Botanical Drugs and Stem Cells

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ABSTRACT

The potential to generate virtually any differentiated cell type from stem cells offers the possibility of creating new sources of cells for regenerative medicine. To realize this potential, it will be essential to control stem cell differentiation. Chinese herbal medicine is a major aspect of traditional Chinese medicine and is a rich source of unique chemicals. As such, individual herbs or extracts may play a role in the proliferation and differentiation of stem cells. In this review, we discuss some of the Chinese herbal medicines that are used to treat human diseases such as neuronal degenerative diseases, cardiovascular diseases, and osteoporosis. We also describe the relationship between Chinese herbal medicines and stem cell regulation.

Key words: stem cell, traditional Chinese medicine (TCM), neuronal degenerative, cardiovascular, osteoporosis

INTRODUCTION

Stem cells are capable of proliferation, self-renewal, and production of differentiated functional progeny that are characteristic of the organ from which they were derived (3,41). Stem cell biology is one of the most challenging areas of biomedicine. Stem cells are undifferentiated cells that have the ability to proliferate for an extended period and to differentiate into specific cell types under appropriate conditions. Stem cells are typically classified as embryonic stem cells (ESCs) and adult stem cells. ESCs are derived from the inner cell mass of the blastocyst, and have an unlimited capacity for self-renewal and the potential to differentiate into cells of all three germ layers. In contrast, adult stem cells are found in differentiated tissues, have a limited self-renewal capacity, and only differentiate into cell types found in the tissues from which they are derived. These characteristics of stem cells suggest that they hold great potential for revolutionizing regenerative medicine and tissue engineering (86). In this discipline, one of the biggest challenges is finding convenient and efficient approaches to modulate the fate of stem cells. Although genetic methods have been widely used in this area, and significant progress has been made in recent years (107), we are still far from the goal of conveniently and easily controlling stem cell fate.

TRADITIONAL CHINESE MEDICINES (TCMs)

Native cultures all over the world have traditionally used herbs to maintain health and treat illnesses. In China, more than 3,200 herbs and 300 mineral and animal extracts are used in more than 400 different formulas. Chinese herbal medicine is a major aspect of TCM, which focuses on restoring a balance of energy, body, and spirit to maintain health rather than treating a particular disease or medical condition. Herbs are used with the goal of restoring balance by nourishing the body. Chinese herbal medicine is not based on conventional Western concepts of medical diagnosis and treatment, but instead treats patients' main complaints or the patterns of their symptoms rather than the underlying causes. Practitioners attempt to prevent and treat imbalances, such as those caused by cancer and other diseases, with complex combinations of herbs, minerals, and plant extracts. One aspect of Chinese herbal medicine aims to restore or strengthen immunity and resistance to disease. Treatments undertaken with this goal are called “Fu Zheng” and are given as complementary therapy intended to reduce the side effects of conventional Western treatments.

TCM AND NEURONAL DEGENERATIVE DISEASE

Parkinson's disease, is a common and debilitating neuronal degenerative disease resulting from massive degenerative loss of dopamine neurons (13). In East Asia, TCM practitioners use certain TCMs to treat neuronal degenerative diseases. A classification of the herbs discussed in this review, as distinguished by function, is presented in Table 1. In addition, many Chinese herbs or herbal extracts such as green tea polyphenols or catechins (5,13,39,40,62,63,69,88), oil from ganoderma lucidum spores (153), triptolide from tripterygium wilfordii hook (64,65), polysaccharides from nerium indicum flowers (13), panax ginseng and ginsenoside (15,94,95,104,128), ginkgo biloba and EGb 761 (8,96,100,115,117,141), and polygonum (66) are able to attenuate degeneration of dopamine neurons and the symptoms caused by the neurotoxins 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine and 6-hydroxydopamine in both in vitro and in vivo conditions. Neuroprotective strategies to rescue nigral dopamine neurons from progressive death are currently being explored, including the use of Chinese herbs and herbal extracts that have shown potential clinical benefits of attenuating the progression of Parkinson's disease (67,146,147). Generally speaking, Chinese herbs or herbal extracts may promote neuronal survival and neurite growth, and may facilitate functional recovery from brain injuries by invoking distinct mechanisms that are related to their neuroprotective roles as antioxidants (67,101), dopamine transporter inhibitors (149,150), monoamine oxidase inhibitors (115,152), free radical scavengers (39,40), modulators of cell survival genes and signaling (63,81), anti-apoptotic agents (53,143,152), and even agents that improve blood circulation in the brain (48).

STEM CELLS DIFFERENTIATE INTO NEURON-LIKE CELLS

Neural precursor or stem cells derived from brain have the capacity to self-renew and to generate progeny capable of differentiating into multiple distinct cell lineages that produce neurons and glia (35,76,83,98). Transplantation of human neural stem cells obtained from embryonic tissue leads to neuronal and astrocytic differentiation (9,84,116) and remyelination in the newborn mouse brain (33). Neural precursor cells derived from adult human brain have been reported to remyelinate axons and provide recovery of impulse conduction following transplantation into demyelinated rodent spinal cords (2). These studies have engendered intense interest because they suggest the possibility of using such cells for repair strategies in neurological diseases (2,9,84,105,116,135). However, difficulties remain regarding the relative inaccessibility of these cells for autologous cell therapies and the need for cell expansion using trophic factors. The potential to generate virtually any differentiated cell type from ESCs offers the possibility of establishing new models of mammalian development and creation of new sources of cells for regenerative medicine (52,86). To realize this potential, it will be essential to control ESC differentiation and to direct specific gene expression in these cells leading to a specific phenotype (Fig. 1). The derivation of human ESCs has brought cell therapy–based regenerative medicine significantly closer to clinical application. However, expansion of undifferentiated cells and their directed differentiation in vitro are difficult to control (123).

Recent work has demonstrated that mesenchymal stem cells (MSCs) have the potential to differentiate into neurons both in vivo and in vitro (28,112-114). Under appropriate experimental conditions, MSCs can differentiate into several types of mesenchymal cells, including osteocytes, chondrocytes, and adipocytes, and they can also differentiate into non-mesenchymal cells, such as neural cells. Many protocols for inducing neuro-differentiation of MSCs in vitro have been reported (6,38,47,61,87,91,103,119,131), which may offer new methods of cell treatment for several types of neural diseases.

TCMs INDUCE NEURO-DIFFERENTIATION

TCMs may enhance mentality, strengthen brain function, promote blood circulation, remove stasis, awaken patients, delay senescence, and modulate the immune system. Recent reports have shown differentiation of human MSCs into neuron-like cells with danshen injection (125,138,139). Increasing numbers of studies have indicated that many Chinese herbs or herbal extracts such as danshen (75,77,78), tetramethylpyrazine (79), panax natoginseng saponins (74,109), *Astragalus* *mongholicus* (29,118), rhizoma gastrodiae (31), and panax ginseng (81,82,127) are able to direct the differentiation of human stem cells into neuron-like cells.

In one of our studies, the natural compound n-butylidenephthalide, which is isolated from a chloroform extract of *Angelica sinensis*, was investigated for its antitumor effects on glioblastoma multiform brain tumors both in vitro and in vivo (121). In a subsequent study, we observed that *Nurr1*, which plays an important role in stem cell differentiation into dopamine neurons (Fig. 1), was found to be upregulated immediately after n-butylidenephthalide treatment (16,71). Thus, many TCM compounds may have important uses in stem cell biology.

A Chinese herbal medicine study reported that ESC differentiation can be directed toward neurons and suggested that an effective inducible pharmaceutical dosage to produce neurons for clinical transplant may be possible. This study also suggested a new approach for developing herbal applications for the differentiation of MSCs and ESCs. New pharmaceutical strategies for treating Parkinson's disease will hopefully be developed by understanding the various active molecules and valuable combinations that contribute to the biological effects of Chinese herbs and herbal extracts.

EFFECTS OF STEM CELL THERAPY COMBINED WITH CHINESE HERBS

ON MYOCARDIAL INFARCTION

Cardiovascular diseases are the most serious groups of diseases in the world, and the prevalence and lethality rate are increasing every year. In America, more than 71 million people suffer from cardiovascular diseases, which are also the leading cause of death in many other countries, including most European and developed countries. Thus, a combination of stem cell therapy and Chinese herbs potentially could be used to treat cardiovascular diseases such as myocardial infarction and stenosis.

Adult cardiomyocytes do not regenerate, and therefore cannot be used to replace damaged cells following myocardial infarction (60,89,142). Recently, some progenitor or stem cells have been shown to differentiate into cardiomyocytes. Because of this property, many groups have attempted to use these progenitor or stem cells to replace damaged cardiomyocytes following myocardial infarction. However, only a portion of bone marrow–derived stem cells (MSCs) differentiate into cardiomyocytes, which distribute in the less-ischemic border zone. Thus, transplanted MSCs cannot be used to form functional cardiac tissue, making transplantation of MSCs for myocardial infarction therapy less than ideal. Consequently, considerable efforts have focused on the search for a new approach to enhance cardiogenic differentiation efficiency. Therefore, determining what kind of stem cell to use (i.e., ESCs, hematopoietic stem cells, or MSCs) and the important molecular steps required to increase their differentiation is important. Surprisingly, many herbal medicines can increase the cardiogenic differentiation ability of MSCs. For example, in a search for molecules that promote cardiogenic differentiation, Cheng et al. found that the traditional herb "Geum japonicum," which is frequently used by the Miao ethnic group in China's Guizhou province, can enhance the cardiogenic differentiation ability of MSCs and significantly repair infarcted hearts (18,68). Further, this group identified a compound from Geum japonicum called cardiogenin, and showed that it is a major compound involved in cardiogenic differentiation (18).

In addition to increasing the differentiation efficiency, promoting stem cells to migrate to the infarcted heart from other tissues such as bone marrow is another strategy under investigation. Yang et al. found that the TCM "Wenyang Huoxue Recipe," which consists of Panax ginseng, Radix Aconiti lateralis preparata, Radix Ilex pubesceus, and Herbal Leonuri, promotes stem cell mobilization. In this study, acute myocardial infarction patients were treated with Wenyang Huoxue Recipe for 10 successive days, which resulted in significantly increased numbers of peripheral $CD34^+$ cells. Through increasing the stem cell mobilization, more stem cells migrate to the infarcted heart area and may differentiate to the cardiomyocyte for cardiogenic repair.

Thus, Wenyang Huoxue Recipe can reduce the infarcted heart area and improved heart function (140).

A third important strategy for myocardial infarction therapy is to increase angiogenesis and endothelial cells in the infarcted heart. In TCM, ginseng has been shown to induce ESCs to differentiate into cardiomyocytes in vitro (106). Furthermore, saponin, a ginseng component, can stimulate myocardial tissue to secrete granulocyte colony-stimulating factor, which induces migration of MSCs to the myocardium. These MSCs can then differentiate into vascular endothelial cells, which can promote capillary regeneration in infarcted myocardial tissue and maintain the blood supply for protection of damaged cardiomyocytes (124,126).

STEM CELL THERAPY COMBINED WITH CHINESE HERBS FOR STENOSIS

Stenosis is one of the most common cardiovascular diseases in the world and is most commonly caused by atherosclerosis, a chronic inflammatory response in the walls of arteries. The process of atherosclerosis is divided into three stages. In the first stage, endothelial cells undergo inflammatory activation, which can be caused by smoking, hypertension, diabetes, autoimmune diseases, infections, or high cholesterol. Inflamed endothelial cells cannot secrete normal amounts of nitric oxide or antithrombotic and vasodilating cytokines. Further, oxidative low-density lipoprotein (ox-LDL) accumulates in the arterial walls, and macrophages are attracted to engulf the ox-LDL. Large numbers of macrophages with ox-LDL, which are called foam cells, form the fatty streaks that are seen on the artery wall. In the second stage, accumulated platelets and foam cells secrete cytokines and growth factors, such as platelet-derived growth factor, epidermal growth factor, and fibroblast growth factor, which induce smooth muscle cells to migrate from the media and proliferate in the intima. The proliferating smooth muscle cells also secrete extracellular matrix, and the fatty streaks become fibrous plaques. In the third stage, fibrous plaques rupture, and platelets aggregate and form thrombi. This phenomenon reduces the lumen area and decreases the blood supply. Thus, atherosclerosis leads to stenosis and can lead to myocardial infarction in the heart during its most serious stages.

Currently, there are two strategies for combining stem cell therapy with TCM for treatment of stenosis. The first is to reduce the inflammatory effect, and the second is to regenerate functional endothelial cells. In 2008, Forte et al. used mesenchymal stem cells to treat balloon-injured rat arteries, an animal model of stenosis. They reported that mesenchymal stem cells can reduce the expression of proinflammatory genes, such as interleukin-1 and chemoattractant protein-1, thus limiting stenosis (34). Many TCMs have been shown to promote stem cell migration and increase the number of stem cells in the circulatory system. For example, the Wenyang Huoxue Recipe can promote stem cell migration to the stenosis area (140), possible reducing inflammation and the extent of stenosis.

In 2005, Yang et al. reported that the traditional Chinese herbs Astragalus membranaceus and Panax notoginseng can increase the proliferation of endothelial progenitor cells (136). In 2007, Ji et al. found that Danshen can significantly enhance the functional activity of endothelial progenitor cells in patients with hypercholesterolemia (46). Furthermore, in 2009, Shi et al. showed that the ginsenoside Rg1 can promote migration, adhesion, and proliferation of endothelial progenitor cells by increasing the number of endothelial progenitor cells in S phase and by decreasing the number of cells in the G0/G1 phase (108). Therefore, using Astragalus membranaceus, Panax notoginseng, and the ginsenoside Rg1 in stenosis therapy to regenerate functional endothelial cells may be beneficial. However, these studies have only been done in vitro, and thus future in vivo studies are required. The traditional Chinese herbs that contribute to stem cell therapy for myocardial infarction and stenosis are shown in Table 2.

FAVORABLE EFFECTS OF TCM ON BONE HEALTH

Accumulating evidence suggests that natural products, such as herbal extracts and dietary supplements, have favorable effects on bone health (93,132). For example, turmeric root (*Curcuma longa*), which has long been used to treat inflammatory diseases, and its active constituents, curcuminoids, are known to have favorable effects on bone metabolism. Acanthopanax senticosus extract affects biochemical markers of bone turnover and increases in bone density in postmenopausal women (44). Fructus Ligustri Lucidi, a kidney-tonifying Chinese herb, can increase osteoblastic differentiation in rat osteoblast-like UMR-106 cells. Fructus Ligustri Lucidi extract improves bone properties in aged rats possibly via its direct action on osteoblastic cells to enhance the mineralization process (148). *To-Sa-Za* (TSZ-AE), the seed of *Cuscuta chinensis*, induces osteogenic activity in human osteoblast-like MG-63 cells (137). *Cistanche salsa*, a Chinese herb was found to contain an anti-osteoporotic compound, (2E,6R)-8-Hydroxy-2,6-dimethyl-2-octenoic Acid ,an extract of *Cistanche salsa* significantly suppresses the bone weight loss that occurs in ovariectomized mice (134). In the search for new naturally occurring anti-osteoporosis agents in plants, Deyama et al. found that *Eucommia ulmoides* Oliv., also called Du-Zhong or Tu-Chung, is one of the earliest and most important edible crude herbs used for various medicinal purposes in China, Japan, and Korea. The leaf and bark of this plant are rich in polyphenolic compounds such as lignans, phenolic acid, and flavonoids (27).

EFFECT OF STEM CELL THERAPY COMBINED WITH CHINESE HERBS ON OSTEOPOROSIS

The two major cell types responsible for bone remodeling are osteoclasts, which resorb bone, and osteoblasts, which form new bone (37). Osteoporosis results from an imbalance in bone resorption and bone formation with a net bone loss that may be induced by several conditions, such as hormonal imbalance, disease, or medications (e.g., corticosteroids or anti-epileptic agents) (37). In TCM, herbs that strengthen bones can be used to treat bone diseases with the same symptoms as osteoporosis (Table 3). The currently available treatment, estrogen replacement therapy, is based on inhibition of bone resorption to prevent further bone loss. Many osteoporotic patients, however, have already lost a substantial amount of bone, and thus a method to increase bone mass by stimulating new bone formation is needed. During bone formation, osteoblasts are the key cell type for bone matrix formation and calcification. Because osteoclasts are responsible for bone resorption, they are one of the main targets for treatment of osteoporosis. Icariin is a prenylated flavonol glycoside contained in the herb

Epimedium, which has long been used to improve bone fracture healing or prevent osteoporosis because of the belief that the herb has bone-strengthening action. Icariin strengthens bones, and one of the mechanisms of this activity is the stimulation of proliferation and enhancement of the osteogenic differentiation of MSCs (12). Icariin can also inhibit the formation of osteoclasts as well as their bone resorption activity, which suggests that this compound may be the component responsible for the bone-strengthening action of Epimedium (11). In another study, osteoclasts were isolated and cultured for in vitro study of the effects of the Chinese herb Guizhou epimedium (Epimedium Leptorrhizum Stearn). Epimedium inhibited osteoclast-mediated bone resorption (144). Furthermore, curcumin (a mixture of curcuminoids) can prevent osteoclastogenesis, and it is also has anti-inflammatory and antioxidant effects (93). Studies of the effect of paeonol on RANKL-induced NF-κB activation and on osteoclastogenesis in osteoclast precursor cells have shown that paeonol inhibits RANKL-induced ERK, p38, and NF-κB activation in macrophages (7).

EFFECT OF STEM CELL THERAPY COMBINED WITH CHINESE HERBS ON OSTEOARTHRITIS

Osteoarthritis is one of the most common chronic age-related disorders, which affects at least one-third of adults over years of age (36). Osteoarthritis is a progressive and multifactorial disease characterized by cartilage degeneration, osteophytes, and synovial fibrosis (49). Current treatments for osteoarthritis are unsatisfactory for restoring full function or returning tissue to its native normal state (122). Until recently, pharmacological management of most patients with osteoarthritis has targeted symptoms of the disease rather than the underlying cause and pathophysiology (19). Analgesics and non-steroidal anti-inflammatory drugs represent the mainstay of treatment. These drugs mainly alleviate symptoms but have many side effects (80). Chinese herbal remedies are the most prevalent and effective treatments for the management of chronic illnesses in many Asian countries. Because indigenous herbs have anti-inflammatory, analgesic, anti-arthritic, and blood microcirculation-enhancing functions and the ability to inhibit enzymatic cartilage degeneration, they have been widely used to treat various inflammatory diseases (59,99). A recent report showed that extracts from several TCM formulae alleviate osteoarthritis symptoms and are beneficial to the pathophysiology of the disease. For example, Diacerein, which is isolated from *Rheum* plants, is as effective as non-steroidal anti-inflammatory drugs for knee and hip osteoarthritis (43). *Clematis* is commonly known for its anti-spasmodic, anti-inflammatory, and analgesic effects (59). SKI 306X, a processed extract from a formula of three TCM herbs (*Clematis manshurica*, *Trichosanthes kirilowii*, and *Prunella vulgaris*), has been used as a anti-arthritic agent (20). Yanghe decoction protects articular cartilage, an effect that is achieved by regulating the expression of HIF-1alpha mRNA (10).

mesenchymal stem cells (MSCs) are an attractive source for tissue engineering and regeneration owing to their ability to differentiate into multiple mesenchymal lineages, including bone, cartilage, muscle, ligament, tendon, adipose, and marrow stroma (92). MSCs have been suggested to play an important role in osteoarthritis treatment because this cell population is resistant to the degenerative changes in bone and cartilage in osteoarthritis (25). Several studies have demonstrated that MSCs can form cartilage *in vivo* and *in vitro* (92). The proliferative capacity of MSCs from patients with osteoarthritis is substantially reduced, but the osteogenic potential of MSCs is equivalent to or greater than that of control subjects (85). Herbal medicine may affect MSCs by promoting osteoblastic differentiation (50,70). TCMs contain agents that can contribute to the proliferation and differentiation of MSCs. Recently, great effort has been devoted to examining the effects of TCMs on cell protection for osteoarthritis treatment using cell culture systems and animal models. For example, *Clematis* was shown to be protective in osteoarthritis by inhibiting apoptosis in chondrocytes. *Rheum* (Diacerein) and *Clematis* can improve the cell proliferative capacity (20,59,99) of MSCs. These results suggest that TCM may play an important therapeutic role in patients with osteoarthritis by improving the proliferative capacity of MSCs and inhibiting mineralization by MSCs (14).

CONCLUSION

In conclusion, growing evidence indicates that Chinese herbs or herbal extracts can greatly impact stem cell biology. For example, 20070721-GX, a health food, contains a mixture of Chinese herb extract and is a potent stem cell growth factor. In the unpublished study, the $CD34^+$ cell numbers of eleven volunteers, after administer 20070721-GX for at least two months, are increased to 4.9 times (1.47 ± 0.11%) than placebo-controlled (0.3 ± 0.1%).

Chinese herbs may be able to efficiently regulate stem cell fate, proliferation, and differentiation. Many kinds of Chinese herbs have been shown to regulate stem cell activity. Most recent reports about the effects of Chinese herbs on stem cell regulation have focused on their effective treatment of various conditions. Few reports have examined the effects of Chinese herbs on stem cell regulation, however. Many scientists do not yet accept the stem cell regulation effects of Chinese herbs because of the lack of molecular biology evidence. Thus, examination of the molecular mechanisms of Chinese herbs on stem cell regulation is the next challenge.

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Table 1. Herbs in traditional Chinese medicines are used by traditional Chinese medicine practitioners to treat neuronal diseases.

Category of use	Latin name (English equivalent)	Chinese name (pinyin)	Referenc(s)
Blood Circulation-Promoting and Stasis-Removing Drugs	*Radix Paeoniae Rubra*	Chi Shao	(30,129,130)
	Radix Achyranthis Bidentatae	Niu Xi	(130)
	Radix Salviae Miltiorrhizae	Dan Shen	(73,133)
	Rhizoma Corydalis	Yan Hu Suo	
	Radix Notoginseng	San Qi	(21,22)
	Rhizoma Chuanxiong	Chuan Xiong	(51)
	Stigma Croci	Xi Hong Hua	
Qi-Regulating Drugs	*Fructus Toosendan*	Chuan Lian Zi	(109,110)
	Fructus Aurantii Immaturus	Zhi Shi	
	Rhizoma Cyperi	Xiang Fu	(57)
Expectorants, Antitussives, and Anti-asthmatics	*Unprocessed Rhizoma Pinelliae*	Sheng Ban Xia	(24,55)
	Ginkgo Leaf	Yin Xing Ye Pian	(1,32,97)
	Unprocessed Rhizome Arisaematis	Sheng Tian Nan Xing	(54)
	Fructus Perillae	Zi Su Zi	(151)
Heat-Clearing Drugs	*Cortex Moutan*	Mu Dan Pi	
	Radix Sophorae Flavescentis	Ku Shen	
	Herba Patriniae	Bai Jiang Cao	
	Herba Houttuyniae	Yu Xing Cao	
	Fructus Gardeniae	Zhi Zi	(42,124)
	Spica Prunellae	Xia Ku Cao	
	Rhizoma Coptidis	Huang Lian	(26,45)
	Radix Scutellariae	Huang Qin	(45,47)
Awakening Drugs	*Borneolum Syntheticum*	Bing Pian	
	Rhizoma Acori Tatarinowii	Shi Chang Pu	
Tranquilizers	*Radix Polygalae*	Yuan Zhi	(23,58,145)
	Semen Ziziphi Spinosae	Suan Zao Ren	(102)
	Cortex Albiziae	He Huan Pi	
	Succinum	Hu Po	
Tonics	*Radix Ginseng*	Ren Shen	(21,22,111)
	Radix Paeniae Alba	Bai Shao	(7,72)
	Radix Codonopsis	Dang Shen	
	Radix Glycyrrhizae	Gan Cao	(17,145)

* Please refer to 1kum Web site (http://www.lkum.com/pages/QJKojpmi.html).

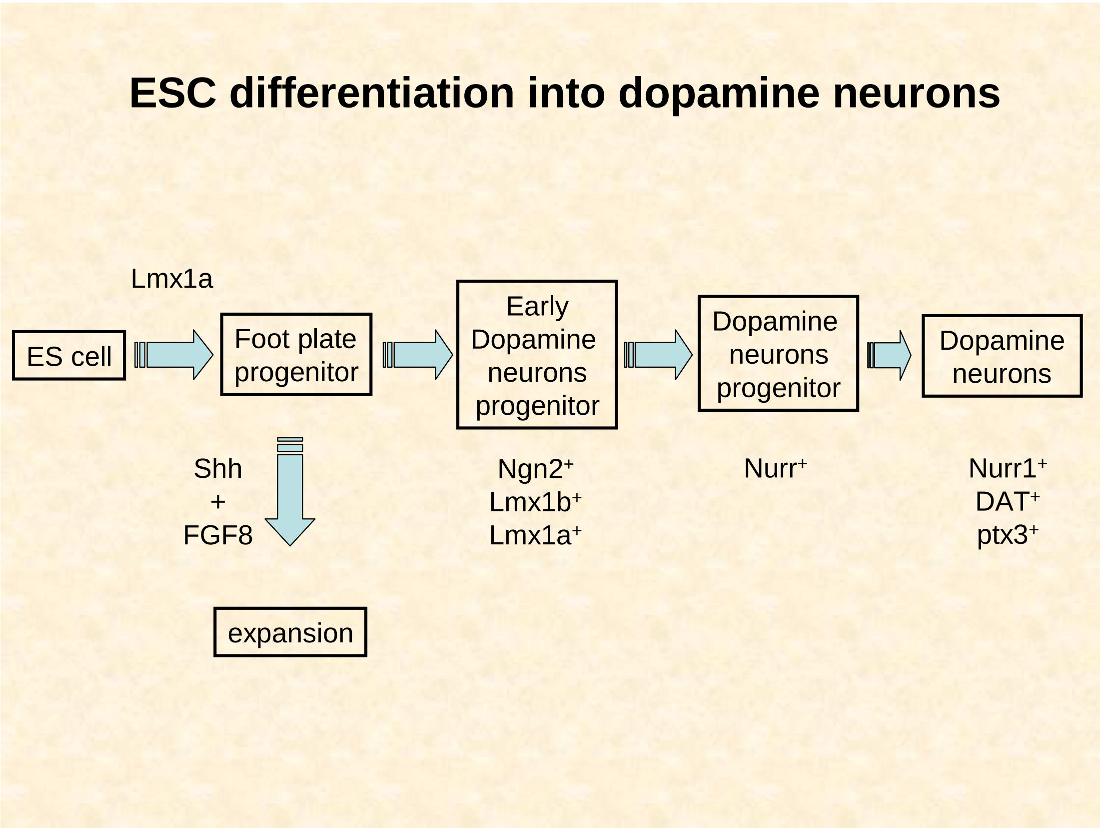
Table 2. Chinese herbs used in stem cell therapy for cardiovascular disease.

Disease	Therapeutic strategy	Chinese herb or compound extracted from Chinese herb	Reference
Myocardial infarction	Increase the cardiogenic differentiation ability of stem cells	*Geum Japonicum*	(18)
		Cardiogenin from *Geum Japonicum*	(18)
		Panax ginseng	(140)
	Increase the migration ability of stem cells	*Panax ginseng*	(140)
		Aconitum carmichaeli	(140)
		Ilex pubescens	(140)
		Leonuri herba	(140)
	Increase angiogenesis	Saponin from *Panax quinquefolius*	(124,126)
Stenosis	Increase the migration ability of stem cells and reduce inflammation	*Panax ginseng*	(140)
		Aconitum carmichaeli	(140)
		Ilex pubescens	(140)
		Leonuri herba	(140)
	Regenerate functional endothelial cells	Ginsenoside Rg1 from *Panax ginseng*	(108)
		Astragalus membranaceus	(136)
		Panax notoginseng	(136)
		Salvia miltiorrhiza (Danshen)	(46)

Table 3. Traditional Chinese medicine applications in osteoporosis

Function	Herb name	Effective composition	Reference(s)
Osteoblastic differentiation	*Wedelia calendulacea*	Wedelolactone	(4)
	Fructus Ligustri Lucidi	Ethanol extract	(148)
	Cistanche salsa	(R)-HDOA	(134)
	Eucommia ulmoides	Cortex extract	(27)
	Acanthopanax senticosus	Water extract	(44)
	Cuscuta chinensis	Flavonoids	(137)
	Glycine max	Menaquinone-7	(42)
	Green tea	Epigallocatechin-3-gallate	(56)
Inhibits bone resorption activity	*Paeonia lactiflora Pallas*	Paeonol	(120)
	Curcuma longa Linn	curcumin	(90)
	Guizhou epimedium	Epimedium extract	(144)
	Epimedium	Icariin	(12)

Figure 1. Differentiation of embryonic stem cells (ESCs) into dopamine neurons and the genes involved.



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