TRADITIONAL AND INTEGRATIVE MEDICINE

Trad Integr Med, Volume 8, Issue 3, Summer 2023

Review

Applications of Phytomedicines in Chondrocytes and Osteocytes Regeneration Therapy: Pre-Clinical and Clinical Studies

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Received: 7 Nov 2022 **Revised:** 28 Jan 2023 **Accepted:** 29 Jan 2023

Abstract

Phytomedicines, also known as plant-derived drugs, possess preventive and therapeutic effects. Herbal medicines exert a wide range of biological and medicinal properties along with beneficial advantages, including fewer side-effects and lower costs compared to their chemical counterparts. Herbal derivates form basis of many available chemical medicines such as Atropine, Hyoscyamine, Quinine, Colchicine, Digoxin, Codeine, and Morphine. Asian and African populations consume herbal medicine for therapeutic purposes by 60-80%. In the United States, 25% of pharmaceutical medications have at least one herbal-derived ingredient in their structure. Regenerative Medicine (RM) employs stem cells and tissue engineering technology to restore injured cells and repair tissue damage. Stem cells are undifferentiated cells, which can be differentiated into numerous cells. Mesenchymal Stem Cells (MSCs) as multipotent stem cells are the most frequently used stem cells in RM, which can be differentiated into several cell types such as adipocytes, osteocytes, and chondrocytes. Bone disorders and cartilage injuries are not responsive to currently available therapies; thus, researchers have focused on herbal-based stem cell therapies. The present study aimed to review the mechanism underlying the therapeutic application of phytomedicines in the RM and their efficacy in osteogenesis and chondrogenesis.

Keywords: Phytomedicine; Regenerative Medicine (RM); Stem cells; Mesenchymal Stem Cells (MSCs); Osteocytes; Chondrocytes

Introduction

Plants provide a natural root for medications, and to date, over twenty-five percent of pharmaceutical medicines in the United States encompasses a plant-derived component as a minimum [1]. Phytomedicines (plant-derived drugs) are herbal medicines with therapeutic and medicinal properties, which have been used to prevent or treat different disorders since ancient times [2,3]. Recently, such medications have been remarkably used worldwide, as they are supposed to be safer than currently available chemical medications with relatively lower side-effects. Various phytochem-

Citation: Sheibani M, Shayan M, Jafari-Sabet M, Mohammad Sharifi A. **Applications of Phytomedicines in Chondrocytes and Osteocytes Regeneration Therapy: Pre-Clinical and Clinical Studies.** Trad Integr Med 2023;8(3):299-315.

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ical and pharmacological studies have recognized the potential therapeutic properties of herbal medicines [4,5]. The beneficial effects of herbs include anti-oxidative, anti-inflammatory, antihypertensive, anti-diabetic, and antithrombotic effects [6-9]. Given the broad spectrum of positive and protective properties of phytomedicines, the clinical applications of these compounds are consistently increasing [10].

Regenerative Medicine (RM) includes a developed and well-established multidisciplinary field of medicine, which aims to replace, repair, and regenerate human cells or tissues and restore normal function in organ damages due to aging, diseases, or hereditary dysfunctions [11,12]. Advances in organ transplanting in the 20th century documented that human body organs could regenerate and regrow new cells. This progress led to tissue engineering development and RM expansion [13,14]. Tissue engineering combines the materials, cells, scaffolds, and growth factors to replace tissues and stimulate endogenous regeneration [15]. Stem Cells (SCs) are unspecialized and undifferentiated human body cells, which can be differentiated into different cell types in an organism and have self-renewal capability [16]. The combination of tissue engineering technology and SCs transplantation is a substantial therapeutic option to treat complicated injuries through tissue repair and restoration [17].

Skeletal system disorders are broadly widespread and are considered one of the leading causes of disability [18]. For this reason, clinicians found bone and cartilage defects caused due to trauma, degenerative diseases, infection, resection, and congenital malformations to be challenging [19]. Bone and cartilage regeneration are a sequence of biological processes, which involve several cell types (osteocytes, osteoblasts, osteoclasts, and osteoprogenitors) and numerous cellular signaling pathways [20,21]. Among plentiful therapeutic approaches to treat such diseases, stem cell therapy appears to be more promising [22]. In this regard, bone and cartilage regeneration research have introduced proteins and growth factors with high therapeutic potential [23]. Recently, scientists have utilized Mesenchymal Stem Cells (MSCs) for tissue regeneration in bone defects and cartilage injury [24,25]. Moreover, phytomedicines may hold potentially effective properties in the SCs differentiation and progression of tissue repair in osteochondral disorders [26]. This review study evaluated the shreds of evidence available for potential and beneficial effects of phytomedicines in the RM for osteogenesis and chondrogenesis in in vivo, in vitro, and human studies.

Methodology

Regarding the research objective, the United States National Library of Medicine and National Institutes of Health (NIH) database was used to search the following key terms in the "title/abstract" sections of the papers: "Herbal medicines," "Phytomedicine," "Medicinal plants," "Osteogenesis," "Osteocyte regeneration," "Osteocyte stem cell therapy," "Chondrocyte regeneration," "chondrogenesis," "Chondrocyte stem cell," and "Osteochondrogenic pathways.".

Applications of phytomedicines in chondrocytes regeneration therapy

Main pathways involved in cartilage regeneration

Various pathways and factors are involved in the chondrogenesis process. The Wingless-related Integration Site (Wnt) signaling pathway is a crucial chondrogenic factor, whose activation is necessary for cartilage development. The activation of the Wnt signaling pathway is stimulated by Glycogen Synthase Kinase 3 (GSK-3) [27]. Wnt signaling engenders chondrocyte hypertrophy, increases SRY-Box Transcription Factor 9 (Sox9) expression, and induces chondrocyte proliferation acting through β-catenin [28,29]. Sox9 is a family member of "high-mobility group-box" transcription factors expressed from multipotent skeletal progenitors [30]. However, Sox9 overexpression can enhance the chondrogenic differentiation of MSCs [31]. Bone Morphogenetic Proteins (BMPs) were recognized as essential controllers in chondrogenesis, and their effect is facilitated by BMPR1 and BMPR2 receptors [32,33]. BMPs play crucial roles in different chondrogenesis stages and directly stimulate the expression of various chondrocyte-specific genes [34]. Moreover, a decrease in BMP-related cascades reduces the expression of Sox5, Sox6, and Sox9 in cartilage tissues, thereby inhibiting chondrocyte formation and maturation [35]. Small Mothers Against Decapentaplegic (SMADs) are a well-known class of proteins, which act as intracellular signaling effectors for the Transforming Growth Factor-B (TGF-β) superfamily and BMP signaling [36]. The binding of TGF-β to its membrane receptors activates several signaling pathways, and the most broadly studied of which is the TGF-β/SMAD pathway. These findings suggest that TGF-β and its associated SMAD signaling pathway contribute to chondrocyte differentiation. Fibroblast Growth Factors (FGFs), another chondrogenic factor, play a vital role in modulating chondrocyte proliferation and initiating chondrocyte differentiation. FGFs regulate various cell types' migration, growth, differentiation, and survival. FGFs receptors 1 and 3 trigger the activation of Runt-related Transcription Factor 2 (Runx2) and ETS Like-1 protein Elk-1, the vital transcription activators in chondrocyte proliferation. Finally, FGFs enhance type II

collagen synthesis, proteoglycan accumulation, and chondrocyte proliferation. Runx family transcription activators are critical in stimulating chondrogenesis and can interplay with BMP-related SMADs proteins to stimulate the expression of chondrocyte hypertrophic genes and chondrocyte maturation [37,38]. Moreover, there is a strong correlation between Runx activation with the upregulation of FGF-2, aggrecanase, and Matrix Metalloproteinase 13 (MMP-13) expression. Pro-inflammatory agents, including Tumor Necrosis Factor-α (TNF-α), Interleukin-1β (IL-1β), MMPs, and Prostaglandins (PGs), are involved in the development of degenerative joint diseases [39]. Inflammatory pathways and cytokines such as Interferon-γ (IFN)-γ and TNF-α can inhibit the chondrogenesis of MSCs. The exposure of BM-MSCs to pro-inflammatory cytokines decreases the expression of Sox-9, TGF-β1, aggrecan, and collagen II. Moreover, IL-1β, another pro-inflammatory cytokine, can inhibit the chondrogenesis of primary MSCs and block its receptor to improve the outcomes of MSCs therapy for cartilage repair [40]. The Nuclear Factor-κB (NF-κB) is a transcription factor stimulating various gene expressions involved in regulating cell proliferation, inflammation, and apoptosis [41-44]. NF-κB has been concerned with both cartilage differentiation and cartilage destruction. Its activation induces chondrocyte proliferation via Insulin-like Growth Factor 1 (IGF-1) and BMP2 expression [45,46]. In the early phases of chondrogenesis, the NF-κB activation promotes chondrocyte differentiation; however, it has negative effects on cell differentiation in the late phases of chondrogenesis by stimulating inflammatory factors such as Cyclooxygenase-2 (COX-2), Inducible Nitric Oxide Synthase (iNOS), Interleukine-6 (IL-6), and TNF-α [47]. Moreover, the apoptosis process is associated with the activation of caspase-3 and the elevation in the BCL2-associated X (Bax)/B-cell lymphoma 2 (BCL2) ratio as an important marker for apoptosis evaluation [48,49] (Table 1).

Applications of phytomedicines in stem cell therapy for chondrogenesis

Cartilages cannot repair on their own, making osteoarthritis treatment challenging. Accordingly, cartilage regeneration and tissue engineering approaches are proposed as innovative, harmless, and more efficient alternatives to the treatment of degenerative joint disorders [50]. The following section explains how herbal agents could regulate the various aspect of regenerative therapy of cartilage (Figure 1).

Curcumin, an active component of Curcuma longa L., is an appropriate stimulatory microenvironment for chondrogenesis. Curcumin significantly activates the Mitogen-activated Protein Kinase (MAPK) signaling cascade; whereas it suppresses the caspase-3 and COX-2 activity. Moreover, curcumin stimulates sufficient chondrogenesis by repressing the IL-1β-induced inflammation [51]. Curcumin can suppress the impact of pro-inflammatory cytokines- IL-1β, TNF-α, or TNF-β-on the cartilage-specific extracellular matrix [52-54]. To sum up, curcumin is a natural anti-inflammatory chemical with cartilage regeneration efficacy in osteoarthritis or rheumatoid arthritis.

Ginger (the rhizome of *Zingiber officinale* Roscoe) is a pain reliever in musculoskeletal diseases and can attenuate inflammatory reactions via NOS or COX-2 suppression [55,56]. Some studies have confirmed that ginger reduces inflammation in the chondrocytes and synoviocytes by inhibiting chemokines and inflammatory agents [57]. The ginger extracts significantly enhance the survival of cartilage tissue grafts by decreasing the production of Prostaglandin E2 (PGE2), Nitric Oxide (NO), and pro-inflammatory cytokines [58]. Moreover, ginger extracts protect against IL-1β-mediated oxidative stress and mitochondrial apoptosis in human chondrocytes [59].

Icariin, derived from Epimedium spp., has been commonly administered to treat atherosclerosis and osteoporosis [60]. Icariin is proposed as a promising medication for cartilage tissue engineering and osteoarthritis treatment due to its anti-inflammatory and anti-apoptotic properties [61]. Moreover, some studies have reported its protecting role in osteoarthritis by inducing chondrocyte differentiation, reducing chondrocyte apoptosis, and intensifying the secretion of specific extracellular matrix by chondrocytes [62]. On the other hand, icariin can excite chondrocyte proliferation, increase collagen synthesis in chondrocytes, and diminish the interruption of the extracellular matrix [63].

Avocado and soybean extract exert anti-inflammatory properties inhibiting cartilage and joint degeneration and stimulating connective tissue regeneration [64]. Moreover, they can enhance chondroprotective effects by provoking type II collagen formation [65]. Piascledin obtained from avocado extract can improve cartilage formation by inhibiting type II collagenase and fibronectin synthesis [66]. Furthermore, Piascledin defeats IL-1β function, a pro-inflammatory cytokine, and stimulates TGF-β1 synthesis and chondrocytes proliferation [67]. Furthermore, these therapeutic effects can be facilitated by inhibiting iNOS and MMP-13, main factors involved in osteoarthritis [68]. In combination, avocado and soybean stimulate chondrogenesis and the regeneration of damaged cartilage.

Pomegranate is the fruit of Punica granatum L. with excellent antioxidant activity [69]. Pomegranate fruit and its derivate are commonly used in tradition-

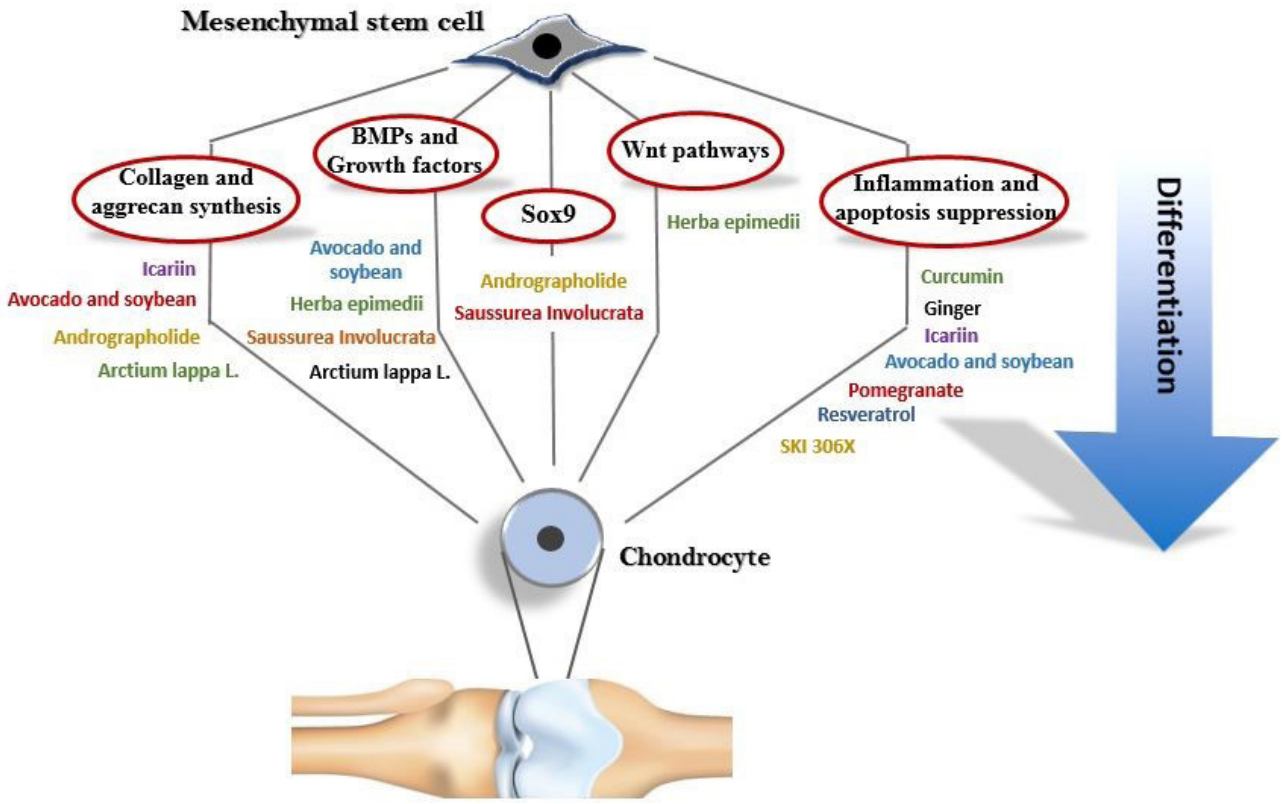

Figure 1. Possible mechanism of action of herbal medicines (phytomedicines) in chondrocytes regeneration therapy. BMPs: Bone Morphogenic Proteins; Sox9: SRY-Box Transcription Factor 9; Wnt: Wingless-related Integration Site

al medical remedies to treat inflammatory diseases such as osteoarthritis [70]. Pomegranate fruit extract prevents the formation of MMPs and NF-κB in chondrocytes [71]. Furthermore, pre-treatment with pomegranate fruit extract in patients suffering from osteoarthritis inhibits the interleukin IL-1β activation and suppresses the Reactive Oxygen Species (ROS) levels [72]. The consumption of pomegranate extract improves physical function and reduces enzymatic cartilage destruction in patients with osteoarthritis [73]. According to previous studies, the administration of pomegranate extract could be chondroinductive and chondroprotective and a favorable recommendation to treat osteoarthritis.

Resveratrol is found in approximately 70 common plant species. Its protective properties, including antioxidative, anti-inflammatory, anti-aging, anticancer, anti-osteoarthritic, cardioprotective, and immunomodulating, are well-documented in the literature [74,75]. Furthermore, many studies have discovered the possible role of resveratrol in the treatment of osteoarthritis. In human chondrocytes, resveratrol can promote chondrocyte proliferation, inhibit ROS production, and block apoptosis [76,77]. Resveratrol suppresses TNF-β-induced apoptotic and morphological changes, elevates cell survival, and promotes proliferation in human chondrocytes [53]. Different concentrations of andrographolide, the main active component of *Andrographis paniculate* (Burm.f.) Nees, remarkably enhance chondrocyte differentiation by upregulating the expression of gene-related chondrogenesis such as Sox9, aggrecan, and collagen II [78]. According to these data, andrographolide can provide an opportunity to translate these findings into clinical settings to promote cartilage and bone regeneration in RM.

Chinese herbal medicine is the basis of traditional Chinese medicine and is an important source of chemical drugs [79]. The therapeutic impacts of SKI 306X, a natural herbal compound derived from some herbs, including *Clematis mandshurica* Hook. & Arn., *Trichosanthes kirilowii* Maxim., and *Prunella vulgaris* L., on articular cartilage defect was investigated in a study. In a rabbit osteoarthritis model, SKI 306X suppressed proteoglycan degradation in cartilage explant culture [80]. Moreover, the pharmacological properties of SKI 306X, which protect against osteoarthritis, are caused by its inhibition effects in chondrocyte apoptosis in rat chondrocyte cell line [81]. Many different types of Chinese herbal medicine, including *Salvia spp*., *Radix astragali*, and *Saussurea involucrata*, have positively affected the chondrogenic differentiation and proliferation of BM-MSCs. It is confirmed that *Salvia* and Saussurea

involucrata Matsum. & Koidz. boost the proliferation of BM-MSCs and TGF-β1-induced chondrogenic differentiation of BM-MSCs [82]. Moreover, *Herba epimedii* induce the proliferation of BM-MSCs and promote the chondrogenic differentiation of BM-MSCs, possibly through BMP and Wnt/β-catenin signaling transduction [83]. *Arctium lappa* L. root (burdock root) exerts antioxidant, anti-inflammatory, and antimicrobial effects. Aqueous extract of burdock root promotes the differentiation and proliferation of MSCs and significantly enhances medium-induced chondrogenesis [84]. It stimulates chondrogenic differentiation by intensifying the expression and nuclear localization of the Sox9 protein. Moreover, activation of Sox9 initiates the stimulation of downstream proteins such as collagen II [85], cartilage oligomeric matrix protein [86], and aggrecan and also potentiates TGF-β downstream signaling [84]. The effects of *Eucomis autumnalis* (Mill.) Chitt. aqueous extracts on the differentiation of Adipose-derived MSCs (ADMSCs) into chondrocytes have been examined. The deposition of glycosaminoglycan and upregulation in gene expression of Sox9 are linked to *Eucomis autumnalis* on chondrocytes differentiation [87]. In sum, these phytomedicines are helpful in treating osteoarthritis and other degeneration of joint cartilage. Table 2 summarizes these herbal agents.

Applications of phytomedicines in osteocytes regeneration therapy

Main pathways involved in bone regeneration

The counterbalance between osteoblasts and osteoclasts is essential in preserving the skeletal structure and function. Accordingly, an imbalance between osteoblasts and osteoclasts leads to osteoporosis or disturbs osteogenesis and bone cell differentiation [88]. BMPs and TGF-β are two types of cytokines (a subfamily of TGF-βs), and they are beneficial in clinical applications to stimulate bone regeneration. BMP/TGF-β axis is one of the main signaling pathways for osteogenesis promotion and is involved in bone formation throughout mammalian development [89-91]. In this regard, BMP-2 can upregulate the expression level of genes associated with osteogenic differentiation, including Runx2, and cause an upsurge in the production of Alkaline Phosphatase (ALP), which is one of the essential inducers of bone mineralization [92]. Osterix (OSX) is a vital transcription factor that promotes osteoblastic differentiation [93], and is an important example of a transcription factor regulated by BMP/SMAD and MAPK family signaling [94]. In combination, Runx2 and OSX are vital transcription factors modulating BMP signaling in the differentiation of MSCs into osteoblasts [95]. Moreover, Runx2 is the principal controller for the expression of osteogenic mediators such as ALP, Osteopontin (OPN), collagen I, and Osteocalcin (OC) [96-98]. According to some evidence, MAPK signaling is involved in essential cellular processes such as cell differentiation, division, and death [99]. The P38/MAPK signaling participates in ALP and OC expression in osteoblastic cells. Moreover, these data indicate that MAPKs regulate osteoblast differentiation [100]. The stimulatory effects of Extracellular Signal-regulated Kinases (ERK), as a member of the MAPK family, on osteoblast differentiation are confirmed in previous research. Moreover, Runx2 phosphorylation is the effect of ERK signaling on osteoblast differentiation [101]. Furthermore, several studies have suggested that Wnt-related signaling pathways play a critical role in osteoblast differentiation and bone mineralization processes due to their stimulatory effects in expressing osteoblast-specific genes [102-104]. β-catenin as a Wnt ligand can promote the differentiation of MSCs from osteoblastic precursor cells into osteoblasts [105] mediated by upregulating the osteogenic stimulators of Runx2 and Osterix [106]. There is a significant correlation between BMP and Wnt signaling. On the other hand, BMP-induced osteogenic differentiation depends on functional Wnt signaling [107,108]. The Wnt and its relevant signaling pathways cooperate in a vast network during osteogenic differentiation [109]. IGF-1, as another osteoinductive, is a growth factor broadly found in the bone matrix and is involved in the progression and preservation of bone tissue repair [110]. IGF-1 is a regulator for osteogenic differentiation, acting through the enhanced production of bone collagen by upregulation in the ALP activity (an initial marker of osteogenic differentiation) [111], Runx2 expression, and stimulation of osteoprogenitor cells proliferation [110]. Finally, IGF-1 can act along with different osteogenic factors such as BMP-9 and OSX to stimulate osteogenic differentiation [94,112] (Table 1).

Applications of phytomedicines in stem cell therapy for osteogenesis

Bone transplantation is one of the most frequent tissue transplants globally; hence, discovering new approaches to exacerbate the osteogenic differentiation potential of MSCs gives rise to novel treatments aiming at bone disorders [95]. The following section explains how herbal agents could regulate various aspects of regenerative therapy of osteogenesis (Figure 2).

In one study, Dipsaci Radix, the dried root of Dipsacus asper Wall. ex C.B. Clarke (a Korean herb), was used for bone fracture healing, and its isolated compound (hedraganin-3-O-(2-O-acetyl)-α-L-arabopyra-

noside) established an osteogenic differentiation properties on bone marrow-derived human MSCs by amplifying the ALP and BMP activities [113]. Resveratrol, a natural phytoestrogen, can promote osteogenesis in human embryonic stem cell-derived mesenchymal progenitors by upregulating the Runx2 and osteocalcin osteogenic gene expression [114]. Runx2 is the main transcription factor starting the osteogenic lineage transcription [115]. Moreover, this phytomedicine activates the activity of Sirtuin 1 (SIRT1), a Sirtuin family member, and subsequently enhances the amount of the SIRT1-Forkhead Box O3 (FOXO3A) complex (increased FOXO3A-dependent transcriptional action) [116]. As a result, the effect of resveratrol on bone formation is mainly modulated by the SIRT1/FOXO3A pathway [114]. In another study, resveratrol could promote the osteoblastic differentiation of multipotent MSCs by over-activating the Wnt signaling pathway [117]. Some well-known medicinal plants, including *Drynaria fortunei* (Kunze ex Mett.) J.Sm. , *Foeniculum vulgare* Mill., and *Anogeissus leiocarpus* (DC.) Guill. & Perr., have been detected to promote bone cell survival, increase bone marrow proliferation, and promote the differentiation of BM-MSCs to osteoblasts and osteocytes, possibly by increasing the ALP activity and bone mineralization [118-120]. Naringin, a flavonoid compound, treats bone complaints such as osteoarthritis and osteoporosis. Naringin can promote the proliferation of SCs and, subsequently, induce osteogenic effects [121]. Increasing the expression of Runx2 and OSX and activating the ERK signaling pathway on human BM-MSCs are involved in osteogenic differentiation [122]. Naringin stimulates osteogenesis via BMP and Wnt-β-catenin signaling transduction in human Amniotic Fluid-derived Stem Cells (hAFSCs). Moreover, upregulating the expression of BMP4, Runx2, cyclin D1, and β-catenin is involved in naringin-induced osteogenesis [123]. Flavanone may become a possible therapeutic target to promote osteogenesis. For example, *Rhizoma drynariae*, a traditional Chinese herbal medicine, is commonly used in the treatment of osteoporosis and bone nonunion. *Rhizoma drynariae* enhances the osteogenic activity of BM-MSCs and exerts higher ALP activity and the protein levels of Runx2 and OSX [124]. *Herba epimedii* is one of the most prescribed phytomedicines in treating osteoporosis in china [125]. Icariin, the main extract of *Herba epimedii*, can promote osteogenic differentiation by initiating the Wnt/β-catenin signaling pathway [126]. Furthermore, it could activate the ERK and p38 MAPK signaling transduction and induce BM-MSCs proliferation in a rat model [127]. In other studies, icariin enhanced the GSK-3β and cyclin D1 protein phosphorylation and incited osteogenesis by enhancing the Runx2 and collagen I synthesis in BM-MSCs [128]. Maohuoside A, a single isolated compound from *Epimedium koreanum* Nakai, was more effective than icariin in enhancing the osteogenesis of rat BM-MSCs cells. Furthermore, ALP assay and the measurement of calcium content confirmed the promoted osteogenesis. BMP and MAPK signaling pathways were involved in the osteogenic effects of Maohuoside A in the rat model [129]. Genistein, a major soy's phytoestrogen, has antioxidant and anticancer properties [130]. It can promote differentiation through BMP-dependent SMADs and Runx2 signaling cascades. Additionally, p38 MAPK-related pathways play critical roles in this process [131]. An *in vitro* investigation illustrates that genistein excites hMSCs-induced cellular proliferation and cell survival and increases anti-apoptotic efficacy [132]. Quercetin, a major dietary flavonoid in onion and other vegetables, can induce the osteogenic differentiation of MSCs, particularly through the ERK and p38 or by activating the MAPK signaling pathways. Accordingly, quercetin can be valuable in bone tissue engineering [133, 134]. Enhancing the phosphorylation of p38 MAPK and ERK1/2, increased the levels of ALP and collagen type I proteins, and the induction of mRNA expression of TGF-1β and BMP-2 was the underlying mechanism of quercetin-induced osteogenesis [135]. Chrysin is a natural flavonoid found in plants and foods such as honey, mushrooms, and passion flowers. Chrysin promotes osteoblast differentiation by activating the ERK/MAPK pathway and enhancing the osteoblast differentiation transcription factor Runx2 [136,137]. Berberine is extracted from several medicinal plants such as *Berberis aristata* DC. and *Coptis chinensis* Franch. can stimulate the osteogenic differentiation of MSCs by activating the p38 MAPK and Wnt/β-catenin signaling pathway or by enhancing Runx2 expression [138-140]. Phlorotannins, a type of tannins isolated from brown algae, promote MSCs differentiation into bone-forming cells by increasing the ALP activity and inducing mineralization and collagen protein synthesis [141]. *Cuminum cyminum* L. has various therapeutic indications as previous studies have indicated that the application of *Cuminum cyminum* stimulates the osteogenic differentiation in SCs derived from bone marrow by regulating the expressions of Runx2, Bone Sialoprotein (BSP), a major constituent of the bone extracellular matrix, collagen type 2A1, and osteocalcin [142]. Moreover, the application of this compound significantly influences the mineralization of SCs [143]. Thymbra spicata var. intricata, an Eastern Mediterranean medicinal plant, promotes osteogenic differentiation by modulating the immunological response of BM-MSCs. It can improve bone regeneration and prevent bone resorption during the

healing and regeneration process [144]. This phytomedicine reduces IL-6 and TNF-α and proves its immunomodulatory effects under inflammatory conditions. Several reports have recommended that IL-6 plays a vital role in osteoclastic bone resorption *in vitro* and in vivo [145]. As a traditional Chinese natural phenolic compound, catechin stimulates osteogenesis by increasing the ALP activity, calcium deposition, and the mRNA expression of Runx2 and osteocalcin. It can enhance the Protein Phosphatases 2A (PP2A) that dephosphorylates extracellular ERK. On the other hand, these findings propose that catechin promotes osteogenesis by enhancing the PP2A level, which untimely hinders the ERK signaling in hMSCs [146]. Dental Pulp Stem Cells (DPSCs) are the major source of osteoprogenitor cells and are also reduce bone regeneration regarding their differentiation potential [147,148]. Aloe vera (L.) Burm.f., a medicinal plant genus Aloe, contains biomolecules with beneficial tissue regenerating effects and plays a vital role in cell proliferation, extracellular matrix synthesis, and bone mineralization [149,150]. In a study on the rat tibias defect model, the therapeutic effects of the implantation of *Aloe vera* extract in combination with colonized collagen sponge and MSCs from human DPSCs on rat bone repair were evaluated [151]. Collagen sponges are already being used in various RM research due to their high availability, biocompatibility, and non-toxic properties [152]. The findings show that *Aloe vera* enhance and accelerate bone regeneration by diminutions in the creation of inflammatory mediators [151]. It can modulate the activity of inflammatory cytokines such as IL-6 and IL-8, suppress macrophage activity, and induce the replication of fibroblasts for tissue repair [153,154]. Moreover, in this study, OPN expression was increased in the *aloe vera*-received group, demonstrating that these groups had higher proliferation and osteoblastic activity [151]. Curculigoside is the main active compound of *Curculigo orchioides* Gaertn., which has been usually used to treat bone disorders and bone repair in Asia. Curculigoside can induce the osteogenic differentiation of hAFSCs by the calcium deposition and stimulation of the ALP activity. Moreover, upregulation in the expression of osteogenic genes such as β-catenin, Cyclin D1, OPN, and collagen I is demonstrated with curculigoside treatment. Further, it can reduce the Receptor Activator of NF-κB Ligand (RANKL), indicating osteoclastogenesis inhibition [155]. Andrographolide is an active compound isolated from the plant Andrographis paniculata (Burm.f.) Nees and is broadly used because of its possible medicinal activity [156]. One study demonstrated that andrographolide promoted the osteogenic differentiation of MSCs by stimulating Runx2 and OPN expression and enhancing calcium deposition. Additionally, andrographolide exerts repressive effects on osteoclastogenesis and osteoclast activities *in vitro* and in vivo via NF-κB and ERK signaling suppression [157]. *Salvia miltiorrhiza* Bunge and its major active phytochemicals (tanshinone IIA) impede osteoclast differentiation, disrupt the actin ring and suppress bone resorption. Moreover, the exact mechanism of tanshinone VI on inhibiting osteoclast differentiation might be through inhibiting NF-κB and RANKL expression [158]. One study suggested that tanshinone IIA suppressed the PGE2 synthesis in osteoblasts and inhibited osteoclast formation and bone injury [159]. BMP-2-induced SMAD stimulation is the other mechanism of tanshinone IIA in bone regeneration and healing [160].

Table 3 presents a summary of all mentioned phytomedicines along with their related models and mechanisms of action.

Conclusion and Future Perspectives

Skeletal disorders are one the leading causes of disability worldwide. The lack of effective therapeutic strategies has motivated researchers to seek better treatment alternatives. SCs can self-renew and differentiate into various cell types. SC therapy in regeneration and transplantation shows promising results in bone and cartilage diseases. Although SC therapy paves the way for finding alternative therapeutic options, synthetic growth factors and other chemical agents used in SC therapy lead to various adverse effects. Therefore, phytomedicines and plant-derived ingredients can be suggested as alternative natural growth factors or SCs differentiation stimulators in stem cell therapy. In this regard, phytomedicines exhibit a promising role in SC regenerative therapy. Plant extracts as herbal medicines' bioactive agents regulate MSCs via various protein pathways. Phytomedicines as inducers markedly affect proliferation and differentiation into multilineage cells. Moreover, medicinal herbs induce fewer toxic effects and can help increase the capability of using MSCs for SC therapy to treat various diseases. Moreover, extensive research on phytomedicines helps substitute synthetic conventional medications with herbal extracts to treat diseases. Although medicinal plants are being extensively accepted and used for disease treatment, they may exert adverse effects on specific medical conditions. Improving our knowledge about the effects of phytomedicines may restrict their undesirable effects. The future of RM and tissue engineering depends on scientists' willingness to work with clinicians to develop innovative ideas using phytomedicines to advance the field [161].

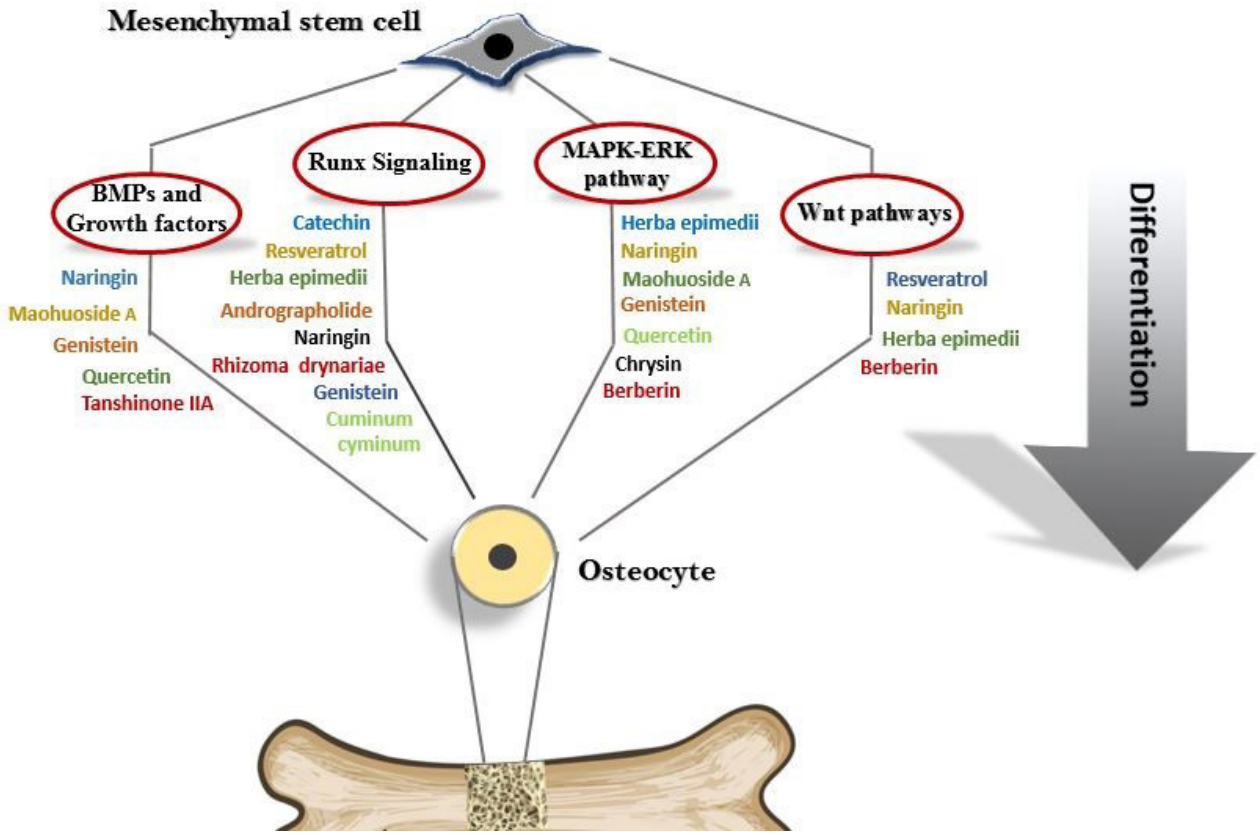

Figure 2. Possible mechanisms of action of herbal medicines (phytomedicines) in osteocytes regeneration therapy. BMPs: Bone Morphogenic Proteins; Runx; Runt-Related Transcription factor; MAPK-ERK: Mitogen-activated Protein Kinase/ Extracellular Signal-regulated Kinase; Wnt: Wingless-related Integration Site

Table 1. Main pathways and factors involved in osteochondral regeneration

Cartilage regeneration	Bone regeneration
Wnt/GSK-3 signaling pathway [27]	BMP/TGF-β signaling pathway [90,91,89]
Wnt/Sox9 signaling pathway [28,29]	BMP/Runx2 signaling pathway [97]
BMP signaling pathway [32,33]	ALP [92]
BMP/Sox9 signaling pathway [35]	OSX [93]
SMADs/TGF-β signaling pathway [36]	BMP/SMAD signaling pathway [94]
FGFs [37,38]	OPN and OC [96-98]
Runx2-related signaling pathway [37,38]	P38/MAPK signaling pathway [100]
IGF-1 [45,46]	ERK-related signaling pathways [101]
NF-κB activation (in early phase) [47]	Wnt/β-catenin signaling pathway [105]
Inhibition of MMP-13, TNF-α, IL-1β, PGs, IF-N)-γ, COX-2, iNOS, IL-6 [39,40,48]	IGF-1 [111,128]

Abbreviations: Wnt: Wingless-related Integration Site; GSK-3: Glycogen Synthase Kinase 3; Sox9: SRY-Box Transcription Factor 9; TGF-β: Transforming Growth Factor-β; SMAD: Small Mothers Against Decapentaplegic Protein; BMP: Bone Morphogenic Protein; FGFs: Fibroblast Growth Factors; IGF-1: Insulin-like Growth Factor-1; NF-κB: Nuclear Factor-Kappa B; Runx2: Runt-Related Transcription Factor 2; MMP: Matrix Metalloproteinase; IL-1β: Interleukin-1β; IL-6: Interleukin-6; TNF-α: Tumor Necrosis Factor-Alpha; IFN-γ: Interferon-γ; COX-2: Cyclooxygenase-2; PGs: Prostaglandins; iNOS: Inducible Nitric Oxide Synthase; ALP: Alkaline Phosphatase; OPN: Osteopontin; OC: Osteocalcin; OSX: Osterix; ERK: Extracellular Signal-regulated Kinase; MAPK: Mitogen-activated Protein Kinase

Table 2. Summary of the effects of several herbal medicines (phytomedicines) in chondrogenic regeneration

Name of herbal medicine (phyto-medicine)	Main active constituent(s)	Origin or category	Model/Type of experiments	Mechanisms of action in chondrogenic regeneration	Ref
Curcumin	Curcumin (curcuminoid)	An active component of *Curcuma loga*	-*In vitro* (mesenchymal stem cells in a high-density culture)	-Activation of the MAPK signaling cascade -Suppression the caspase-3, COX-2, and inflammatory cytokines (IL-1β-, TNF-α, or TNF-β) activity	[51]
Ginger	Gingerols (phenolic compounds)	*Zingiber officinale* (an Asian herbal medicines)	-*In vitro* (sow chondrocyte cells)	-Reduction in production of PGE2, NO, and pro-inflammatory cytokines	[58]
Icariin	Icariin (flavonoid glycoside)	Isolated from *Herba Epimedii* (Chinese Herbal Medicine)	-*In vitro* (male Sprague-Dawley rats chondrocytes) -*In vitro* (isolated BMSCs) -*In vitro* (neonatal mice chondrocytes)	-Exerts anti-inflammatory and anti-apoptotic effects -Increase the secretion of specific extra cellular matrix elements and -Synthesis of collagen in chondrocytes	[61-63]
Avocado and soybean extracts	Avocado: unsaturated fatty acids such as oleic, linoleic, linolenic Soybean: isoflavones such as genistein, daidzein, and glycitein	Made from fruits and seeds of avocado and soybean	-*In vitro* (isolated ADSCs) -*In vivo* (experimental dog osteoarthritis)	-Production of type II collagen -Synthesis of TGF-β1 -Inhibition of the expression of iNOS, MMP-13, and pro-inflammatory cytokines such as IL-1β	[67, 68]
Pomegranate	Allagic acid, ellagitannins, and anthocyanins	Pomegranate *Punica granatum* (polyphenolic compound)	-*In vitro* (human chondrocytes) - *In vivo* and *in vitro* (mesenchymal cells of mouse fetuses)	-Prevents the construction of MMPs and transcription factor NF-κB in chondrocytes -Inhibition of the IL-1β and ROS activation	[71, 72, 162]
Resveratrol	Resveratrol	A naturally phytoestrogen	-*In vitro* human mammary epithelial cells -*In vitro* (primary human chondrocytes)	-Inhibition of the COX-2 expression -Inhibition of ROS production and blocking apoptosis -Suppresses of the TNF-β activity	[76, 77, 53]
Andrographolide	Andrographolide (labdane diterpenoid)	Isolated from the stem and leaves of *Andrographis paniculata*	-*In vitro* (Rabbit articular chondrocytes)	-Upregulation of the genes-related chondrogenesis such as Sox9 and Aggrecan	[78]

SKI 306X	Clematosides, trichobenzolignan, ligballinol, pinoresinol, ehletianol, luteolin, triterpenoids, steroids, and flavonoids	Mixture of Clematis *mandshurica, Trichosanthes kirilowii,* and *Prunella vulgaris*	-*In vitro* (culture of rabbit articular cartilage) -*In vitro* rat chondrocyte cell line	-Suppression of the degradation of proteoglycan -Inhibition the chondrocytes apoptosis	[80, 81]
Salvia, Radix astragali, and Saussurea involucrata	*Salvia*: Carnosol, rosmarinic acid, and carnosic acid *Radix astragali*: astragaloside IV, cycloastragenol, and *astragalus polysaccharide* Saussurea Involucrata: phenylpropanoid, flavonoids, coumarins, and steroids	Chinese herbal medicines	-*In vitro* (BMSCs isolated from Sprague-Dawley rats)	-Promote the of TGF-β1-induced BMSCs proliferation	[82]
Herba Epimedii	Icariin, icariside II, and icaritin (flavonoid glycoside)	A flavonoid compound (Chinese herbal medicine)	-*In vitro* (BMSCs)	-BMP and Wnt/β-catenin signaling pathway	[83]
Arctium lappa	Arctigenin, arctiin, tannins, and caffeic acid	Eurasian species of plants in the Aster family	-*In vitro* (BMSCs)	-Increase in the expression Sox9 protein, collagen II, and Aggrecan -Potentiate TGF-β downstream signaling	[84]
Eucomis autumnalis	Homoisoflavanones, terpenoids, and diben-α-pyrones	Autumn pineapple flower	-*In vitro* (porcine ADMSCs)	-Increase deposition of glycosaminoglycan and upregulation in gene expression of Sox9	[87]

Abbreviations: BMSCs: Bone Marrow Mesenchymal Stem Cells; ADSCs: Adipose-derived Stem Cells; ADMSCs: Adipose-derived Mesenchymal Stem Cells; BMP: Bone Morphogenic Protein; MAPK: Mitogen-activated Protein Kinase; TGF-1β: Transforming Growth Factor 1β; IL-6: Interleukin-6; TNF-α: Tumor Necrosis Factor-α; TNF-β: Tumor Necrosis Factor-β; PGE2: Prostaglandin E2; NO: Nitric Oxide; iNOS: Inducible Nitric Oxide Synthase; MMP-13: Matrix Metalloproteinase-13; NF-κB: Nuclear Factor kappa B; COX-2: Cyclooxygenase-2; ROS: Reactive Oxygen Species; BMSC: Bone Marrow-derived Stem Cell; Sox9: SRY-Box Transcription Factor 9

Table 3. Summary of the effects of several herbal medicines (phytomedicines) in osteogenic regeneration

Name of herbal medicine (phytomedicine)	Main active constituent(s)	Origin or category	Model/Type of experiments	Mechanisms of action in osteogenic regeneration	Ref
Dipsaci Radix	Phenolic acids such as caffeic acid, 2,6-dihydroxycinnamic acid, vanillic acid, 2'-O-caffeoyl-D-glucopyranoside ester, and caffeoylquinic acid	Dried root of Dipsacus asper (a Korean herb)	-*In vitro* (ABM-MSCs)	-Upregulation of ALP and BMP activity	[113]

Resveratrol	Resveratrol	A natural phytoestrogen	-*In vitro* (human MSCs) -*In vitro* (multipotent MSCs)	-Upregulation of the of Runx2 and osteocalcin expression -SIRT1/FOXO3A and -Wnt signaling pathway activity	[114, 117]
Drynaria fortune, Foeniculum vulgare, and Anogeissus leiocarpus	Drynaria fortune: flavonoids, triterpenes and phenylpropanoids Foeniculum vulgare: (E)-anethole, fenchone, methyl-chavicol, and limonene Anogeissus leiocarpus: Alkaloids, tannins, flavonoids, and phenolics	Traditional Chinese herbal medicines	-In vitro (human BM-MSCs)	-Elevation in ALP activity and bone mineralization	[119, 120]
Naringin	Naringenin attached to the hydroxyl	A flavonoid compound (extracted from citrus fruits)	-*In vitro* (hAFSCs)	-Increase in the Runx2 and OSX expression -Activating of the BMP and Wnt-β-catenin signaling pathways	[123]
Rhizoma drynariae	Flavonoids, triterpenes, and phenylpropanoids	A Chinese herbal medicine	-In vivo (Sprague-Dawley rats)	-Increase in the ALP activity and protein levels of Runx2 and OSX	[124]
Icariin	Icariin (flavonoid glycoside)	Isolated from Herba Epimedii (Chinese Herbal Medicine)	-*In vitro* (BMSCs in Sprague-Dawley rats)	-Wnt/β-catenin, ERK, and p38 MAPK signaling pathway -Enhancing the Runx2 and collagen I synthesis	[126-128]
Maohuoside A	Maohuoside A (flavonoid)	Isolated from *Epimedium koreanum*	-*In vitro* (rat BM-MSCs cells)	-Activating BMP and MAPK signaling pathways	[129]
Genistein	Genistein (Isoflavone)	A major phytoestrogen of soy (Isoflavone compound)	-*In vitro* (human-BM-MSCs)	-Activation of BMP-dependent SMADs and Runx2 signaling cascades	[131]
Quercetin	Quercetin (flavonoid)	A major dietary flavonoid in onion and other vegetables	-*In vitro* (rat MSCs)	-Activation in the ERK and MAPK signaling pathways increase in levels of ALP and collagen type I proteins -Induction of mNRA expression of TGF-1β and BMP-2	[135]
Chrysin	Chrysin (flavonoid)	A natural flavonoid found in plants and food such as honey	-*In vitro* (preosteoblast MC3T3-E1 cells) -*In vitro* (mouse MSCs)	-Activation of ERK/MAPK pathway -Enhancement of Runx2 transcription factor	[136, 137]
Berberine	Berberine (isoquinoline alkaloid)	Extracted from *Berberis aristata*, and *Coptis chinensis*	-*In vitro* (primary BM cells isolated from mice	-Activation of MAPK and Wnt/β-catenin signaling pathway -Enhancing Runx2 expression	[139, 140]
Phlorotannins	Phlorotannins (phenolic compounds)	A type of tannins (isolated from brown algae)	-*In vitro* (MSCs)	Increase in ALP activity, induction of mineralization, and collagen protein synthesis	[141]

Cuminum cyminum	Cuminaldehyde and cuminic alcohol	An aromatic herb of the Apicaceae family	-*In vitro* (human BM-SCs)	-Stimulation of the expressions of Runx2, bone sialoprotein collagen type 2A1, and osteocalcin	[142]
Thymbra spicata var. intricata	Thymol, carvacrol, p-cymene, and γ-terpinene	An eastern Mediterranean medicinal plant	-*In vitro* (Dental pulp MSCs)	-Improve bone regeneration and prevent bone resorption by reduction in IL-6 and TNF-α levels	[144]
Catechin	Catechin (polyphenolic compound)	A flavonoid	-*In vitro* (human MSCs)	-Stimulation of the osteogenesis by increasing ALP activity, calcium deposition, and mRNA expression of Runx2 and osteocalcin	[146]
Aloe vera	Aloe-emodin, aloin, and anthraquinone	A succulent plant species of the genus Aloe	-*In vitro* (rat dental pulp MSCs)	-Modulation of inflammatory pathways -Elevation in the OPN expression	[151]
Curculigoside	Curculigoside (phenolic glycoside)	Main active compound of Curculigo orchioides	-*In vitro* (hAFSCs)	-Stimulation of ALP activity, -Upregulation in the expression of β-catenin, Cyclin D1, OPN, and Collagen type I	[155]
Andrographolide	Andrographolide (labdane diterpenoid)	Extracted from Andrographis paniculata	-*In vitro* (human MSCs)	-Stimulation of the expression of Runx2 and OPN -Enhancement of the calcium deposition	[157]
Tanshinone IIA	Tanshinone IIA (diterpenoid naphthoquinone)	Extracted from Salvia miltiorrhiza	-*In vitro* (human BM cells) -*In vitro* (BM cells from male ICR mice) -*In vitro* (mesenchymal precursor C2C12 cells)	-Suppression in the PGE2 synthesis in osteoblasts -Inhibition of osteoclast formation by NF-κB and RANKL expression -BMP-2-induced SMAD activation	[159, 158, 160]

Abbreviations

RM: Regenerative Medicine; SCs: Stem Cells; MSCs: Mesenchymal Stem Cells; BM-MSCs: Bone Marrow-derived Mesenchymal Stem Cells; AD-MSCs: Adipose-derived Mesenchymal Stem Cells; PB-MSCs: Peripheral Blood Mesenchymal Stem Cells; SMSCs: Synovial Membrane Stem Cells; TD-MSCs: Tendon-derived Mesenchymal Stem Cells; P-MSCs; Periosteum Mesenchymal Stem Cells; hAFSCs: Human Amniotic Fluid-derived Stem Cells; hiPSC: Human-induced Pluripotent Stem Cells; DP-SCs: Dental Pulp Stem Cells; FGFs: Fibroblast Growth Factors; PDGF: Platelet-derived Growth Factors; IGF-1: Insulin-like Growth Factor-1; TGF-β: Transforming Growth Factor-β; GDF5: Growth and Differentiation Factor-5; MMP: Matrix Metalloproteinase; IL-1β: Interleukin-1β; IL-6: Interleukin-6; TNF-α: Tumor Necrosis Factor-Alpha; IFN-γ: Interferon-γ; NF-κB: Nuclear Factor-Kappa B; RANKL: Receptor Activator of NF-κB Ligand; PGE2: Prostaglandin E2; PP2A: Protein Phosphatases 2A; COX-2: Cyclooxygenase-2; NO: Nitric Oxide; iNOS: Inducible Nitric Oxide Synthase; ROS: Reactive Oxygen Species; BCL2: B-cell Lymphoma 2; Bax: BCL2 Associated X Protein; ALP: Alkaline Phosphatase; OPN: Osteopontin; OC: Osteocalcin; GSK-3: Glycogen Synthase Kinase 3; Sox9: SRY-Box Transcription Factor 9; Runx2: Runt-Related Transcription Factor 2; SIRT1: Sirtuin 1; FOXO3A: Forkhead Box O3A; OSX: Osterix; SMAD: Small Mothers Against Decapentaplegic Protein; BSP: Bone Sialoprotein; MAPK: Mitogen-activated Protein Kinase; ERK: Extracellular Signal-regulated Kinase; ECM: Extra Cellular Matrix; BMP: Bone Morphogenic Protein; Wnt: Wingless-related Integration Site; JNK: c-Jun N-terminal Kinase

Conflicts of Interest

None.

Acknowledgments

None.

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