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REVIEW ARTICLE

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Phytochemicals impact on osteogenic differentiation of mesenchymal stem cells

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Abstract

Medicinal plants have always been utilized for the prevention and treatment of the spread of different diseases all around the world. To name some traditional medicine that has been used over centuries, we can refer to phytochemicals such as naringin, icariin, genistein, and resveratrol gained from plants. Osteogenic differentiation and mineralization of stem cells can be the result of specific bioactive compounds from plants. One of the most appealing choices for therapy can be mesenchymal stem cells (MSCs) because it has a great capability of self-renewal and differentiation into three descendants, namely, endoderm, mesoderm, and ectoderm. Stem cell gives us the glad tidings of great advances in tissue regeneration and transplantation field for treatment of diseases. Using plant bioactive phytochemicals also holds tremendous promises in treating diseases such as osteoporosis. The purpose of the present review article thus is to investigate what are the roles and consequences of phytochemicals on osteogenic differentiation of MSCs.

Abbreviations: ALP, alkaline phosphatase; Asp8, eight aspartate residues; ATF4, transcription factor 4; AT-MSCs, adipose tissue mesenchymal stem cells; BFR, bone formation rate; BMP4, bone morphogenetic protein4; BMSCs, bone marrow-derived mesenchymal stem cells; Cbf β, core-binding factor beta; CHOP, C/EBP homologous protein; C-MSCs, circulating mesenchymal stem cells; CXCR4, cysteine (C)-X-C motif chemokine receptor 4; Dlx5 d, istal-less homeobox 5; DPSCs, dental pulp stem cells; EGCG, epigallocatechin gallate; ERK, extracellular signal regulated kinase; ERK1/2, extracellular signal-regulated kinase 1/2; GC, glucocorticoid; GCIOP, glucocorticoids-induced osteoporosis; H_2O_2, hydrogen peroxide; H3K14, histone3 lisine14; H3K9, histone3 lisine9; hADSCs, human stem cell-derived adipose tissue; hAFSCs, human amniotic fluid; hMSCs, human mesenchymal stem cells; hPDLSCs, human periodontal ligament stem cells; HUC-MSCs, human umbilical cord derived mesenchymal stem cells; MAPK, mitogen-activated protein kinase; M-CSF, macrophage colony-stimulating factor; mMSCs, mouse mesenchymal stem cells; MOF, metal–organic framework; MSCs, mesenchymal stem cells; nfatc1, nuclear factor of activated T cells cl; NF-κb, nuclear factor-κb; ONFH, osteonecrosis of the femoral head; Osx, osterix; P-MSCs, periosteum mesenchymal stem cells; RANKL, nuclear factor kappa B ligand; rMSCs, rat mesenchymal stem cells; RSV, resveratrol; Runx2, runt-related transcription factor 2; S-MSCs, synovial mesenchymal stem cells; TCM, traditional Chinese medicine; TD-MSCs, tendon-derived mesenchymal stem cells; βecd, beta-ecdysone.

KEYWORDS
mesenchymal stem cells, osteoblast, osteogenic differentiation, phytochemicals

1 | INTRODUCTION

Stem cells can be regarded as elemental biological cells that can renew themselves and also have the ability to be differentiated into multiple grown cells.[1] Embryonic stem cells and adult stem cells are two major categorizations of stem cells. Stem cells can further be divided into unipotent, multipotent, pluripotent, or totipotent ones depending on their differentiation capability. These cells help us to check cellular development, maintenance, and differentiation more closely.[2] Mesenchymal stem cells (MSCs) are stem cells that have different potentials. They are nonhematopoietic and are able to be differentiated into multilineage cells. According to several studies done by different researchers, MSCs, under a standard environmental condition, can be insulated from different aspects such as the adipose tissue, bone marrow, dental pulp, umbilical cord, placenta, amniotic fluid, periodontal ligament, cord and, peripheral blood, fetal lungs, fetal liver, compact bone, trabecular bone, cruciate ligaments, synovial membrane, and endometrium.[3–21]

Many different diseases are cured through curative plants all over the world. Plant derivatives, according to the World Health Organization (WHO), are the main resources of a great majority of drugs.[22]

Wide ranges of biologically active compounds are phytochemicals that can be found in plants containing vital medicinal and nutritional attributes.[23–26] Plant components, in comparison with traditional semibiological and synthesized stimuli, have also raised hopes in the treatment of illnesses such as neurodegenerative disorders, osteoporosis, and other tissue degenerative disorders assisted by human mesenchymal stem cells (hMSCs).[27]

Despite the fact that the majority of plants have been used both in accordance with tradition and new therapy, the exact process of action on MSCs of only some of the phytochemicals has been verified.[28] Hence, the focus of the current study is to maintain the role of bioactive compounds derived from plant excerpts on proliferation and osteogenic differentiation of MSCs and their application in bone regenerative treatment.

2 | MSCS MULTILINEAGE DIFFERENTIATION POTENTIAL

In conformity with ISCT standards, MSCs have to be capable of differentiating into multilineage cells namely adipocytes, osteoblasts, and chondroblasts, but it is dependent on in vitro conditions along with the cell source.[29] In consideration of the source, UC-MSCs are of high capability of differentiating into adipocyte, chondrocyte, osteoblast, endothelial cells, skeletal muscle cells, neuronal cells, and cardiomyocyte-like cells. BM-MSCs can be differentiated into chondrocyte, osteoblast, tenocyte, adipocyte, and vascular smooth muscle cells. Adipose tissue MSCs (AT-MSCs), synovial MSCs (S-MSCs), periosteum MSCs (P-MSCs), tendon-derived MSCs (TD-MSCs), circulating MSCs (C-MSCs), and are also capable of multilineage differentiation under the condition of in vitro standard.[30]

3 | OSTEOGENIC DIFFERENTIATION OF MSCS

Osterix (Osx) and runt-related transcription factor 2 (Runx2) are the two fundamental transcription elements that boost osteoblastic differentiation.[31] Runx2 particularly is bonded to the Osx promoter section regulating osteoblast differentiation in vitro and in vivo, also regulates Osx, which is sometimes called Sp7 as well and belongs to the Sp transcription factor family.[32] In osteogenic regulation, Runx2 acts by the construction of heterodimer with co-transcription factor, core-binding factor beta (Cbf β), and binding to DNA.[33,34] Additionally, for osteogenic differentiation of MSCs, expression of early-marker alkaline phosphatase (ALP) and late-marker osteopontin genes increase.[18] Having been from various foundations of MSCs differentiating into osteoblast-like BM-MSCs,[35] AT-MSCs,[36] or S-MSCs, P-MSCs,[37] in vitro supplements containing ascorbic acid, β-glycerophosphate, dexamethasone, and 1.25-dihydroxy-vitamin D3 offer support in osteogenic differentiation from MSCs.[38–41] The differentiation can be demonstrated by the discovery of the Runx2 gene through a subatomic technique and by staining methods of von Kossa or alizarin red.

4 | PHYTOCHEMICALS WITH OSTEOGENIC DIFFERENTIATION EFFECT ON MSCS

Plant extracts have great importance in treating communicable and noncommunicable diseases. This is because they include phytochemicals such as flavonoids,

polyphenols, and several other natural compounds and chemical substances.[42] Phytochemicals from plants generate an excessive deal of interest owing to their health benefits, making them worthy of further scientific assessment.[43] It has been shown that the natural composites derived from carnosine, green tea, blueberry, catechin, and vitamin D3 increased the bone marrow stem cell proliferation.[44] Figure 1 show the applications of phytochemicals for osteogenic differentiation of MSCs in vitro, in vivo and human clinical trials. Phytochemicals with osteogenic differentiation effect on MSCs can be classified into different classes (Figure 2).

Boosted bone markers expression and deposition of mineral on mesenchymal stem populations from human beings, which is mainly based on bone marrow-derived mesenchymal stem cells (BMSCs) and dental pulp stem cells (DPSCs), has been the subject of many other articles.[45–48] Table 1 is the list of some phytochemicals with osteoinductive effect.

4.1 | Icaritin

The main active ingredient of Herba Epimedii is icariin (C33H40O15; molecular weight, 676.67) which is a typical flavonol glycoside and shows osteoinductive effect. The proliferation and osteogenic differentiation of BMSCs were improved by icariin. It also facilitated the treatment of defected bones of *New Zealand* rabbits through integrating with scaffolds in vitro.[91–94] Nevertheless, recently it has been proved that icariin is enzymatically hydrolyzed by intestinal bacteria and is then metabolized to icaritin (C21H22O7; molecular weight, 386.4) and desmethylicaritin in vitro.[95,96] Noticeably, it was discovered that the pharmacological activities of icaritin were more effective than those of icariin in vitro.[97,98] According to recent investigations, icaritin, which has an estrogen-like function, can enhance osteoblast proliferation and differentiation, and promote matrix calcification.[99,100] It is also capable of hindering the function of osteoclasts in vitro, exerting bone-protective function by enhancing the formation of bone and preventing bone resorption.[97,101,102] There is more evidence that icaritin is capable of boosting the mRNA expression of osteogenic-related in hBMSCs.[103] It has already been integrated with different biomaterials to improve bone repair.[104–106] The findings mean that icaritin is highly capable of being an osteogenic inductive agent and can be very useful in bone tissue engineering. Furthermore, being a small molecule, icaritin has many advantages such as it is readily available, chemical stabile not denature, inexpensive, and needs a simple extraction

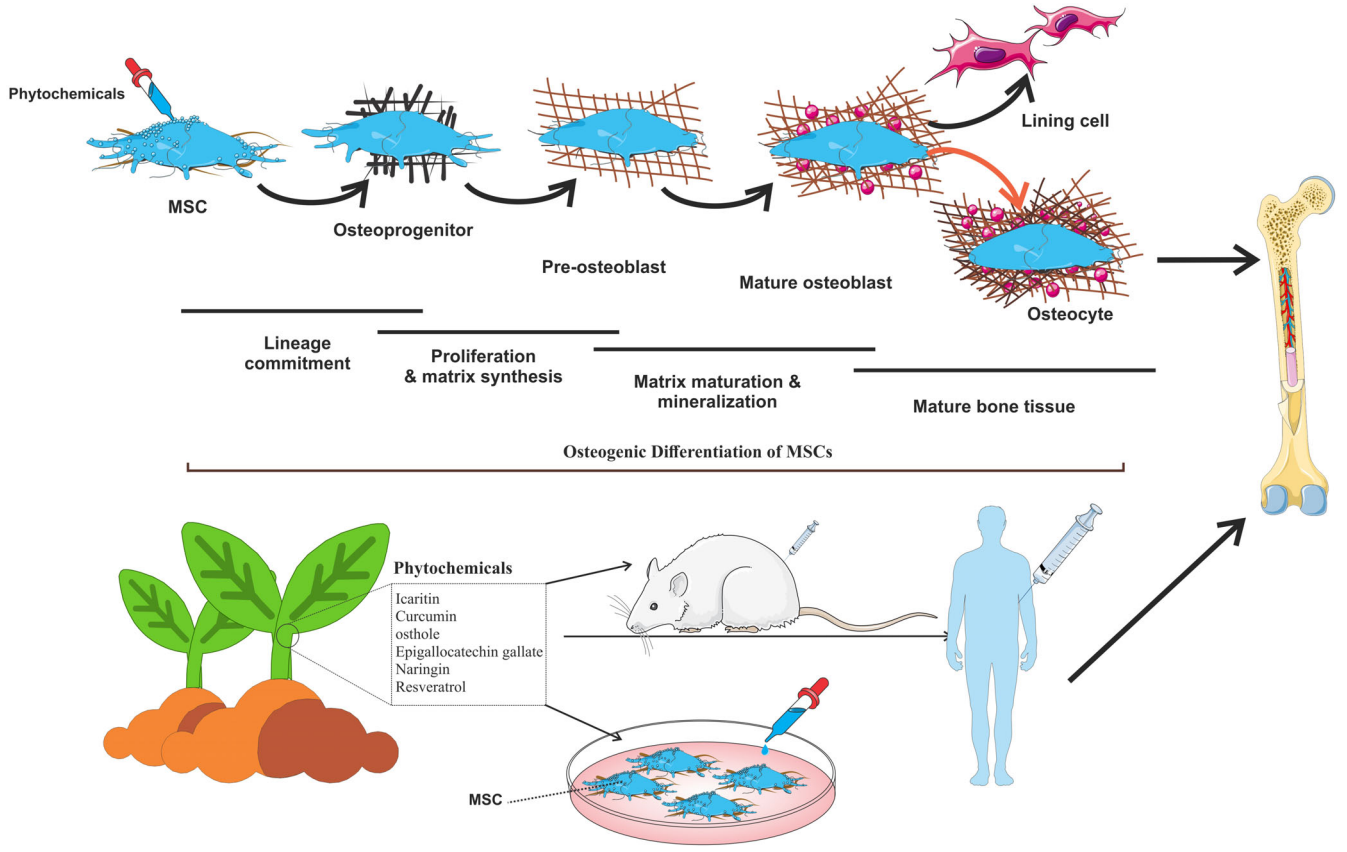

FIGURE 1 Outline of applications of phytochemicals for osteogenic differentiation of MSCs in vitro, in vivo, and human clinical trials

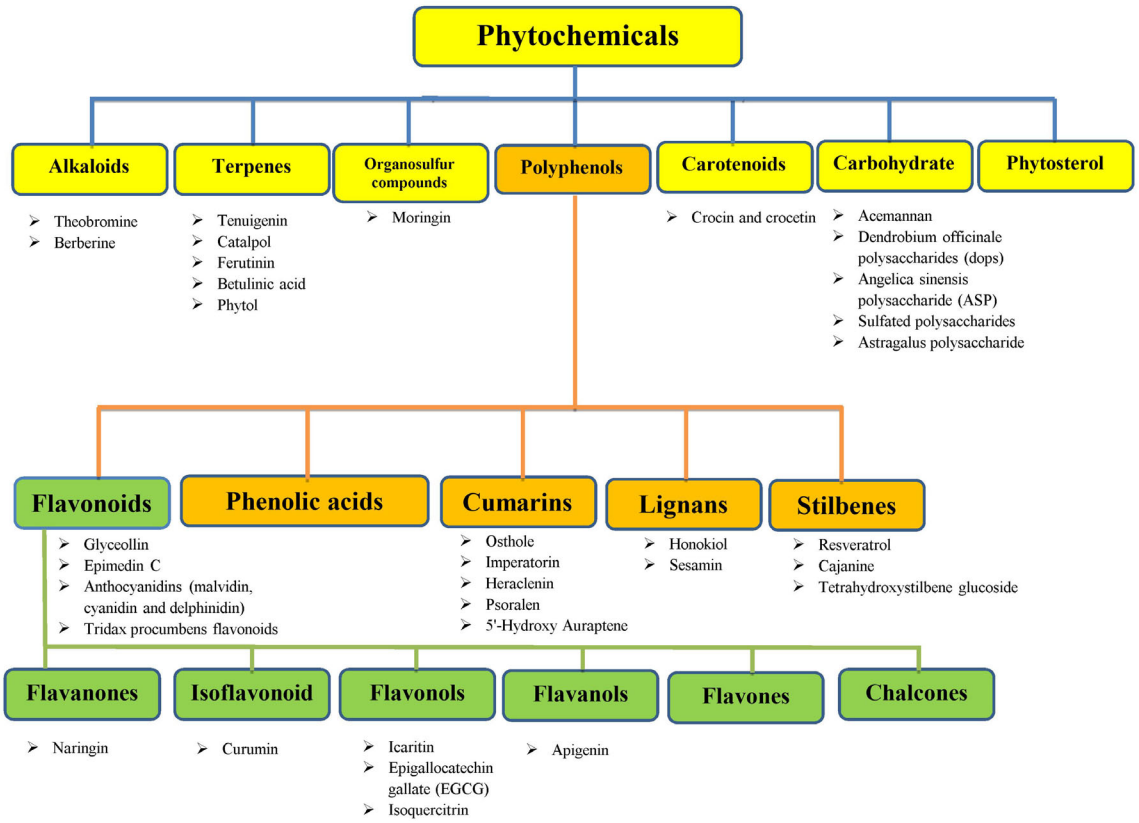

FIGURE 2 Classification of phytochemicals with osteogenic differentiation effect on MSCs

method.[107] Therefore, icaritine presents a reliable approach for forming drug-loading scaffolds.[108]

The effects of icaritin, on the osteogenic differentiation of human stem cell-derived adipose tissue (hADSCs) and hBMSCs in vitro were systematically studied. It was revealed that icaritin had a considerable role in the increase of ALP activity, calcium deposition, and OC secretion at different time points. Moreover, icaritin stimulated the mRNA expression of genes for bone matrix proteins (ALP, Col-1, and OC), bone transcription factors (Dlx5 and Runx2), and bone morphogenetic proteins (BMP-2, -4, and -7). In addition, icaritin raised the level of Runx2, BMPs, and OC. It can be derived from the findings that icaritin has an effective role in the increase of the osteogenic differentiation of hADSCs and hBMSCS. Icaritin probably applies its innate osteogenic effect by directly agitating the BMPs production. Though the osteogenic effect of icaritin in vitro was lower than rhBMP 2, icaritin showed better results than icariin. Furthermore, as a bone regenerative medicine, some characteristics like the simple extraction method, low cost, and an abundance of icaritin, make icaritin an attractive medicine.[108,109]

The icaritin has a short half-life in blood and only trace quantities of icaritin reach to the bone tissue. To minimize this restriction, the aim was to develop a bone-targeting liposome compromising an oligopeptide of eight aspartate residues (Asp8) that had already been displayed to target especially the bone, encapsulating icaritin. In contrast to an icaritin-liposome control lacking the Asp8 moiety, bone formation in ovariectomized mice was enhanced by Asp8-icaritin-liposome. Studies were discovered that icaritin impeded adipogenesis using an Akt/GSK-3β/β-catenin signaling pathway.[110] Refer Table 2.

4.2 | Curcumin

Throughout the years, *Curcuma longa* L. (Zingiberaceae family) rhizomes, turmeric, has been commonly applied in inherent medicine to treat a number of inflammatory disorders and other illnesses. The therapeutic properties of turmeric were primarily due to the curcuminoids, and the key element existing in the rhizome contains curcumin (diferuloylmethane)— (1,7-bis (4-hydroxy3-methoxyphenyl)-1,6-hepadiene-3,5-dione). Throughout the years, a variety of experiments have attempted to investigate the pharmacokinetics of curcumin, which is feebly absorbed from the intestine after oral administration of different quantities of curcumin in rats.[120–122] It has been shown that curcumin

TABLE 1 The list of some phytochemicals with osteoinductive effect

Name of phytochemical	Source	Stem cell source	Status	Results and mechanism of action	Ref.
Glyceollins	Soybean	BMSCs AT-MSCs	In vitro	• Upregulates of expression of cholesterol homeostasis-related genes (ABCA1, ABCA2, ABCG1, ABCG8, lxrα, lxrβ, APOA1) and LXR-specific gene which LXR-mediated signaling pathways were reported. • Upregulate the ABCG1 and APOA1 expression • Initiate signaling that contributes to crosstalk with the cholesterol homeostasis genes glyceollin II is not likely to be triggering LXR-mediated signaling pathways exactly in this cell type. • The osteoinductive activities are primarily ER-mediated in ASCs. On the contrary, lxrα, lxrβ, ABCA1, ABCA2, ABCG1, and APOA1 were upregulated by glyceollin II in the BMSCs.	49
Costunolide	Lettuce	C3H10T1/2 cells	In vitro	• Increase the expression of distal-less Runx2, ALP, Dlx5, and OC • Increases matrix mineralization and activity of ALP • Increases ER stress by Bip, activating C/EBP homologous protein (CHOP) and transcription factor 4 (ATF4). • Increases expression of HO-1. Moreover, the HO-1 inhibitor, Sn (IV) Protoporphyrin IX dichloride (snpp) was prevented costunolide-induced Runx2 expression.	50
Honokiol	Trees belonging to the genus Magnolia	Human umbilical cord derived mesenchymal stem cells (HUC-MSCs)	In vitro	• IL-1β stimulation increased cell necrosis and apoptosis and activated the expression of matrix metalloproteinase (MMP)-1, −9, 13, cyclooxygenase-2 (COX-2), caspase-3, and interleukin-6 (IL-6). • The expression of box 9 (SOX-9), SRY-related high-mobility group aggrecan, and col2α1 was repressed. • Downregulates expression of p-p65, p-iκbα, and p-ikkα/β in time and concentration-dependent manner so relieved these negative influences induced by IL-1β and suppressed nuclear factor-κb (NF-κb) pathway.	51
Sesamin	Bark of Fagara plants and from sesame oil.	M-CSF and RANKL induced human PBMCs	In vitro	• Decreases the quantity of differentiated osteoclasts evaluated by TRAP staining; nonetheless, sesamin inhibition was not the result of the modification of precursor cell proliferation. • Not reductions in expression of nfatc1 gene, which was against the declining trend of cathk and TRAP expression. In the presence of sesamin, DC-STAMP, but not Atp6v0d2 declines. • Downregulates expressions of CCR2b and CCR4 as chemokine receptors. • Mediates the prevention of differentiation of human osteoclast, the recruitment of precursor cells, and formation of F-Actin. • Reduces in the area of the resorption pits and the released collagen from the bone slices under sesamin treatment indicated the preventive effects on both the function and differentiation of osteoclasts.	52
Zaluzani C	Vernonia arborea	C3H10T1/2 and MC3T3-E1 cells	In vitro	• Regulates the key osteogenic genes expression in the early stage of differentiation, such as Runx2, DNA-binding protein inhibitor (Id1), and distal-less Dlx5. • Increase Runx2 protein level and Runx2 promoter activity. • May enhance osteoblast differentiation by rising of the osteogenic genes' expression, especially early stage such as Runx2, Id1, and Dlx5.	53

(Continues)

TABLE 1 (Continued)

Name of phytochemical	Source	Stem cell source	Status	Results and mechanism of action	Ref.
Theobromine	Cacao plant	hMSCs	In vitro In vivo	• Increases the osteogenesis of osteoprogenitors of bone marrow, and nutritional supplementation of an appropriate quantity of theobromine accelerates skeletal development in their offspring in expectant mothers during the postnatal period.	54
Tenuigenin	Polygala tenuifolia root	BMSCs	In vitro In vivo	• Increases ALP activity, mineralized nodules and the expression of osteogenic markers like Runx2, Osx, OCN, collagen Iα1, β-catenin, and glycogen synthase kinase-3β. • Enhances WNT/β-catenin signaling.	55
Obtusilactone A	Cinnamomum kotoense	BMSCs	In vitro In vivo	• Increases expression of osteogenesis markers col I, Runx2, BMP2, and Osteocalcin. • Increase the formation of new bone and volume of trabecular bone in tibias in rat model. • Persuades an osteoinductive outcome on BMSCs via increase in expression of osteogenic marker genes, such as Runx2 and BMP2 and subsequently increases the ALP activity and mineralization.	56
Moringin	*Moringa oleifera* seeds	PDLSCs	In vitro	• Increases expression of RUNX-2 and ALP genes	57
Catalpol	The roots of the small flowering plant species Rehmannia glutinosa Libosch	BMSCs	In vitro In vivo	• Increases the osteogenic differentiation of rat BMSCs through the activation of the Wnt/β-catenin signaling pathway. • Increases the bone curing capability of BMSCs in a rat critical-sized calvarial defect model and decreases bone loss in a rat ovariectomy model.	58
Acemannan	*Aloe vera*	Rat BM-MSCs	In vitro In vivo	• Increases BMSC proliferation, ALP activity, mineralization, BMP-2, VEGF, bone sialoprotein, and osteopontin expression in vitro. • Cause faster bone healing and higher bone mineral density in vivo. A significant ingrowth of bone trabeculae was noticed in acemannan-treated groups.	59
Crocin and crocetin	Saffron	Rat BM-MSCs	In vitro	• Increase ALZ intensity, ALP activity and ALP mRNA expression.	60
Zingerone	Ginger	Mouse mesenchymal stem cells (mMSCs)	In vitro	• Enhances osteoblast differentiation by more calcium deposits. • Stimulate the Runx2 expression and other marker genes of osteoblast differentiation in mMSCs. • Upregulates mir-590, an antagonist of TGF-β1 signaling, a positive regulator of Runx2 by targeting Smad7.	61
Berberine	Coptidis Rhizoma	BMSCs	In vitro	• Restores the downregulation of osteogenic genes expression in BMSCs resulted from Porphyromonas gingivalis infection. • Increases the expression of osteogenic genes like ALP, COLI, OSX, OCN, and OPN. • Increases accumulation of nuclear β-catenin and total β-catenin. • Increases transcriptional activity of β-catenin/TCF. • Wnt/β-catenin signaling pathway was involved in the osteogenic differentiation.	62

TABLE 1 (Continued)

Name of phytochemical	Source	Stem cell source	Status	Results and mechanism of action	Ref.
Imperatorin	*Angelica archangelica* and *Peucedanum praeruptorum*	Rat BM-MSCs	In vitro In vivo	• *Activate RUNX2, COL1A, and OCN by promoting the Ser9 phosphorylation of GSK3β and entry of β-catenin into the nucleus.* • *Enhances the production of an upstream factor, phospho-AKT (Ser473), which promotes the Ser9 phosphorylation of GSK3β.* • *Induces osteogenesis through AKT/GSK3β/β-catenin pathway.*	63
Ferutinin	*Ferula hermonis*	*DPSCs*	In vitro	• *Increases protein level of COL1, OCN, and OPN.* • *Increases in calcium deposition.*	64
Cajanine	*Cajanus cajan* L. Millsp	BMSCs	In vitro	• Activates the cell cycle signal transduction pathway, then stimulates cells to enter the G1/S phase and boosts cells entering the G2/M phase.	65
Gastrodin	Orchid Gastrodia elata and the rhizome of Galeola faberi	BMSCs	In vitro	• Retardes RANKL-induced osteoclast differentiation effectively by diminishing expression of a main factor in RANKL-mediated osteoclastogenesis, nuclear factor of activated T cells cl (nfatc1). • Prevents osteoclast migration and maturation by thwarting the expression of an osteoclastic-specific gene in dendrocyte that controls the movement of cells and fusion. • Prevents RANKL-induced osteoclastic bone erosion. • Prevents formation of osteoclasts and resorption of bone through obstruction of nfatc1 activity, and induce osseointegration.	66
Apigenin	Found in many plants	hMSCs	In vitro	• Stimulates the osteogenesis of hMSCs via activation of JNK and p38 MAPK signal pathways which leads to expression of OSX and Runx2 to stimulate the of bone nodule formation	67
Epimedin C	Herba Epimedii (Yinyanghuo)	C3H/10 T1/2 in BALB/c nude mice.	In vivo	• Promotes vascularization both in the BMP2-depended bone formation model and in the 4 T1 mammary tumor-bearing model by stimulating an endothelial-like differentiation.	68
Tanshinone IIA	Chinese herb Danshen	Mouse BM-MSCs	In vivo	• Upregulates both ALP activity and calcium content throughout the osteogenesis of mouse BM-MSCs, shows that it stimulated the osteogenesis at both early and late stages. • Promotes osteogenesis and inhibits osteoclastogenesis • Upregulates BMP and Wnt signaling. • Co-treatment with BMP inhibitor (noggin) or Wnt inhibitor (DKK-1) significantly reduced the TSA-promoted osteogenesis, displaying that upregulation of BMP and Wnt signaling has a vital role and adds to the TSA-promoted osteogenesis.	69
Tetrahydroxystilbene glucoside	*Polygonum multiflorum* Thunb	rMSCs and in zebrafish	In vitro In vivo	• Promotes the ALP activity and increases the content of osteocalcin in vitro. • Protects against further bone loss induced by dexamethasone in zebrafish.	70
Tetramethylpyrazine or ligustrazine	Chuanxiong	Rat BMSCs	In vitro In vivo	• Protects BMSCs from exposure to excess glucocorticoids by inducing autophagy via AMPK/mtor pathway and can be an effectual agent for the inhibition and treatment of glucocorticoid-induced osteoporosis.	71

(Continues)

TABLE 1 (Continued)

Name of phytochemical	Source	Stem cell source	Status	Results and mechanism of action	Ref.
Annatto (antt)	*Bixa Orellana*	Murine MC3T3-E1 preosteoblastic cells	In vitro	• Increases OCN, COL1α1, ALP, and OSX • Increases col I level, ALP activity and mineralization.	72
Mangiferin	Mango trees	MSCs from subchondral bone of rabbit	In vitro	• Reverse the production of TGF-β, Col2α1, BMP-2, BMP-4, SOX9, cartilage link protein, and aggrecan, as well MMP-1, M MP-13, and a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS5) in IL-1β-stimulated MSCs. • Upregulate the phosphorylation of SOX9, Smad 2, Smad 3, and Smad 1/5/8 in IL-1β-stimulated MSCs. • In the presence of mangiferin, SOX9 siRNA suppresses the activation of Smad 2, Smad 3, Smad 1/5/8, aggrecan, and Col2α1 expression. • Displays both chondrogenic and chondroprotective activities on damaged MSCs and mediate these actions by the SOX9 and Smad signaling pathways.	73
Dendrobium officinale polysaccharides (dops)	Dendrobium officinale	BMSCs	In vitro In vivo	• Rescue H_2O_2-induced change of BMSCs differentiation fate in vitro. This impact was eradicated in BMSCs when interfered with Nrf2 siRNA. • Increases the bone mass and decreases the marrow adipose tissue (MAT) accompanied by reduced BMSCs oxidative stress in aged mice. • Attenuate MAT accumulation and bone loss via NRF2 antioxidant signaling, that may operate in the treatment of age-related osteoporosis.	74
Anthocyanidins (malvidin, cyanidin, and delphinidin)	Berries, vegetables and flowers	AT-MSCs	In vitro	• Delphinidin inhibites MSC adipogenesis and downregulates adiponectin and fatty acid binding protein 4 (FABP4) genes. • Malvidin induces a higher accumulation of calcium deposits in cells, as well as upregulates the Runx-2 and BMP-2 genes and induces secretion of BMP-2. • Delphinidin and cyanidin demonstrate a chondrogenesis inducing activities by upregulation of aggrecan and Col2a1.	75
Tridax procumbens flavonoids	*Tridax procumbens*	Primary osteoclast cells and low calcium diet mice	In vitro In vivo	• Suppresses the bone resorption and RANKL-induced osteoclasts differentiation • Increases bone mineral density and bone mineral content. • Increases bone formation-related indices like osteoblast number, bone volume, osteoblast surface, mineral apposition rate, mineralizing surface, and bone formation rate in mice.	76,77
Betulinic acid	Bark of birch trees	MC3T3-E1 preosteoblasts and male C57BL/6 mice	In vitro In vivo	• Enhances osteogenic potentials of BMP2, possibly through inducing Smad 1/5/8 and p38 pathways in vivo.	78

TABLE 1 (Continued)

Name of phytochemical	Source	Stem cell source	Status	Results and mechanism of action	Ref.
Heraclenin	Bael	MMSCs, C3H10T1/2)	In vitro	• Stimulates the expression of Runx2 mRNA and promotes osteoblast differentiation and mineralization.	79
Hydroxy Safflower Yellow A	*Carthamus tinctorius* L	BMSCs and zebrafish	In vitro In vivo	• Promotes bone formation in normal zebrafish. • Reversing glucocorticoid-induced bone loss based upopn the intervention of HYA in upregulating the region of mineralized bones, inhibiting bone resorption related gene expression (TRACP), inducing bone formation related gene expression (Runx2, OPG, AKP, type I, and OCN), elevating cumulative optical density, and increasing levels of whole-body trace mineral elements (Zn, P, K, Ca, Mg, and Fe). • It has the potentiality to halt and heal glucocorticoids-induced osteoporosis (GCIOP) by inducing bone mineralization, viability of osteoblasts, and expression of bone collagen and preventing bone resorption.	80
Angelica sinensis polysaccharide (ASP)	Angelica sinensis	BMSCs of rats with high glucose levels	In vivo	• The number of calcium nodules of BMSCs; ALP activity; and the expression of Runx2, Col-1, OCN, Osx, cyclind1, and β-catenin in the high glucose group were lower related with ASP + high glucose groups and normal control.	81
Beta-ecdysone	Seeds and roots of the asteraceae and achyranthes plants	Male Swiss-Webster mice	In vivo	• Concurrent treatment of beta-ecdysone (βecd) and glucocorticoid (GC) completely inhibited the GC-induced reduction in bone formation rate (BFR), a partially inhibited cortical bone loss and trabecular bone volume. • Prevents the GC increase in autophagy of the bone marrow stromal cells and whole bone in vitro. • Prevents GC encouraged alterations in bone cell viability, bone formation, and bone mass.	82
Sulfated polysaccharides	The green seaweed *Caulerpa prolifera*	MSCs isolated from Wharton jelly (hMSCs-WJ)	In vitro	• Increases ALP activity and calcium accumulation.	83
N-(3-methoxybenzyl)-(9Z,12Z,15Z)-octadecatrienamide (MBOC)	Maca (*Lepidium meyenii* Walp.)	Ovariectomized (OVX) mouse model	In vivo In vitro	• Increase the levels of osteocalcin and Runx2 in vivo, as well as the expression of Runx2, Osx, and ALP in vitro. • Induces the canonical Wnt/β-catenin signaling pathway by preventing GSK-3β phosphorylation at Tyr216 and maintaining β-catenin expression.	84
Isoquercitrin	Fruits, vegetables and medicinal herbs	BMSCs	In vitro	• Promotes the cell proliferation of osteoblasts at low concentrations. • Promotes the osteogenic differentiation via RUNX2 expression in osteoblasts and via the BMP pathway in BMSCs in high concentrations. • Inhibits of RUNX2 expression in osteoblasts by siRNA.	85

(Continues)

TABLE 1 (Continued)

Name of phytochemical	Source	Stem cell source	Status	Results and mechanism of action	Ref.
Psoralen	Seed of *Psoralea corylifolia*	Primary mouse calvarial osteoblasts	In vitro	• Stimulate osteoblast differentiation by increase of expressions of osteoblast-specific marker genes including bone sialoprotein, col I, OCN, and improvement of ALP activity. • Upregulates the expression of Bmp2 and Bmp4 genes, increases the protein level of phospho-Smad1/5/8, and activates BMP reporter (12xsbe-OC-Luc) activity in a concentration-dependent manner, as well as enhances the expression of Osx, the direct target gene of BMP signaling. • Removal of the Bmp2 and Bmp4 genes abolished the stimulatory effect of psoralen on the expression of osteogenesis marker genes, for example, Bsp, ALP, Col1, and OC. • Activates of BMP signaling to induce osteogenic differentiation.	86
Astragalus polysaccharide	*Astragali radix*	Bone mesenchymal stem cells	In vitro	• Promote differentiation and proliferation by increasing viable cells, downregulating p21, upregulating cyclind1, and increasing OPN, OCN, Runx2, and Col-1 expressions. • Promote proliferation and osteogenic differentiation of cells by downregulating mir-152 and upregulating BMP9 and stimulating Wnt/β-catenin and PI3K/AKT pathways.	87
Chelidonic acid	Saussurea controversa leaves	Human adipose-derived multipotent mesenchymal stromal cells (hAMMSCs)	In vitro	• Combination of calcium [$Ca(cha)(H_2O)_3$] and chelidonic acid known saucalchelin (cacha). Cacha stimulates the cell proliferation and osteogenic differentiation.	88
5′-Hydroxy Auraptene	Lotus lalambensis	mBMSCs	In vitro	• Promotes the osteogenesis with inducing BMP2 in mBMSCs through activating Smad1/5/8 phosphorylation and increases expression of Smad4. • Blocking of BMP signaling through BMPR1 selective inhibitor LDN-193189 remarkably inhibits the stimulatory effect of 5′-HA on osteogenesis. • Stimulate the mBMSCs differentiation into osteoblasts in BMP-signaling dependent mechanism.	89
Phytol	Chlorophyll	C3H10T1/2	In vitro	• Promotes osteoblast differentiation via Runx2 due to downregulation of Smad7 by mir-21a.	90

TABLE 2 Some studies on mechanism of osteoinductive effect of icariin on MSCs

Stem cell source	Status	Results and mechanism of action	Ref
Primary human MSCs	In vitro	• Increases MSC proliferation, chemotaxis to SDF-1 and osteogenic differentiation via the activation of STAT-3, with an increase in the activity and expression of cysteine (C)-X-C motif chemokine receptor 4 (CXCR4).	111
Multipotent mesenchymal progenitor C2C12 cells	In vitro	• Enhance of BMP2-mediated osteoblastic differentiation in a dose-dependent manner.	112
rBMSCs	In vitro	• Stimulate rBMSC proliferation and activity of ALP. • amplifies the expression of the osteogenic genes Runx2, col I and BMP-2. • Reduces the expression of the adipogenic differentiation markers CCAAT/enhancer-binding protein α and peroxisome proliferator-activated receptor gamma. • Treatment of rBMSCs with an ER antagonist, ICI182780, blocked the icariin effects. • Prevents adipogenic differentiation and induces of osteoblast differentiation through the stimulation of the ER signaling pathway.	113
BMSCs	In vivo In vitro	• Increases the BMSCs migration capacity. • Provokes Actin stress fiber formation. • Stimulation of the MAPK signaling pathway was essential for formation of actin stress fiber and icariin-induced migration. • Promotes the employment of BMSCs to the cartilage defect area in vivo. • Stimulates migration of BMSC in vitro and in vivo by prompting formation of actin stress fiber through the MAPK signaling pathway.	114
Postmenopausal persons	Clinical trial	• Operative in inhibiting postmenopausal osteoporosis with moderately low side effects in a 24-month randomized double-blind placebo-controlled clinical trial reported. • Represents bone-promoting effect that can be used for postmenopausal osteoporosis treatment.	115
mMSCs	In vivo In vitro	• Reduces titanium-particle prevention of MSCs osteogenic differentiation. • Upsurges bone mass and reduces bone loss in titanium-particle-induced osteolytic regions. • Prevents stability of reduced β-catenin induced by titanium particles in vitro and in vivo. • ICG-001, a selective Wnt/β-catenin inhibitor, decreased the effects of icariin on mineralization of MSCs. • Induces osteogenic differentiation and stimulates formation of new bone at a titanium-particle-induced osteolytic region through stimulation of the Wnt/β-catenin signaling pathway.	116
Rat BMSCs	In vitro	• Does not have improved effect on cell proliferation. • Increases osteogenic differentiation, by boosting ALP activity and gene expression of *Col I*, *OCN*, and *OPN*. • Icariin quickly phosphorylated extracellular signal regulated kinase (ERK), p38 kinase and c-Jun N terminal kinase (JNK).	117
BMSCs from ovariectomy (OVX) rats	In vivo In vitro	• The osteogenic differentiation significantly declined in BMSCs of ovariectomy rats in vitro. • Restores and promotes the mineralization and osteogenic differentiation of OVX-BMSCs through the pathway of estrogen, which are foiled by the increase of age and estrogen deficiency.	118
MSCs in patients with osteonecrosis	Clinical trial	• Reestablishes the dynamic balance between adipogenic and osteogenic differentiation of MSCs in patients with osteonecrosis of the femoral head (ONFH) through demethylation of ABCB1-promoter. • MSCs of the steroid-associated ONFH displayed decreased proliferation capability, increased level of ROS, weakened osteogenesis, depressed MMP, and improved adipogenesis while low P-gp activity, oxidative stress-concerning genes, and transcription level of ABCB1, as well as aberrant CpG islands hypermethylation of ABCB1, were also noted in steroid-associated ONFH group. • Causes reduced oxidative stress, de novo expression of P-gp, and stimulated osteogenesis.	119

holds several pharmacological effects like antimicrobial effects, antioxidant, wound healing, anticancer, and anti-inflammatory.[123–132] Curcumin is capable of boosting osteogenic differentiation of rat MSC (rMSCs) and inhibiting the formation of adipocyte.[133]

Gu et al. studied the impacts of curcumin on the differentiation of rMSCs into adipocytes and osteoblasts. ALP's activity and expression of osteocalcin and Runx2 (when used from osteogenic medium) were enhanced by curcumin. In contrast, differentiation of adipocyte was decreased by curcumin and it prevented adipocyte-specific genes expression of C/EBPα and PPARγ2 when used from the adipogenic medium. During rMSCs osteogenic differentiation, the expression of HO-1 was increased.[133]

Wang et al. evidence that curcumin protects cells from hydrogen peroxide (H_2O_2) induced death in hAD-MSCs in vitro. It is important to note that curcumin has been discovered to be capable of increasing the osteoblast differentiation of hAD-MSCs prevented by H_2O_2. Noticeably, the curcumin treatment debilitates both inhibitions of Wnt/β-catenin signaling and oxidative stress. These findings are indicative of the fact that curcumin could well improve the osteoblast differentiation of MSCs and defend the suppressive activities of oxidative injury. The results confirmed a potential use of relevant antioxidants such as curcumin for disease-related to oxidative stress-induced bone loss in MSC-based bone regeneration.[134]

Son et al. demonstrated that Curcumin enhances the expression of osteogenic genes like distal-less homeobox 5 (Dlx5), ALP, Runx2, and OC. Curcumin activates the expression of ATF6 together with ER stress marker genes like BMP2. In addition, curcumin controls Smad 1/5/9 phosphorylation and stimulates Runx2 mediated transcription increase of the ATF6 gene in mouse mesenchymal stem cells (C3H10T1/2).[135]

Li et al. showed that curcumin impedes osteogenesis of hADSCs in a dose-dependent manner. Curcumin regulates the expression of miRNAs in hADSCs such as miR-126a-3p during osteogenesis. The osteogenesis effect of curcumin requires inhibition or overexpression of miR-126a-3p. Some more research showed that miR-126a-3p specifically targets and prevents LRP6 by binding to its 3′-UTR, and afterward prevents activation of WNT. They were indicative of the fact that, the utilize of curcumin as an anticancer agent, by suppressing osteogenesis, may result in a reduced bone mass.[75]

4.3 | Osthole

In order to refer to a natural coumarin, we can refer to Osthole (also called osthol), 7-methoxy-8-(3-methyl-2-butenyl)-2H-1-benzopyran-2-one, which was firstly derived from Cnidium plant. The mature fruit of *Cnidium monnieri* (Fructus cnidii) contains an abundant amount of osthole, which is generally used in the traditional Chinese medicine (TCM), whereas it is as well extensively exists in other therapeutic plants such as clausena, archangelica, angelica, citrus. To mention some advantages of Fructus cnidii, we can refer to its ability to strengthening the immune system and improving male function, by soothing rheumatic pain and with the removal of dampness. It is believed that many of these medicinal characteristics are related to osthole, a major bioactive component.[136–138]

As demonstrated by Zheng et al., BMMSCs (OBMMSCs) treated by osthole brought a better outcome compared to BMMSCs alone in estrogen deficiency-induced osteoporosis model. Moreover, previously increased levels of autophagy were believed to be the basic mechanism of osthole's capability to boost osteoblast differentiation, shown by the upregulation of the protein and mRNA expression level of autophagy-associated genes, Beclin1and LC3.[139]

Sun and coworkers showed the capability of osthole in restoring defective osteogenic differentiation of P-PDLSCs through epigenetic modification. They found that the best concentration of osthole for proliferation and osteogenic differentiation of P-PDLSCs is 10^{-7} mol/l. One of their findings, in mechanical terms, was that Osthole upregulates MORF and MOZ, histone acetylases that specifically catalyze acetylation of histone3 lisine9 (H3K9) and histone3 lisine14 (H3K14), which are basic regulators in P-PDLSCs osteogenic differentiation.[140]

One of the findings of Hu and coworkers was that multiplication of rMSCs is impeded by osthole in a concentration-dependent manner and osthole also holds back osteogenic differentiation of rMSCs through down-regulating the functions of Erk1/2-MAPK and Wnt/β-catenin signaling.[141]

4.4 | *Epigallocatechin* gallate

Green tea, as one of the most popular drinks consumed by humans, is useful according to epidemiological studies by reducing the risk of many chronic diseases like diabetes, different cancers, and cardiovascular diseases.[142–146] Catechins are the main bioactive elements of green tea, that has a significant role in the usefulness and effectiveness of drink. *Epigallocatechin* gallate (EGCG) is a common phenolic flavonoid-3 ol compound with eight free hydroxyl groups, making it biologically active and has several biological functions. Previous studies have shown that EGCG, as well as some tannin compounds, are able to eliminate free radicals more effectively among

common phenolic compounds.[147] Typically, phenolic compounds, including EGCG, have low bioavailability.

In order to have biological effects and health benefits of EGCG, its absorption and metabolism in the intestine are very important.[148] The study of Madhurakkat et al. showed that EGCG coating on PLLA nanofibers improved osteogenic differentiation of ADSCs and suppressed the adipogenesis of ADSCs. It was also significantly able to diminish macrophage to osteoclast maturity in mice.[149]

In addition, EGCG coating protected ADSCs from the oxidative stress of H_2O_2.ultimately, implantation of nanofibers coated with EGCG into the defect created in the mouse calvarium, significantly increased bone regeneration(61.10 ± 28.10 61 61.5) compared to the defect (11.07 ± 48/17).[149]

In a study of osteogenic differentiation, which was applied simultaneously 3% distraction and EGCG, Jay Won Shin et al. showed that the competent combination of mechanical distraction and EGCG increases the osteogenic differentiation synergistically.[150]

4.5 | Naringin

Naringin (naringenin 7-O neohesperidose), a component of the flavonoid family, which is basically an antioxidant and has anticancer properties, can lower cholesterol levels. It is also useful in bone disease treatment like osteoarthritis and osteoporosis and induces proosteogenic effects improving the proliferation of stem cells.[151]

In in vitro studies, increases the expression of OCN, OXS, and Runx2 Col1so promotes osteogenic differentiation and activates the ERK signaling pathway in human BM-MSCs and increases proliferation.[152] Naringin upregulates the osteogenic genes in BMSCs of rats. In stem cells resulting from human amniotic fluid (hAFSCs), naringin improves osteogenesis through BMP and Wnt-β-catenin signaling pathways. Moreover, it has been shown that the expression of bone morphogenetic protein4 (BMP4), cyclin D1, β-catenin, and Runx2 have been increased by prescribing 1–100 μg/ml naringin, dose-dependently.[153]

At a concentration of 1 μmol induced the production and differentiation of human periodontal ligament stem cells (hPDLSCs) in both in vivo and in vitro.[154]

A dog model study of BM-MSCs indicated a dose-dependent association of proliferation and differentiation with naringin. In TCM, Rhizoma drynariae is known as a treatment for osteoporosis and bone nonunion.[45]

The flavanone can be an alternative treatment for the improvement of osteogenesis. In order to control the naringin release, Mengfei Yu et al. constructed multifunctional mineralized collagen covering with titanium, using a metal–organic framework (MOF) nanocrystals. They concluded significant enhancement of the attachment, proliferation, osteogenic differentiation, and mineralization of MSCs.[155]

4.6 | Resveratrol

Resveratrol (RSVL) is a polyphenolic phytoestrogen that is abundant in blueberries, peanuts, red grapes and other plants.[156] Many studies indicated that RSVL affects stem cells. RSVL increases the proliferation of hBMSC and differentiates osteocytes by activating P38 mitogen-activated protein kinase (MAPK) and extracellular signal-regulated kinase 1/2 (ERK1/2) via an ER-dependent mechanism.[157]

RSVL exhibited its impact on hMSC in time and concentration reliant manner for production and differentiation, so that 0.1 μmol RSVL enhances cell proliferation; however, 5 μmol or higher concentrations suppress cell renewal by rising the aging rate and cell cycle stop in the S phase. Furthermore, it induces MSCs differentiation into osteogenic cells and reduces adipogenic ones.[158]

Resveratrol upregulates HMSC mediated via the SIRT1/FOXO3A and Runx2 gene expression therefor promotes osteogenic differentiation. On the other hand, it activates SIRT1 and enhances FOXO3A proteins.[159]

According to a study done by Chen et al. who examined Polydatin effects and mechanism in osteogenesis of hBMSC cells, they showed that Polydatin significantly increased hBMSCs proliferation and ALP activity. In addition, significant osteogenic genes expression like OPN, DLX5, OCN, Runx2, Col I, and BMP2 and components of the Wnt signaling pathway (β catechins, c-jun, TCF7, Lef1, cyclin D, and c myc) increased. These effects of osteogenesis enhancement from Polydatin were blocked by Noggin, which suppresses the BMP pathway, and also by DKK1, which inhibits the Wnt/β-catenin pathway. Although, it has been shown that DKK1 is not effective in expressing BMP2 due to polydatin.[160]

Benedetto et al. studied resveratrol and polydatin effect in DBSCs differentiation and ultimately osteogenesis. They reported that polydatin and resveratrol both increase osteogenic differentiation of MSCs demonstrating similar characteristics.[161]

Sreekumar et al. showed that the interaction of CSE-exposed SCP-1 cells with resveratrol (1 μmol concentration) can be protective because of its significant reduction in free radical productions, therefore protects primary cilia and promotes osteogenic differentiation.

They reported smoking adverse effects on cilia in hMSCs while osteogenic differentiation and resveratrol therapy can reduce the adverse effects of smoking and improves differentiation.[162]

5 | EFFECT OF PHYTOCHEMICALS ON OSTEOCLASTS

Osteoclasts are multinucleated cells derived from hematopoietic precursor cells of the monocyte–macrophage lineage, and the process of bone resorption is closely related to the size of the pool of active osteoclasts.[163,164]

The receptor activator of nuclear factor kappa B ligand (RANKL) and the macrophage colony-stimulating factor (M-CSF), which are produced by the stromal and osteoblast cell lineage are critical factors needed for development of osteoclast.[165]

Several hormones, cytokines and growth factors regulate the physiological resorption of bone by controlling both the differentiation and recruitment of new osteoclasts or the lifespan of existing osteoclasts by reducing apoptosis rate.[166] There is an abnormally high bone turnover with increased osteoclastic bone resorption in pathophysiological situations such as postmenopausal osteoporosis. Postmenopausal estrogen deficiency increases the active osteoclasts number, which is the main pathological factor responsible for postmenopausal bone loss.[166]

One of the most important ways to prevent nonpharmacological bone loss after menopause is to identify each components of the nutrition that can counteract the usual increase in postmenopausal bone loss. Soybeans are rich in isoflavonoids generally represented by daidzein and genistein, which considerably prohibited bone loss in ovariectomized rats, and have positive effects on both osteoclast and osteoblast activities.[167–171] There is structural similarity of daidzein and genistein with natural estrogen, and their useful effects are related to their capability to bind the estrogen receptor. In a recent study, flavonols may have a positive effect on bone remodeling,[172] which showed that rutin, a glycoside of quercetin, prevents ovariectomy-induced osteopenia in vivo.[173]

Icaritin is also capable of hindering the function of osteoclasts in vitro, exerting bone-protective activity by enhancing bone formation and preventing bone resorption.[97,101,102] Sesamin decreases the quantity of differentiated osteoclasts; nevertheless, it inhibition did not result from the modification of precursor cell proliferation. Sesamin mediates the prevention of differentiation of human osteoclast, the recruitment of precursor cells and formation of F-actin. In the region of the resorption pits and the released collagen from the bone slices under sesamin treatment showed the preventive effects on both the function and differentiation of osteoclasts.[52] Gastrodin efficiently retardes differentiation of RANKL-induced osteoclast by decreasing expression of a main factor in RANKL-mediated osteoclastogenesis, nuclear factor of activated T cells cl (nfatc1). Gastrodin prevents formation of osteoclasts and resorption of bone through blockage of nfatc1 activity, and induce osseointegration.[66] Tanshinone IIA promotes osteogenesis and inhibits osteoclastogenesis.[69] *Tridax procumbens* flavonoids Suppresse the bone resorption and RANKL-induced osteoclasts differentiation.[76,77]

6 | FUTURE PROSPECTIVE

Significant advances in the science and technology and advanced studies of phytochemicals indicate their important role in regenerative and remedial medicine. Because very little information is available about the exact site, mechanism and also adverse effects of using phytochemicals, extensive studies are necessary in order to substitute artificial drugs.

MSCs play a very important part in regenerative treatments as their higher differentiation ability. MSCs are an ideal cell source for osteochondral tissue engineering owing to their high potential for proliferation and differentiation into osteogenic and chondrogenic lineage in a suitable physiological setting.

In recent decades, researchers have been used mesenchymal stem cells to regenerate tissue in bone damage and cartilage damage.[174,175] Although very few adverse effects of phytochemicals have been reported in humans, the side effects of the drug still need to be considered for some medical conditions that are not well known. By gaining more knowledge about phytochemicals effects, we can limit their side effects in certain situations.

Also, by recognizing the therapeutic doses, the desired effects can be well applied, and also the toxic effects can be controlled. Therefore, plant-derived compounds are considered as an ideal stem cell therapeutic agent with easy accessibility and a reasonable price with minimal or no adverse effects. Furthermore, the use from nanotechnology to increase the delivery of phytochemicals especially about insoluble agents is can be a promising method for more induction of stem cells to differentiation. Moreover, the use of phytochemical containing scaffolds for tissue engineering aims can be an excellent option.

7 | CONCLUSION

Mesenchymal stem cells in combination with phytochemicals have shown promising results in regenerative treatments. Phytochemicals induce significant proliferation and differentiation effects into different cell types.

The biologically active compounds of herbs affect different protein pathways to modify mesenchymal cell regulation. Pharmaceutical plants are very important due to their low toxicity, low cost, and capability to enhance the treatment of bone-related diseases. Further studies in order to use phytochemicals will promote the proliferation and differentiation of MSCs, leading to cost-effective technology in the treatment of bone disorders. Furthermore, the design of phytochemical containing scaffolds can be promising for tissue engineering application.

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CONFLICT OF INTEREST

The writers announce that there are no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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