchymal Stem Cell-Based Periodontal Regeneration: A Novel Prospective." Biomed Res Int **2018**: 7571363.

Periodontitis is a common chronic inflammatory disease, which causes the destruction of both the soft and mineralized tissues. However, current treatments such as bone graft materials, barrier membranes, and protein products all have difficulties in regenerating the complete periodontal tissue structure. Stem cell-based tissue engineering has now emerged as one of the most effective treatments for the patients suffering from periodontal diseases. Plants not only can be substrates for life processes, but also contain hormones or functional molecules. Numbers of preclinical studies have revealed that products from plant can be successfully applied in modulating proliferation and differentiation of human mesenchymal stem cells. Plant-derived substances can induce stem cells osteogenic differentiation, and they also possess angiogenic potency. Furthermore, in the field of tissue engineering, plant-derived compounds or plant extracts can be incorporated with biomaterials or utilized as biomaterials for cell transplantation. So it is speculated that botanical products may become a new perspective in stem cell-based periodontal regeneration. However, the lack of achieving predict clinical efficacy and quality control has been the major impediment to its extensive application. This review gives an overview of the prospect of applying different plant-derived substances in various human mesenchymal stem cells-based periodontal regeneration.

Zhang, P., et al. (2009). "Effects of naringin on the proliferation and osteogenic differentiation of human bone mesenchymal stem cell." Eur J Pharmacol **607**(1-3): 1-5.

Rhizoma drynariae is used commonly in the treatment of osteoporosis and bone nonunion in traditional Chinese medicine. Modern pharmacological research indicates that naringin is the main effective component of rhizoma drynariae, which can induce the expression of the osteogenic marker in the osteoblast cell line. However, no former study has described its effect on bone mesenchymal stem cells (BMSCs). In our experiment, we co-cultured human BMSCs with different concentrations of naringin solution, then the osteogenic differentiation markers and proliferation ability were analyzed. The results indicated that a certain concentration (1-100 microg/ml) of the naringin solution may enhance the proliferation and osteogenic differentiation of human BMSCs. Also, our research explains excellently the anti-osteoporotic and bone nonunion treatment mechanism of rhizoma drynariae, thus contributing to the exploration of osteogenic differentiation agents from Chinese herbs.

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