Physiology and Pharmacology 29 (2025) 350-374
Review Article

Applications of phytomedicines in cardiovascular regeneration therapy: pre-clinical and clinical studies

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ABSTRACT

Cardiovascular diseases (CVDs) are the leading cause of death in human societies. Several medicinal and interventional therapeutic approaches are approved for the treatment of CVDs, one of which is phytomedicine. Phytomedicine is described as the exploitation of the therapeutic properties of herbal medicines. The cardioprotective effects of phytochemicals are due to their anti-oxidative, anti-hypercholesterolemia, anti-inflammatory, antiangiogenic, and anti-ischemic activities, reducing the risk factors of developing CVDs. Regenerative medicine (RM) is a well-established field that aims to replace, repair, and regenerate diseased and injured human cells, tissues, or organs. Stem cells' (SC) potential to differentiate into various cell types and their self-renewal capabilities have made them an excellent tool for applying RM in CVD. The intersection of phytomedicines and regenerative medicine can be categorized into two main areas. Phytochemicals have been shown to significantly enhance the proliferation and differentiation of mesenchymal stem cells (MSCs). For example, certain plant extracts promote osteogenic (bone-forming) and chondrogenic (cartilage-forming) differentiation of MSCs, thereby enhancing stem cell function. Additionally, plant-derived compounds can mitigate the side effects associated with conventional therapies while offering effective treatment options for tissue regeneration (natural alternatives to traditional therapeutics).

This paper reviews current evidence and studies on the beneficial properties of phytomedicines in cardiac RM, both in animal models and in humans. In summary, all of the mentioned studies suggestthat the use of phytomedicine may be directly or indirectly involved in cardiogenesis and angiogenesis by stimulating endogenous SCs and their secretory activity, modulating cytokine release, signal transduction, and elevating the levels of several cardiac regeneration factors.

On the other hand, various mechanisms through which these herbal medicines act, such as reducing oxidative stress, controlling inflammation, and promoting angiogenesis, underscore their potential as viable alternatives or adjuncts to conventional therapies for cardiovascular diseases.

The integration of phytomedicine into clinical practice could lead to enhanced overall therapeutic efficacy, more effective and personalized treatment, fewer cardiovascular risks and better health outcomes. Further research is required to elucidate the specific molecular pathways through which phytomedicines exert their beneficial effects on cardiac tissue. Understanding these mechanisms will help in developing targeted therapies.

Keywords:
Phytomedicine
Regenerative medicine
Stem cells
Mesenchymal stem cells
Cardiac regeneration
Angiogenesis

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Received 17 March 2024; Revised from 13 October 2024; Accepted 17 February 2025
Citation: Sheibani M, Shayan M, Mohammadgholi-Beiki A, Sharifi M. A., Jafari-Sabet M, Sharifi A. M. Applications of phytomedicines in cardiovascular regeneration therapy: pre-clinical and clinical studies. Physiology and Pharmacology 2025; 29: 350-374. http://dx.doi.org/10.61186/phypha.29.4.350

Introduction

Herbal medicines (phytomedicines) have been globally used throughout history to prevent and treat diseases (Sajid et al., 2019). In recent years, there has been a notable increase in the popularity of herbal medicine, with many individuals around the world preferring it as a primary healthcare choice over synthetic alternatives (Farid et al., 2022; Nagalingam 2017; Yousefi-Manesh et al., 2021). Currently, the potential therapeutic properties of herbal medicines have been the focus of various phytochemical and pharmacological investigations (Bagheri et al., 2020; Mazzanti 2005). Some examples of effective bioactive compounds found in herbal medicines include flavonoids, resveratrol, quercetin, alkaloids, saponins, and carotenoids (Chandrasekara and Shahidi 2018). Studies have revealed a positive correlation between the use of phytomedicines and cardiovascular health (Kumar et al., 2021) due to their antioxidative, antihypertensive, antihypercholesterolemic, anti-inflammatory, antiangiogenic, vasorelaxant, and anti-ischemic properties (Shaito et al., 2020).

Regenerative medicine (RM) is a well-established field of medicine that exploits the capacity of stem cells, employing tissue engineering techniques (Chang Chien and Stogicza 2021) to replace, repair, or regenerate human cells and organs that have failed or been injured because of diseases, age, or congenital abnormalities (Ntege et al., 2020). As a subfield of RM, tissue engineering seeks to stimulate endogenous regeneration by reconstructing and mimicking the regenerative microenvironment using nanomaterials, cells, scaffolds, and growth factors (Furth and Atala 2014). Stem cells, with their capability to differentiate into various cell types (Zakrzewski et al., 2019), have made them an adequate candidate to be used in tissue engineering to repair and restore damaged tissues (Ude et al., 2018). For example, both tissue engineering and stem cell therapy present exciting opportunities for advancing treatment options for cardiovascular diseases. As research progresses, these innovative approaches hold the potential not only to improve patient outcomes but also to fundamentally alter the management of heart disease (Mahmud et al., 2022).

Cardiovascular diseases (CVDs) are the leading cause of death worldwide. Pharmacological and interventional treatments for CVD have been improved over many years; however, the prognosis of these diseases is poorly understood (Taylor et al., 2012). Taking advantage of stem cell (SC) therapy in CVD treatment has shed light on new approaches that can alter conventional treatment methods (Orlic et al., 2001). Mechanisms in cardiac RM aim to stimulate and promote endogenous regenerative pathways in injured myocardium in cardiac disorders such as myocardial infarction (Choi and Poss 2012). Recent studies have documented that plant-derived medicine can promote regeneration in cardiac tissue by influencing SC proliferation and differentiation (Alaribe and Motaung 2019). This review focuses on current evidence and studies addressing the role of phytomedicines in cardiovascular regenerative therapy in in vitro, in vivo, and clinical studies.

Methodology

The literature review process involved defining clear objectives and the scope of the review. Multiple databases were utilized to gather relevant studies, ensuring a comprehensive search. Reliable inclusion and exclusion criteria were applied to effectively filter the studies. Additionally, the literature review was completed within a timeframe of 4 to 5 weeks.

The United States National Library of Medicine and the National Institutes of Health (NIH) databases served as the primary reference platforms for this study. The following keywords were used for the literature review in the 'title/abstract' section. 'herbal medicines', 'phytomedicines', 'medicinal plants', 'cardiac regeneration', 'cardiogenesis', 'IHD', 'angiogenesis', 'endothelial regeneration', 'cardiac stem cells'. Only English-language publications were included.

More than 500 manuscripts were searched, and 150 of them were used for the study.

Inclusion/Exclusion Criteria

Study Design: All types of experimental studies, randomized controlled trials (RCTs), narrative reviews, cohort studies, and meta-analyses published in peer-reviewed journals in the field of phytomedicines and stem cell therapy applications in cardiovascular diseases.

Intervention: Studies that evaluate therapy for cardiovascular disorders using stem cell therapy and herbal medicine administration.

Outcome Measures: Studies must report positive and stimulatory effects of phytomedicine applications on stem cell therapy and tissue engineering interventions in the cardiovascular system.

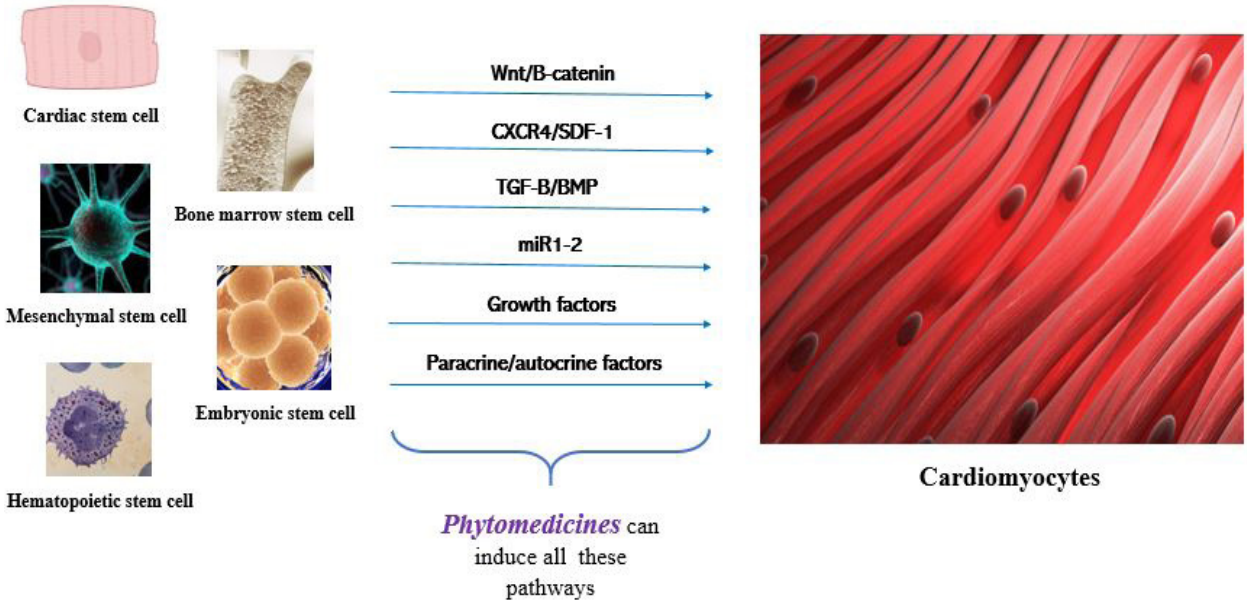

FIGURE 1. Molecular pathways associated with the effects of phytomedicine in cardiovascular regeneration therapy. Wnt: Wingless-related Integration Site; CXCR4: C-X-C Chemokine Receptor Type 4; SDF-1: Stromal Cell-Derived Factor; TGF-β: Transforming Growth Factor Beta; BMP: Bone Morphogenetic Protein.

Publication Date: Articles published between 2000 and 2024.

Non-Peer-Reviewed Articles: Exclude conference abstracts, opinion pieces, and unpublished studies.

Comorbid Conditions: Studies involving animals or humans with severe comorbid disorders that could interfere with treatment have been excluded.

Language: Non-English language publications have been excluded.

Sample Size: Studies with fewer than 30 participants have been excluded to ensure adequate power for analysis.

Findings

Stem cell types for cardiovascular stem cell therapy

Studies have shown that stem cell transplantation via cardiac, intravenous, and endocardial injections has beneficial effects on cardiovascular diseases. Various types of SC have been exploited for transplantation in patients with cardiovascular diseases based on their regeneration capacity : (I) bone marrow (BM)-derived stem cells (BMSCs) (Orlic et al., 2001), BM-derived mononuclear cells (MNCs) (Strauer et al., 2002), BM-derived hematopoietic stem cells (HSCs), endothelial progenitor cells (EPCs) (Stamm et al., 2007), BM-derived mesenchymal stem cells (MSCs) (Kanelidis et al., 2017), cardiac stem and progenitor cells (Bergmann et al., 2009), cardiac stem cells (CSCs) (Senyo et al., 2013), embryonic stem cells (ESCs) (Talkhabi et al., 2016), and induced pluripotent stem cells (iPSCs) (Takahashi and Yamanaka 2006).

The main factors and pathways involved in cardiovascular regeneration

Wnt-related pathways

Wingless-related integration site (Wnt) pathways, including the Wnt/β-catenin signaling pathway, play an essential regulatory role in cell proliferation, tissue renewal, and organ regeneration of the heart muscles (MacDonald et al., 2009) (Figure 1). Disturbances in Wnt signaling have been identified as risk factors and might be an adequate marker for CVD prediction (Foulquier et al., 2018). Current studies demonstrate that Wnt/β-catenin signaling regulates cardiac repair, endothelialization, and angiogenesis in heart tissues (Pahnke et al., 2016). Wnt/β-catenin signaling is also involved in myogenesis, vasculature remodeling, and SC renewal and differentiation (Wu and Pan 2010) (Table 1).

MiR-1-2 activity

Small regulatory microRNAs (miRNAs) are a class of non-coding RNAs that play a critical role in various bio-

TABLE 1: The main factors and pathway involved in cardiovascular regeneration with mentioning their main mechanisms or effects.

Factors/Pathways	Mechanisms/Effects
Wnt-related pathways	- Promotion of cardiac repair, endothelialization, angiogenesis, myogenesis, and vasculature remodeling
miR1-2 activity	- Maintenance of cardiac progenitor cells during regeneration. - Promotion of BMSC differentiation via the Wnt/β-catenin signaling pathway. - Induction of cardiac Troponin I (cTnI) and Nkx2.5 (central regulator of heart development)
Paracrine and autocrine secretions	- Paracrine/autocrine secretions such as angiopoietins, Vascular endothelial growth factor (VEGF), and Stromal cell-derived factor-1 (SDF-1) are involved in neovascularization. - Also, the paracrine factors exert anti-inflammatory effects by reducing Tumor necrosis factor-α (TNF-α), Interleukin-6 (IL-6), and Interleukin-1β (IL-1β).
Growth factors	- Regeneration of damaged myocardium. - Promotion of cell proliferation and reduction of cardiac fibrosis. - Decrease in apoptosis of cardiomyocytes. - Stimulating the myogenic differentiation of MSCs.
SDF-1/CXCR4 pathway	- Facilitating effective homing and promoting organ regeneration and repair. - Stimulation of endothelial progenitor cells to migrate into the ischemic area. - SDF-1α/CXCR4 signaling can be stimulated by hypoxic conditions.
Homeobox protein Nkx2-5 and Notch signalling pathway	- Regulation of tissue-specific gene expression and heart regeneration pathways. - SC differentiation, endothelial cell proliferation, angiogenesis, and myocardium regeneration

Wnt: Wingless-related Integration Site; BMSCs: Bone Marrow Stem Cells; cTnI: Cardiac Troponin I; SCs: Stem Cells; Nkx 2.5: Homeobox Protein Nkx-2.5; TNF-α: Tumor Necrosis Factor-Alpha; IL-6: Interleukin-6; IL-1β: Interleukin-1β; MSCs: Mesenchymal Stem Cells; VEGF: Vascular Endothelial Growth Factor; SDF-1α: Stromal Cell-derived Factor-1α; CXCR4: C-X-C Chemokine Receptor type 4.

logical events in cardiovascular development (Figure 1). For example, they contribute to cardiac cell specification and maintenance of cardiac progenitor cells during regeneration and promote cardiomyocyte differentiation (Pang et al., 2019). Furthermore, it has been documented that the overexpression of miR-1-2 promotes BMSC differentiation via the Wnt/β-catenin signaling pathway (Shen et al., 2017). Moreover, the overexpression of miR1-2 in BMSCs induces the expression of cardiac-specific genes such as cardiac Troponin I (cTnI), Nkx2.5 (central regulator of heart development), and GATA4 (Carresi et al., 2021a).

Paracrine and autocrine secretions

The interaction of paracrine and autocrine factors (growth factors, chemokines, etc.) secreted by SCs regulates the restoration and regeneration of the tissue (Chen et al., 2008) (Figure 1). For example, MSCs release high levels of pro-angiogenic factors such as angiopoietins, vascular endothelial growth factor (VEGF), stromal cell-derived factor-1 (SDF-1), fibroblast growth factor (FGF), and hepatocyte growth factor (HGF), which are involved in MSC-mediated neovascularization (Kinnaird et al., 2004). On the other hand, the paracrine factors of MSCs exert anti-inflammatory effects by reducing tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and interleukin-1β (IL-1β) (Miao et al., 2017). Furthermore, MSCs or cardiac SCs can exert their regulatory effect through exosome secretion (Wang et al., 2016) (Table 1).

Growth factors

Several studies propose that using growth factors can be beneficial for cardiac regeneration (Figure 1). For example, the injection of insulin-like growth factor 1 (IGF-1) and HGF could regenerate damaged myocardium, promote proliferation, and reduce cardiac fibrosis in an experimental model of acute myocardial infarction (MI) (Nadal-Ginard et al., 2014). The preconditioned medium rich in VEGF, FGF, IL-1β, platelet-derived growth factor (PDGF), IGF-1, and transforming growth factor-β (TGF-β) of BM-mononuclear cells improves angiogenesis and cardiac function and decreases the apoptosis of cardiomyocytes (Song et al., 2017). Furthermore, TGFβ1 stimulation dictates the myogenic differentiation of MSCs (Gu et al., 2018). It has been suggested that post-MI, angiogenic effects of growth factors potentially lead to forming new capillaries and,

consequently, the recovery of the infarcted tissue (Cochain et al., 2013) (Table 1).

SDF-1/CXCR4 pathway

SDF-1 is a member of the CXC chemokine family, and its regulatory effects are mediated by C-X-C chemokine receptor type 4 (CXCR4). SDF-1α and CXCR4 are ubiquitously expressed and play a crucial role in cell migration, survival, and proliferation (Kucia et al., 2004). SDF-1/CXCR4 signaling plays a pivotal role in response to tissue injury. The local secretion of SDF-1α acts as a chemoattractant, driving circulating CXCR4-expressing cells and other stem cells to the injured tissue, facilitating effective homing and promoting organ regeneration and repair (Wen et al., 2012). An additional protective mechanism of SDF-1α is that it prompts endothelial progenitor cells to migrate into the ischemic area (Kijowski et al., 2001). Moreover, SDF-1α/CXCR4 signaling can be stimulated with hypoxic preconditioning factors, Granulocyte colony-stimulating factor (G-CSF), and Hypoxia-inducible factor-1α (HIF-1α) (Tang et al., 2009).

Other important pathways and factors

The molecular players in an inflammatory cascade, which can be either destructive or protective depending on the inflammatory stage, are potential therapeutic targets (Saxena et al., 2013). To mention a few, IL-1 and reactive oxygen species (ROS) are stimulants of apoptosis. IL-1 suppresses fibroblast proliferation, inhibits differentiation of fibroblasts into myocytes, and retards activation of reparative responses (Brønnum et al., 2013). ROS activates nuclear factor kappa B (NF-κB) signaling and results in apoptosis and autophagy in various cell lines (Khalilzadeh et al., 2022; Sheibani et al., 2020; Shi et al., 2017). While inflammatory pathways negatively impact cardiac regeneration, transcription factors play an essential role in promoting it. On the other hand, transcription factors play an essential role in cardiac regeneration. For instance, Homeobox protein Nkx2-5 regulates tissue-specific gene expression and heart regeneration pathways (Cambier et al., 2014). Furthermore, signaling pathways regulate many biological processes. Such as the Notch signaling pathway, which regulates SC differentiation, endothelial cell proliferation, angiogenesis, and myocardium regeneration (Grego-Bessa et al., 2007) (Table 1).

Phytomedicines applications in cardiac regeneration therapy

The rising interest in phytomedicines for cardiac therapy reflects a growing recognition of the therapeutic potential of traditional herbal remedies in managing cardiovascular diseases (CVDs). Historically, medicinal plants have been utilized for centuries to treat various cardiovascular conditions, including congestive heart failure, hypertension, and arrhythmias (Rastogi et al., 2016; Sheibani et al., 2018).

In addition, cardiac SC therapy creates a revolution in RM and enables the restoration of cardiac function lost due to aging, diseases, or damage (Rosenstrauch et al., 2005). However, this method suffers from several pitfalls, such as tumorigenicity, immune rejection, SC incompetence, and invasive harvesting techniques (Nussbaum et al., 2007). Existing studies suggest that herbal medicines might stimulate the regeneration and reconstruction of injured myocardium (Qu et al., 2015b). Accordingly, they can introduce new alternatives for SC therapy by mimicking specific downstream effects. Here are a few examples of such herbal agents. The following section explains how herbal agents could regulate cardiogenesis (Figure 2).

Rosa laevigata Michx

Rosa laevigata Michx is a medicinal plant native to China that has shown various therapeutic effects in different conditions, including renal and hepatic damage, diarrhoea, and asthma (Qu et al., 2015a). Furthermore, some studies have indicated that administering *Rosa laevigata michxa* extract improves patient survival rates and tends to prevent ischemic reperfusion injury (Zhang et al., 2013). In a rat model of MI (ligation of the LAD coronary artery), the extract of *Rosa laevigata Michx* promoted cardiogenesis both *in vitro* and *in vivo,* augmenting the cardiogenic differentiation of MSCs and facilitating myocardial regeneration (Qu et al., 2015b). The demonstrated properties of this plant highlight its anti-inflammatory, anti-apoptosis, and anti-oxidative stress characteristics. It is important to note that the transient upregulation of NF-κB in rats treated with *Rosa laevigata Michx* may lead to the migration and accumulation of CSCs/MSCs in the myocardium-infarcted area (Guo et al., 2009; Qu et al., 2015b).

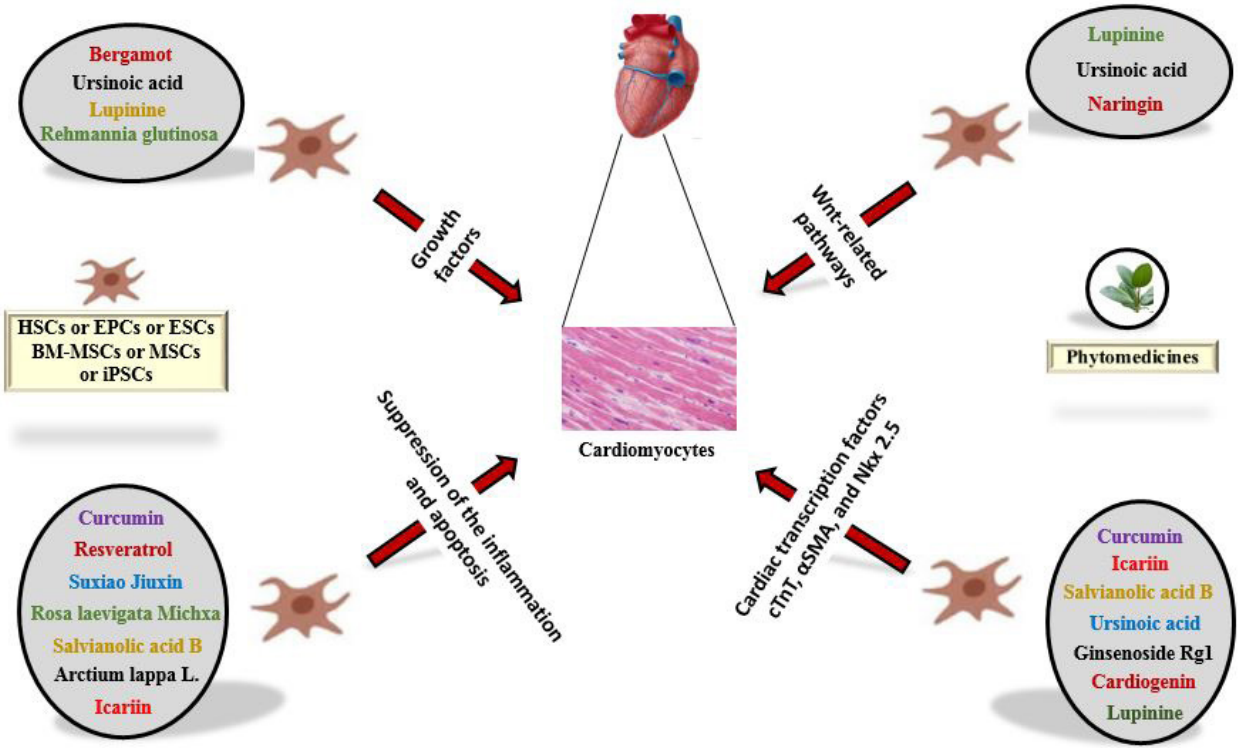

FIGURE 2. Possible mechanism of action of herbal medicines (phytomedicines) in cardiogenesis. HSCs: BM-derived hematopoietic stem cells; EPCs: endothelial progenitor cells; ESCs: embryonic stem cells; BM-MSCs: bone marrow-mesenchymal stem cells; MSCs: mesenchymal stem cells; iPSCs: induced pluripotent stem cells.

Suxiao Jiuxin Pill

Suxiao Jiuxin Pill, with the main components of tetramethylpyrazine and borneol, is another example of Chinese herbal medicine, with remarkable cardioprotective effects (Lu et al., 2015). The cardioprotective properties of this herb are related to its anti-inflammatory effect as a result of down-regulation of NF-κB and reduction of superoxide dismutase (SOD) activity (LI et al., 2011). It has been demonstrated that *Suxiao Jiuxin* promotes cardiomyocyte differentiation through the stimulation of exosome release from cardiac mesenchymal stem cells (C-MSCs) in ischemic myocardium (Ruan et al., 2018). *Suxiao Jiuxin* treatment notably upregulates Rab27a and Rab27b, proteins that regulate exosome secretion. These proteins are members of the Rab subfamily of GTPases, which regulates exosome secretion. Therefore, *Suxiao Jiuxin* treatment can consequently stimulate exosome secretion from C-MSCs (Guo et al., 2015).

Salvia miltiorrhiza (Danshen)

Salvia miltiorrhiza (Danshen) is another herb valued in traditional Chinese medicine for its therapeutic properties found in its roots. The most abundant compound extracted from *Salvia miltiorrhiza* (Danshen) is Salvianolic acid B, which stimulates functional cardiomyocyte differentiation in embryonic stem cells (ESCs). Previous studies have indicated that upon treatment, the upregulation of proteins involved in cardiac structure maturation, including sarcomeric α-actinin and cardiac troponin I, was observed (Chan et al., 2009b). Other beneficial effects of Salvianolic acid B include dilation in the coronary arteries, promotion of angiogenesis, anti-inflammatory and anti-oxidative effects, and anti-apoptosis activity (Gurusamy et al., 2010). This herb has the potential to address the limitations of SC therapy in cardiac diseases (Segers and Lee 2008).

Grapes

Grapes from the genus *Vitis* contain a polyphenolic antioxidant known as resveratrol, which is also present in red wine. This non-enzymatic antioxidant enhances the antioxidant defence system (Bertelli and Das 2009). Further observed effects of resveratrol *in vivo* were lipid peroxidation reduction and increased antioxidant capacity in plasma (Baur and Sinclair 2006). Nuclear factor

erythroid 2–related factor 2 (Nrf2) plays a leading role in the endogenous antioxidant defence system. It has been shown that Nrf2 activity was considerably elevated in resveratrol-treated rats in the MI model, noting that this activation is positively correlated with the localization of SCs. Animal studies have demonstrated that resveratrol administration improves the engraftment of transplanted SCs. This improvement is likely to correlate with the prolonged induction of Nrf2, Ref-1, and NF-κB. Nrf2 and Ref-1 are redox proteins commonly present in cardiac cells (Gorbunov et al., 2012).

Geum japonicum

This plant is native to North America and East Asia, particularly Japan. Cardiogenin, the main effective component extracted from *Geum japonicum,* promotes the differentiation of cardiac cells of endogenous BMSCs and leads to myocardial regeneration in an animal model of acute MI (Cheng et al., 2009). *Geum japonicum*/ cardiogenin activates several signaling pathways crucial for myocardial regeneration (Pandur et al., 2002). For example, bone morphogenic protein (BMP)-associated pathways and cell survival-related pathways such as JAK/STAT and NF-κB pathways. Furthermore, the up-regulation of proteins AKT1 and Bcl2 leads to further signaling cascades. In summary, this plant potentially increases the viability of cardiomyocytes, leading to a higher migration rate of MSCs to the infarcted area and bringing up the potential for post-MI treatment (Cheng et al., 2009).

Crataegus pentagyna

Crataegus pentagyna (hawthorn), native to southeastern Europe, has shown anti-arrhythmic effects on cardiomyocytes derived from human ESCs and induced pluripotent stem cells (iPSCs). These SCs are an appropriate cell-based model for studying cardiac arrhythmias. For example, human iPSC-derived cardiomyocytes have been extensively studied for this purpose. *Crataegus pentagyna* has demonstrated anti-arrhythmic effects on cardiomyocytes differentiated from different human ESCs and iPSC lines. It has been documented that *Crataegus pentagyna* leaf extract may have a negative chronotropic effect on isoproterenol-induced arrhythmic episodes in patients with polymorphic ventricular tachycardia. This effect may be mediated by the activation of muscarinic receptors expressed on human PSC-derived cardiomyocytes, followed by alteration in signaling pathways and Ca^{2+} transport (Pahlavan et al., 2018). The downregulation of repolarizing potassium currents may also contribute to cardiac electrophysiological changes caused by *Crataegus pentagyna* extract (Müller et al., 1999).

Angelica ursina, Lupinus luteus

It has been demonstrated that the co-treatment of these two plants leads to higher cardiomyocyte differentiation in PSCs (Lee et al., 2019). Lupinine, the main alkaloid in the seeds of *Lupinus luteus* (Kinder and Knecht 2011), and ursinoic acid, an aromatic oxo acid isolated from *Angelica ursina* (Nikonov and Yagudaev 1970), are the main compounds responsible for this effect. An *in vivo* study showed the higher differentiation capacity of mouse embryonic cardiac SCs when co-treated with these plants compared to untreated ones (Carresi et al., 2021b). The upregulation of two transcription factors, GATA-binding protein 4 (GATA-4) and Nkx 2.5, as biomarkers for cardiac-specific differentiation, is a downstream effect caused by lupinine and ursinoic acid. Additionally, the upregulation of PDGFR-α and Flk was observed as markers for cardiac progenitor cells. Further observation in treated cells showed up-regulatory effects in α-SMA, cTnT, and Connexin 43 (Cx43) (Lee et al., 2019). Another study has suggested that ursinoic acid and lupinine promoted cardiogenesis by activating Wnt signaling pathways (Carresi et al., 2021b).

Panax ginseng

Panax ginseng is well known for its numerous medicinal properties. Ginsenoside Rg1, an active component of ginseng, has antioxidant and anti-inflammatory properties, which can alter the hematopoietic microenvironment of BMSCs in rats (Chan et al., 2009a). Its up-regulatory effects on the Nkx 2.5 transcription factor and cTnI promote differentiation in hESC-derived cardiac progenitor cells (Kim et al., 2010). Interestingly, ginseng has water-soluble components that can enhance the differentiation of MSCs into cardiomyocytes and viable beating cells at certain levels (Sasaki et al., 2008). G-CSF, a critical component for homing and the differentiation of BMSCs to vascular endothelial cells, is secreted following the treatment of ginsenoside Rg1 (Carresi et al., 2021a). Moreover, the decreased infarcted size after MI is also observed (He et al., 2020). For

example, an in vivo study using a rat model of acute MI demonstrated the enhancement of CD34+ SCs in blood, which consequently dictates the migration of SCs to the infarcted area, the reduction of infarct size, and the significant induction of myocardial regeneration in a rat model of acute MI (Yang et al., 2008).

Bergamot (Citrus bergamia)

Bergamot (*Citrus bergamia*), a hybrid fruit of lemon and bitter orange, is highly enriched in polyphenols and has been well studied for its therapeutic effects (Walker et al., 2014). Bergamot polyphenolic fraction (BPF) could prevent CSC attrition and increase the number of newly formed cardiomyocytes. Several studies propose that the ROS-scavenging characteristics of BPF promote differentiation and proliferation of the CSCs (Carresi et al., 2018). Naringin, one of the most important flavonoids in BPF, defends human adipose-derived MSCs from the destructive effects of H2O2. Studies have shown that BPF-derived naringin might exert its effect through the regulation of Wnt signaling (Wang et al., 2015a). Moreover, citrus-derived flavonoids have been shown to possess estrogenic-like activity, which might stimulate progenitor cell differentiation (Su et al., 2015).

Icariin

Icariin, another effective flavonoid derived from several plant species, also stimulates cardiomyogenesis by activating signaling pathways. It has been reported that icariin treatment in the early stages of cardiac development increases the myosin heavy chain-α isoform (MHC-α) and myosin light chain 2v (MLC2v) (ZHU and LOU 2005). Some other studies have confirmed that icariin regulates the differentiation of ESCs into cardiomyocytes by modulating the nitric oxide (NO)-cGMP signaling pathway (ZHU and LOU 2006). Moreover, the upregulation of β-adrenergic receptors and several myocardial biomarkers such as GATA-4, Nkx 2.5, MHC-α, and MLC2v was observed after icariin treatment in the early stages of differentiation. Moreover, a decrease in ROS levels has a stimulating effect on ESC differentiation (Wo et al., 2008). Furthermore, icariin has exhibited a stimulatory impact on the differentiation of MSCs derived from adipose tissues, most probably via the ERK pathway (Jin et al., 2010).

Curcumin

Curcumin, produced by plants of the *Curcuma longa* species, is a polyphenol and has been long used in herbal medicines due to its various pharmacological effects (Sharma et al., 2005). One study indicated that curcumin regulated cardiogenesis by inhibiting histone acetylation (Carresi et al., 2021a).

In an animal model of cardiac ischemic reperfusion injury, the pre-treatment of adipose MSCs with curcumin enhances myocardial regeneration. Furthermore, in vitro data have indicated that curcumin protects SCs by reducing oxygen-free radical production, decreasing apoptosis by mediating AKT phosphorylation, increasing HO-1 expression, and suppressing the caspase-3 expression level (Liu et al., 2015). Curcumin has also stimulated ESC differentiation into the cardiac lineage by regulating the NO-cGMP pathway. Moreover, increased levels of several cardiac-specific markers, such as Nkx 2.5, cTnI, and MHC-α, are observed following curcumin administration (Mujoo et al., 2012). Curcumin significantly reduces caspase-3 activity and elevates Cyclin-dependent kinase inhibitor (CDKI) p21, as well as several specific cardiac proteins (Myelin-like chain kinase-2 and cTnI). Additionally, curcumin protects cells from mitochondrial dysfunction and nuclear condensation, and inhibits cell loss induced by hypoxia and reoxygenation. Moreover, curcumin improves BMSCs' survival rate by inhibiting HIF-1α expression, elevating Epac1 levels, and inhibiting Erk1/2, p38, and AKT phosphorylation (Wang et al., 2019).

Salvia miltiorrhiza (Tanshinone II)

Tanshinone II extracted from *Salvia miltiorrhiza* is known for increasing BMSCs engraftment in the ischemic myocardium. Tanshinone II regenerates the myocardium, accelerates cardiac function recovery, and enhances the efficacy of BMSCs transplantation treatment in myocardial damage in acute MI. Furthermore, it has antioxidant, anti-inflammatory, and antiapoptotic effects on cardiomyocytes (Tong et al., 2011). The expression of SDF-1α is increased in the infarcted area during MI, which plays an important role in recruiting BMSCs to the infarcted heart. Moreover, research has documented that the overexpression of SDF-1 can enhance the migration of stem and progenitor cells to the heart. Tanshinone IIA can promote the SDF-1α expression in the infarct zone.

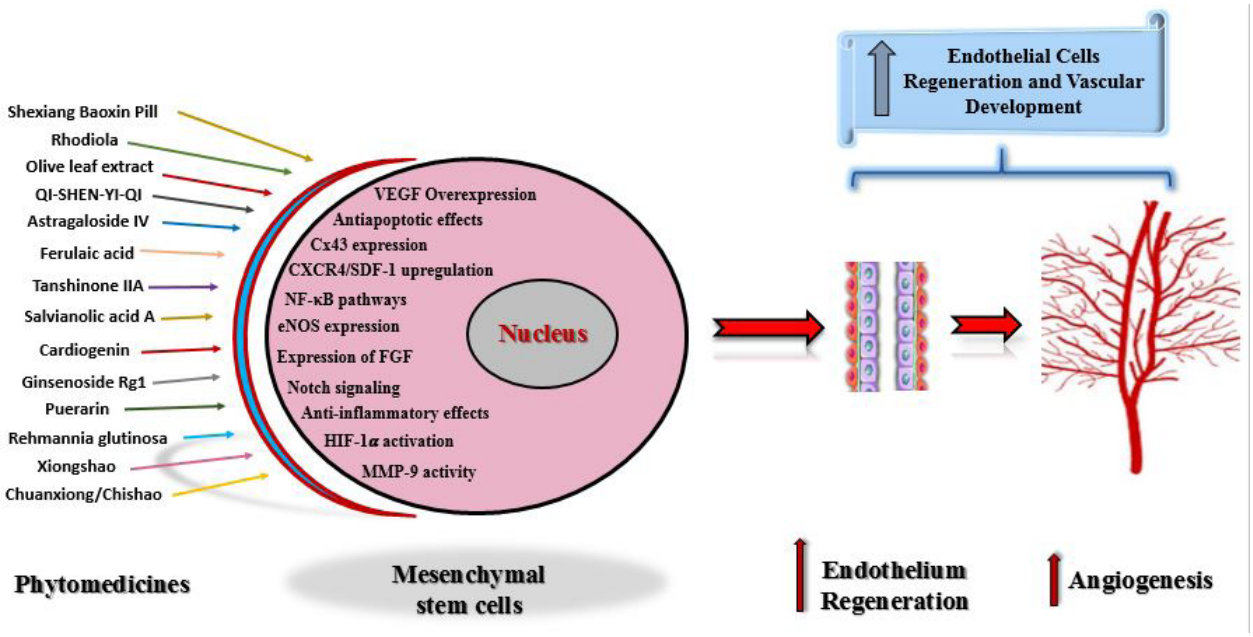

FIGURE 3. Possible mechanisms of action of herbal medicines (phytomedicines) in angiogenesis include the modulation of various factors such as Vascular Endothelial Growth Factor (VEGF), Connexin 43 (Cx43), C-X-C Chemokine Receptor Type 4 (CXCR4), Nuclear Factor-Kappa B (NF-κB), Endothelial Nitric Oxide Synthase (eNOS), Fibroblast Growth Factors (FGFs), Hypoxia Inducible Factor (HIF), and Matrix Metalloproteinase (MMP).

Moreover, this phytomedicine protects cardiomyocytes against ischemia/reperfusion by decreasing apoptosis, elevating SOD activity, and decreasing MDA concentration (Tong et al., 2011). Tanshinone IIA has exhibited stimulatory effects on the migration of BMSCs via the SDF-1/CXCR4 axis. The overexpression of CXCR4 has been confirmed to respond to lower levels of SDF-1, leading to improved mobilization and engraftment of MSCs into the ischemic area in vivo (Kahn et al., 2004; Zhang et al., 2008). Table 2. summarizes the aforementioned phytomedicines along with their related models and action mechanisms.

Effects of phytomedicines on endothelial cell regeneration and angiogenesis

The ability of phytomedicines to improve endothelial function and promote angiogenesis is especially important in cases of ischemic conditions, where blood supply is compromised. Studies have shown that different phytomedicines can stimulate the production of crucial angiogenic factors, which are necessary for the proliferation and movement of endothelial cells. Moreover, the therapeutic use of phytomedicines goes beyond just cell proliferation; they can also aid in the recruitment of EPCs to injury sites, thereby enhancing tissue repair processes (Avagimyan et al., 2022; Scioli et al., 2021; Terriaca et al., 2021).

Given the importance of angiogenesis in CVDs, ischemic disorders, ulcers, wound healing, vascularization, and endothelial cell proliferation have been addressed in experimental and clinical studies. Enhancing the differentiation of SCs into endothelial progenitor cells or mature endothelial cells is a therapeutic strategy for these disorders (Gomez et al., 2012). On the other hand, therapeutic angiogenesis presents an attractive option for CVDs. Several investigations have confirmed that MSCs can differentiate into endothelial cells in vitro (Oswald et al., 2004). Moreover, in a rat model of dilated cardiomyopathy, transplanted MSCs have been shown to develop into endothelial cells to improve cardiac functions (Nagaya et al., 2005). In this regard, olive leaf extracts could promote the endothelial differentiation of human MSCs by overexpressing the VEGF receptor-1 (VEGFR-1) gene, VEGF gene, and PDGF receptor gene (Gomez et al., 2012). The following section explains how herbal agents could regulate angiogenesis (Figure 3).

Astragaloside

Astragaloside IV is extracted from *Astragalus membranaceus* and can enhance the migration of MSCs to the ischemic area of the myocardium by upregulating

TABLE 2: Summary of the effects of several herbal medicines (phytomedicines) in cardiac regeneration.

Name of herbal medicine (phyto-medicine)	Origin or category	Model/Type of experiment	Mechanisms of action in cardiac regeneration	Ref
Rosa laevigata Michxa	A White, fragrant rose native to southern China and Taiwan, south to Laos and Vietnam	- *In vitro* (BMSCs isolated from MI-induced Sprague-Dawley rats)	- Anti-inflammatory, anti-apoptosis, and anti-oxidative stress effects - Upregulation in the expression of NF-κB	(Guo et al., 2009; Qu et al., 2015b)
Suxiao Jiuxin	A Chinese herbal medicine	- *In vivo* (Sprague-Dawley rats) - *In vitro* (mouse C-MSCs)	- Suppression in the production of NFκB and SOD - Stimulation of exosome release	(LI et al., 2011; Ruan et al., 2018)
Salvianolic acid B	Extracted from *Salvia miltiorrhiza* (Chinese herbal medicine)	- *In vitro* (ESCs)	- Anti-inflammatory effects and anti-apoptosis activity - Expression of sarcomeric a-actinin and cardiac troponin I	(Chan et al., 2009b)
Resveratrol	A polyphenolic compound present in red wine and grapes	- *In vitro* (cardiac stem cells isolated from rats)	- Reduce lipid peroxidation, increase plasma antioxidant capacity, and free radical scavenging - Activation of Nrf2 and Ref-1	(Gorbunov et al., 2012)
Cardiogenin	The main effective component extracted from the *Geum japonicum*	- *In vitro* (BMSCs isolated from MI-induced Sprague-Dawley rats)	- Stimulate BMP-associated pathways - Upregulation of AKT1and Bcl2 - Increase the cardiomyocytes' migration to the infarct area	(Cheng et al., 2009)
Crataegus pentagyna	Hawthorn leaf extract (flavonoid compound)	- *In vitro* (cardiomyocytes derived from human PSCs)	- Exert a negative chronotropic effect - Activation of muscarinic receptors expressed in cardiomyocytes	(Pahlavan et al., 2018)
Lupinine	The main alkaloid in the seeds of *Lupinus luteus*	- *In vitro* (mouse embryo-derived P19 teratocarcinoma cell line)	- Increase the levels of the GATA-binding protein 4 and Nkx 2.5 transcription factor - Increase the levels of α-SMA, PDGFR-α, cTnT, and Cx43 - Activation of the Wnt signaling pathway	(Lee et al., 2019)
Ursinoic acid	An aromatic oxo acid isolated from the *Angelica ursina*	- *In vitro* (mouse embryo-derived P19 teratocarcinoma cell line)	- Increase the levels of the GATA-binding protein 4 and Nkx 2.5 transcription factor - Increase the levels of α-SMA, PDGFR-α, cTnT, and Cx43 - Activation of the Wnt signaling pathway	(Lee et al., 2019)

TABLE 2 continues

Name of herbal medicine (phytomedicine)	Origin or category	Model/Type of experiment	Mechanisms of action in cardiac regeneration	Ref
Ginsenoside Rg1	An active component of Ginseng	- *In vitro* (human ESCs) - *In vitro* (BMSCs isolated from MI-induced Sprague-Dawley rats)	- Increase in the levels of Nkx 2.5 transcription factor and cTnI - Enhancement of the migration of stem cells to the infarcted area	(Kim et al., 2010; Yang et al., 2008)
Bergamot	Highly enriched in polyphenols such as *Citrus bergamia*	- *In vivo* (male Wistar rats)	- Direct ROS-scavenging properties	(Carresi et al., 2018)
Naringin	A flavonoid (contained in polyphenolic fraction of bergamot)	- *In vitro* (human adipose-derived MSCs)	- Attenuation of H2O2-induced cytotoxicity - Regulation of the Wnt signaling	(Wang et al., 2015a)
Icariin	A type of flavonoid	- *In vitro* (mouse ESCs) - *In vitro* (mouse adipose-derived SCs)	- Reduction of apoptosis - Increase in the GATA-4, Nkx 2.5, α-MHC, and MLC2v - Modulation of the NO-cGMP pathway - Modulation of ROS levels - Initiation of the ERK pathway	(Jin et al., 2010; Wo et al., 2008; ZHU and LOU 2006)
Curcumin	A polyphenol isolated from *Curcuma Longa*	- *In vitro* (rat adipose-derived MSCs) - *In vitro* (human ESCs) - *In vitro* (rat BM-MSCs)	- Reduction in oxygen free radicals and apoptosis, and caspase-3 expression - Increase HO-1 expression - Regulation of the NO-cyclic GMP pathway - Increase the levels of Nkx 2.5, cTnI and α-MHC - Downregulation of ERK1/2 and p38, and AKT phosphorylation	(Liu et al., 2015; Mujoo et al., 2012; Wang et al., 2019)
Tanshinone II	Extracted from *Salvia miltiorrhiza*	- *In vitro* (BMSCs isolated from MI-induced Sprague-Dawley rats	- Expression of SDF-1α - Enhance the stem and progenitor cell migration to the heart - Stimulation of BMSCs migration via the SDF-1/CXCR4 axis	(Tong et al., 2011)

SCs: Stem Cells; MSCs: Mesenchymal Stem Cells; BM-MSCs: Bone Marrow Mesenchymal Stem Cells; BMSCs: Bone Marrow Stem Cells; C-MSCs: Cardiac Mesenchymal Stem Cells; ESCs: Embryonic Stem Cells; PSCs: Pluripotent Stem Cells; MI: Myocardial Infarction; NF-κB: Nuclear Factor kappa B; SOD: Superoxide Dismutase; BMP: Bone Morphogenic Protein; MSCs: Mesenchymal Stem Cells; PDGFR-α: Platelet-derived Growth Factor-α; cTnT: Cardiac Troponin; Cx43: Connexin 43; G-CSF: Granulocyte Colony Stimulating Factor; TGF-1β: Transforming Growth Factor 1β; BMSCs: Bone Marrow Stem Cells; ROS: Reactive Oxygen Species; MLC2v: Myosin Like Chain 2v; NO: Nitric Oxide; cGMP: Cyclic Guanosine Monophosphate; ERK: Extracellular Signal-Regulated kinases; MDA: Malondialdehyde; VEGFR2: Vascular Endothelial Growth Factor Receptor 2; SDF-1α: Stromal Cell-derived Factor-1α; CXCR4: C-X-C Chemokine Receptor type 4; Bcl2: B-Cell Lymphoma 2; Nrf2: Nuclear factor-erythroid factor 2-Related Factor 2; Ref-1: Redox Effector Factor-1; AKT1: AKT Serine/Threonine Kinase 1; GATA: GATA Transcription Factor; Nkx 2.5: Homeobox Protein Nkx-2.5; α-SMA: Alpha Smooth Muscle Actin; MHC-α: Myosin heavy chain-α isoform; HO-1: Heme Oxygenase-1

the CXCR4 pathway (Xie et al., 2013). Moreover, astragaloside IV can promote the proliferation and angiogenesis of human umbilical vein ECs (Wang et al., 2015b). Gap junctions are assembled from connexins, a family of structurally related transmembrane proteins (Leybaert et al., 2017) and play a crucial role in regulating the metabolism (Cronier et al., 2001), proliferation, and differentiation of different cell types, including endothelial cells (El-Sabban et al., 2003). Connexin 37 (Cx37), Cx40, and Cx43 are the most expressed connexins in the vascular endothelium (Simon and McWhorter 2003). In a study, the expression of all these three proteins was remarkably increased in the astragaloside IV-treated groups compared to the control group. On the other hand, this extract could promote endothelial cell differentiation by upregulating Cx37, Cx40, and Cx43 levels (Li et al., 2018). Astragaloside enhanced the VEGF and FGF expression, which may relate to the promotion of angiogenesis in a rat model of myocardial infarction (Yu et al., 2015).

Tanshinone IIA

With similar mechanisms, tanshinone IIA, isolated from ***Salvia miltiorrhiza*** as a Chinese herbal medicine, can promote the proliferation and differentiation of endothelial progenitor cells and angiogenesis. The compound's role in angiogenesis is significant; it promotes the formation of new blood vessels from existing ones. Research has demonstrated that Tanshinone IIA can improve microcirculation and blood flow, which are essential for tissue regeneration and repair (Qin et al., 2023). Additionally, its anti-inflammatory properties may contribute to a more favorable environment for angiogenesis by reducing oxidative stress and inflammation within the vascular system (Zhu et al., 2017). Although the synergistic effects of astragaloside IV and tanshinone IIA on angiogenesis and the differentiation of endothelial SCs are confirmed, the synergistic role of these two compounds in treating coronary heart diseases (CHDs) with MSCs needs further *in vivo* and *in vitro* research (Li et al., 2018). In summary, Tanshinone IIA exhibits significant promise in enhancing endothelial regeneration through its effects on EPC proliferation, differentiation, and angiogenesis.

Salvianolic acid A

Chinese traditional medicine formulas, extracts, and compounds from herbal medicines exert pro-angiogenic activity (Bu et al., 2020). Salvianolic acid A, another bioactive compound of *Salvia miltiorrhiza*, can elevate EGF and VEGFR-2 in the infarcted zone in animal models. VEGFR-2 is pivotal for angiogenesis, mediating endothelial cell survival, migration, and tube formation. Matrix metalloproteinase-9 (MMP-9) is also an important target for myocardial remodeling by stimulating proliferation, migration, and collagen synthesis. It facilitates the degradation of extracellular matrix components, allowing for cellular migration and proliferation essential for tissue repair. Salvianolic acid A significantly promotes MMP-9 activity during cardiac injury. Moreover, the secretion of MMP-9 is also a supportive factor for angiogenesis. Accordingly, this agent's angiogenic properties depend on VEGF/VEGFR-2 and MMP-9-related pathways (Li et al., 2014). In conclusion, salvianolic acid A represents a promising candidate for enhancing endothelial regeneration through its pro-angiogenic properties mediated by EGF, VEGFR-2, and MMP-9 pathways.

Cardiogenin

Geum japonicum/cardiogenin can promote the stimulation of many new vessels in the entire infarcted zone in a rat model of MI. Treatment with cardiogenin resulted in a significant increase in vascular density within the infarcted myocardium, suggesting its role as a potent angiogenic agent (Cheng et al., 2009). Given the critical role of angiogenesis in the survival and growth of cells in the repair process of an infarcted heart, the potential angiogenic properties of cardiogenin (an active compound of *Geum japonicum*) are evaluated. The angiogenic and antiapoptotic effects of cardiogenin are related to the JAK-STAT and NF-κB pathways (Karin and Lin 2002). Accordingly, the initiation of these pathways in cardiogenically-treated MSCs may also enhance endothelial regeneration, promote the renovation of injured coronary arteries, and further inhibit the cell death of transplanted MSCs for effective MI reparation (Cheng et al., 2009). In conclusion, the potential impact of Cardiogenin on endothelial regeneration presents a promising avenue for enhancing cardiac repair following myocardial infarction. By leveraging its angiogenic properties through critical signaling pathways, Cardiogenin could play a vital role in improving recovery outcomes for patients suffering from ischemic heart disease.

Ginsenoside Rg1

In addition to the points mentioned about ginseng, one of the cardioprotective mechanisms of ginseng is the upregulation of NO levels. It has garnered attention for its cardioprotective properties, particularly its role in endothelial regeneration.

Ginsenoside Rg1, a main bioactive component of *Ginseng quinquefolium (L.)*, is an angiogenesis inducer of endothelial nitric oxide synthase (eNOS) expression. Ginsenoside Rg1 could reduce miR-214, appears to inhibit eNOS formation in human umbilical vein endothelial cells (HUVECs), suggesting a potential angiogenic mechanism induced by Ginsenoside Rg1 (Chan et al., 2009a). By reducing miR-214 levels, Rg1 may facilitate increased eNOS expression and NO production, thereby enhancing endothelial function and regeneration (Huang et al., 2012).

Moreover, ginsenoside Rg1 can induce the expression of VEGFR-2 in HUVEC cells, particularly under inflammatory conditions induced by TNF-α (Chan et al., 2013). These mechanisms collectively support improved angiogenesis and endothelial cell functionality, making ginsenoside Rg1 a promising candidate for therapeutic strategies aimed at cardiovascular health and recovery from vascular injuries.

Xiongshao

Xiongshao, extracted from *Rhizoma ligusticum wallichii* and *Radix paeonia rubracan*, enhances angiogenesis in endothelial cells by stimulating the expression of FGF and VEGF, suggesting that xiongshao may be a probable new beneficial alternative for the treatment of ischemic heart diseases. Xiongshao capsule can significantly increase the migration and formation of HUVEC capillary tube in a dose-dependent manner (Yuan et al., 2018). On the other hand, Xiongshao may improve the proliferation and differentiation of EPCs, thereby increasing their availability for endothelial repair.

By modulating inflammatory responses, Xiongshao could create a more favorable environment for endothelial regeneration. Compounds within Xiongshao may stimulate angiogenic pathways, facilitating new blood vessel formation essential for tissue repair (Feng-qin et al., 2004).

Ferulic acid

Ferulic acid is a key component of *Radix angelica sinensis*. The transplantation of pre-treated BMSCs with sodium ferulate into the ischemic area elevated the VEGF production and angiogenesis via the AKT/mTOR signaling pathway (Zhang et al., 2017). Furthermore, VEGF stimulates the expression of angiopoietin-1 (Ang1)/Tie2, leading to the development of new blood vessel networks (Chen et al., 2014). In another study, ferulic acid exerted angiogenic effects through endothelial cell migration. Ferulic acid augmented VEGF and platelet-derived growth factor (PDGF) activities in HUVECs. Moreover, the levels of hypoxic-HIF-1α (one of the main modulators of VEGF and PDGF), mitogen-activated protein kinase (MAPK), and PI3K pathways are upregulated by ferulic acid. All these factors are involved in the angiogenic properties of ferulic acid (Lin et al., 2010).

Puerarin

Puerarin is an effective component extracted from traditional Chinese medicine (*Radix puerariae*). Puerarin treatment can promote angiogenesis and reduce the infarcted size in the ischemic heart in a rat model of myocardial infarction. Its underlying cellular mechanisms probably promote the expression of VEGF and the endothelial eNOS enzyme. Increased VEGF expression facilitates the migration and differentiation of EPCs, which are essential for vascular repair and regeneration (Zhang et al., 2006). In a rat model of myocardial infarction, puerarin treatment resulted in a significant reduction in infarct size, correlating with increased angiogenesis and enhanced endothelial function. Histological analyses demonstrated an increase in capillary density and improved myocardial tissue architecture following puerarin administration. These findings suggest that puerarin not only protects against ischemic damage but also actively contributes to the regeneration of the endothelial layer (Guo et al., 2018).

QI-SHEN-YI-QI

This compound is made from a mixture of several herbal medicines (*Panax notoginseng*, *Radix salvia miltiorrhiza bge*, *Radix astragalus membranaceus bge,* and *Dalbergia odorifera T*). It also has many beneficial effects on cardiovascular disorders such as congestive heart failure, myocardial infarction, and CHDs (Zhang et al., 2010). According to the crucial role of growth factors in the angiogenesis process, the angiogenic effects

of this compound have been evaluated with an emphasis on the role of growth factors. PDGF, FGF-2, basic FGF, and VEGF are the main regulators in the migration and differentiation of endothelial cells (Parsons-Wingerter et al., 2000). In an animal study, QI-SHEN-YI-QI could significantly increase the protein levels of PDGF-B, VEGF, and the mRNA level of FGF. Moreover, elevated vessel formation and reduced size the of left ventricle infarct were observed with QI-SHEN-YI-QI treatment. In the MI model, this phytomedicine enhances the blood flow in the infarcted heart by forming a new coronary microvessel network (Zhang et al., 2010).

Rhodiola

Rhodiola (*Radix et rhizoma*) may improve angiogenesis in ischemic myocardium after MI injury. It up-regulates the creation of Flt-1 and Tie-2 in the ischemic area (Li et al., 2005). Flt-1, VEGF receptor-1 (VEGFR-1), is a type of tyrosine kinase. VEGF induces the angiogenesis process by stimulating VEGFR-1 and VEGFR-2 (Cudmore et al., 2012). Tie-2 is the receptor of angiopoietins. The angiopoietins-Ties axis is essential for forming vascular beds (Hennings et al., 2016). An animal study of acute MI described that *Radix et rhizoma rhodiolae kirilowii* might enhance angiogenesis by activating HIF-1α, HIF-1β, and VEGF. Moreover, the expression of von Willebrand factor (vWF), a marker of endothelial proliferation, also remarkably increased (Gao et al., 2009).

Chuanxiong and Chishao

Ligusticum chuanxiong, also known as Chuanxiong, and Red *Paeonia lactiflora rubra*, also known as Chishao, have shown cardioprotective effects, which may be caused by the promotion of angiogenesis (Shi et al., 2019). Tissue hypoxia and HIF-1α activation are the main stimulatory factors for angiogenesis (Shohet and Garcia 2007). Mechanistically, HIF-1α stimulates the expression of numerous proteins, including VEGF, VEGF receptor flt-1, and basic FGF (Pugh and Ratcliffe 2003). Moreover, the expression of HIF-1α and FGF receptor-1 significantly increased with Chuanxiong/Chishao treatment in the MI model (Shi et al., 2019). It has been confirmed that the activation of the SDF-1/CXCR-4 pathway can remarkably improve the mobilization and migration of SCs to the ischemic area. SDF-1 accelerates vascular formation, facilitates the homing of bone mesenchymal SCs, and induces angiogenesis in ischemia (Marquez-Curtis and Janowska-Wieczorek 2013). Chuanxiong/Chishao administration also stimulates SDF-1 and CXCR-4 angiogenic factors (Shi et al., 2019). Cardiotrophin1 is an effective cytokine for promoting cell engraftment and conserving cardiac function by enhancing the cardiac differentiation of SCs in infarcted hearts (Bortolotti et al., 2017). Notch signaling is one of the main pathways for the regulation of endothelial cell proliferation, the differentiation of arteries and veins, and the angiogenic development of the blood capillary network (Roca and Adams 2007). Up to now, four receptors (Notch1-4) and five ligands (DII1, DII3, DII4, Jagged l, and Jagged 2) have been recognized for the Notch signaling pathway in mammalian cells. The activation of the Notch signaling pathway leads to the release of Notch intracellular domain (NICD) from the cell membrane. Then, NICD moves to the nucleus to stimulate gene transcription involved in cell proliferation and differentiation (Kopan and Ilagan 2009). The Notch1/NICD cascade is also involved in angiogenesis and cardiomyocyte differentiation of SCs in the ischemic heart (Ren et al., 2018). Chuanxiong/Chishao upregulates Notch and NICD expression; therefore, it may play a significant role in promoting angiogenesis, the formation of new capillaries, and improving bloodstream in the ischemic myocardium (Shi et al., 2019).

Shexiang Baoxin

Shexiang Baoxin pill (a classic patent medicine derived from traditional Chinese medicine) may be partly effective in inducing angiogenesis in rabbit models of atherosclerosis and myocardial infarction (Shen et al., 2010). Moreover, echocardiography data have indicated that Shexiang Baoxin can improve cardiac functions. Mechanistically, the increased expressions of VEGF and VEGFR-2 suggest that this agent promotes angiogenesis (Shen et al., 2010). In a rat model of myocardial infarction, Shexiang Baoxin pills could promote the mobilization of circulating endothelial progenitor cells and the expression of VEGF (Huang et al., 2017). Table 3 presents the aforementioned phytomedicines along with their related models and action mechanisms.

Conclusion

All of these studies suggest that the use of phytomedicine could be directly or indirectly involved in

TABLE 3: Summary of the effects of several herbal medicines (phytomedicines) in endothelial regeneration and angiogenesis.

Name of herbal medicine (phytomedicine)	Origin or category	Model/Type of experiments	Mechanisms of action in vascular (endothelial) regeneration	Ref
Olive leaf extract	A species of small tree in the family of *Oleaceae*	- *In vitro* (human MSCs)	- Overexpression of VEGFR-1, VEGF, and PDGF receptor genes	(Gomez et al., 2012)
Astragaloside IV	Extracted from *Astragalus membranaceus*	- *In vitro* (mouse BM-MSCs) - *In vitro* (BM-MSCs from Sprague Dawley rats) - *In vivo* (MI model of Wistar rats)	- Upregulation of the CXCR4 pathway - Upregulation of the Cx37, Cx40 and Cx43 expression - Enhancement of the VEGF and FGF expression	(Li et al., 2018; Xie et al., 2013; Yu et al., 2015)
Tanshinone IIA	Isolated from *Salvia miltiorrhiza* (Chinese herbal medicine)	- *In vitro* (mouse BM-MSCs) - *In vitro* (BM-MSCs from Sprague Dawley rats)	Upregulation of the CXCR4 pathway - Upregulation of the Cx37, Cx40 and Cx43 expression	(Li et al., 2018)
Salvianolic acid A	Bioactive compound of *Salvia miltiorrhiza*	- *In vivo* (MI model of Sprague-Dawley rats)	- Elevation of EGF and VEGFR-2 in the infarcted zone - Promotion of MMP-9 activity	(Li et al., 2014)
Cardiogenin	The main effective component extracted from the *Geum japonicum*	- *In vivo* (MI model of Sprague-Dawley rats)	- Angiogenic and antiapoptotic effects via JAK-STAT and NF-κB pathways	(Cheng et al., 2009)
Ginsenoside Rg1	A main bioactive component of Ginseng	- *In vitro* (HUVECs)	- Induction of the eNOS expression - Increase the expression of VEGFR-2	(Chan et al., 2013; Chan et al., 2009a)
Xiongshao	Extracted from *Rhizoma Ligusticum Wallichii* and *Radix Paeonia Rubracan*	- *In vivo* (MI model of rats)	- Stimulation of the expression of FGF and VEGF	(Yuan et al., 2018)
Ferulaic acid	A key component of *Radix Angelica Sinensis*	- *In vitro* (BM-MSCs from Sprague Dawley rats)	- Elevation of the VEGF production - Stimulation of Akt/mTOR signaling pathway	(Zhang et al., 2017)
Puerarin	A component extracted from *Radix puerariae* (traditional Chinese medicine)	- *In vivo* (MI model of Sprague–Dawley rats)	- Promotion of the expression of VEGF and endothelial eNOS enzyme	(Zhang et al., 2006)
QI-SHEN-YI-QI	Made from a mixture of *Panax notoginseng, Radix Salvia, miltiorrrhiza Bge, Radix Astragalus, membranaceus Bge,* and *Dalbergia odorifera T*	- *In vivo* (MI model of Sprague–Dawley rats)	- Increase the protein levels of PDGF-B, VEGF, and the mRNA level of FGF	(Zhang et al., 2010)

TABLE 3 continues

Name of herbal medicine (phytomedicine)	Origin or category	Model/Type of experiments	Mechanisms of action in vascular (endothelial) regeneration	Ref
Rhodiola	Extracted from *Radix et Rhizoma*	- *In vivo* (MI model of Sprague–Dawley rats)	- Upregulation the expression of Flt-1, Tie-2, VEGFR-1, and VEGFR2	(Li et al., 2005)
Radix et Rhizoma Rhodiolae Kirilowii	A flowering plant in the knotweed family of *Polygonaceae*	- *In vivo* (MI model of Wistar rats)	- Stimulation of the HIF-1α, HIF-1β, VEGF, and vWF	(Gao et al., 2009)
Chuanxiong/Chishao	Extracted from *Ligusticum Chuanxiong* and *Paeonia lactiflora Rubra*	- *In vivo* (MI model of C57BL/6 mice)	- HIF-1α activation - VEGF, VEGF receptor Flt-1, and FGF expression - SDF-1/CXCR-4 pathway activation - Increase SDF-1 and cardiotrophin1 expression - Activation of Notch signaling pathway	(Shi et al., 2019)
Shexiang Baoxin Pill	Derived from the traditional Chinese medicine	- *In vivo* (MI model New-Zealand rabbits) - *In vivo* (MI model of Sprague-Dawley rats)	- Increase the VEGF and VEGFR expression - Promotion of circulating endothelial progenitor cells mobilization	(Huang et al., 2017; Shen et al., 2010)

SCs: Stem Cells; MSCs: Mesenchymal Stem Cells; BM-MSCs: Bone Marrow-Mesenchymal Stem Cells; VEGFR-1: Vascular Endothelial Growth Factor Receptor-1; PDGF: Platelet-Derived Growth Factor; HUVECs: Human Umbilical Vein Endothelial Cells; CXCR4: C-X-C Chemokine Receptor type 4; Cx: Connexin; EGF: Epidermal Growth Factor; MMP-9: Matrix metallopeptidase 9; JAK: Janus Kinase; STAT: Signal Transducer and Activator of Transcription; NF-κB: Nuclear Factor kappa B; SDF-1α: Stromal cell-Derived Factor-1α; Bcl-2: B-Cell Lymphoma 2; AKT: Protein Kinase B; mTOR: Mammalian Target Of Rapamycin; eNOS: Endothelial Nitric Oxide Synthase; FGF: Fibroblast Growth Factor; Flt-1: Vascular Endothelial Growth Factor Receptor 1; Tie-2: Tie Receptor Tyrosine Kinase 2; HIF-1α: Hypoxia-Induced Factor-2; vWF: Von Willebrand Factor

cardiogenesis and angiogenesis of different SC types by stimulating endogenous SCs and their secretory activity, modulating cytokine release and signal transduction, and elevating the level of several cardiac-specific regeneration factors. On the other hand, phytomedicine holds significant promise in cardiovascular stem cell therapy, particularly for cardiac regeneration. By modulating key signaling pathways, phytomedicines can enhance the proliferation and differentiation of stem cells, thereby improving heart tissue repair. According to the literature review, the main mechanisms of phytomedicines in cardiovascular regeneration are described in this review. For example, the Wnt/β-catenin pathway is involved in regulating stem cell fate and promoting cardiomyocyte differentiation. ERK signaling is critical for cellular responses to growth factors and supports cardiomyocyte proliferation and survival. TGF-β/BMP signaling plays essential roles in cellular differentiation and ECM remodeling, which are vital for effective cardiac repair. The PI3K/AKT pathway supports CM survival and growth, influencing metabolic processes that are essential during cardiac regeneration. SDF-1/CXCR4 signaling plays a pivotal role in response to tissue injury. The local secretion of SDF-1α acts as a chemoattractant, driving circulating CXCR4-expressing cells and other stem cells to the injured tissue, facilitating effective homing and promoting organ regeneration and repair (Wen et al., 2012). The data recommend a potential future approach to finding an ideal strategy for effective cardiac regeneration with the use of phytomedicine inducers.

Incorporating phytomedicines into therapeutic strategies may optimize these pathways, leading to more effective treatments for cardiovascular diseases. As research progresses, the integration of phytomedicine could revolutionize approaches to cardiac regeneration, offering safer and more accessible alternatives to conventional therapies (Farboud et al., 2024; Mohammad Jafari et al., 2018; Wang et al., 2024).

Future research directions and implications

The application of phytomedicines in cardiovascular stem cell therapy holds significant potential for enhancing regenerative outcomes. Future research should prioritize mechanistic studies, clinical trials, interdisciplinary collaborations, and regulatory considerations to fully realize this potential. By addressing these areas, researchers can pave the way for innovative therapies that leverage both traditional medicine and cutting-edge regenerative techniques. On the other hand, further research is required to elucidate the specific molecular pathways through which phytomedicines exert their beneficial effects on cardiac tissue. Understanding these mechanisms will help in developing targeted therapies. In addition, the transition from the laboratory to clinical settings is essential for validating the use of phytomedicines in cardiovascular therapies.

Acknowledgement

The present study was supported by the Deputy of Research, School of Medicine, Iran University of Medical Sciences, Tehran, Iran.

Conflict of interest

The authors declare that there are no conflicts of interest.

Ethics approval

The protocol of this study was approved by the Ethics Committee of Iran University of Medical Sciences.

Author Contributions

Data collection: M. Sheibani, M Shayan, A Sharifi; Design of the study: A.M. Sharifi, M. Jafari-Sabet; Analysis and interpretation of the data: M. Sheibani, M Shayan, A.M. Sharifi, M. Jafari-Sabet; Drafting the manuscript: M. Sheibani, M Shayan, A Mohammadgholi-Beiki; Critical revision of the manuscript: M. Sheibani, M Shayan, A Sharifi, A.M. Sharifi, M. Jafari-Sabet.

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