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Potential Role of Herbal Remedies on Mesenchymal Stem Cells: An Overview of New Therapeutic Strategies for Osteoporosis

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Abstract

Worldwide, osteoporosis（OP）affects more than 200 million people, and as people get older, the disease is more common. It is anticipated that by 2025, aging country populations will increase the prevalence by as much as 50%. Osteoporosis is a degenerative skeletal condition that causes decreased bone mass and degeneration of the bone microstructure, which raises the risk of fracture and increases bone fragility. The irreversible nature of bone loss in the body makes osteoporosis a difficult illness for doctors to treat. Mesenchymal stem cells (MSCs), a multipotential cell with the capacity to self-renew and specialize into a number of cell types, are currently the source of preference for cell-based therapies due to their crucial role in tissue repair and synthetic biology. Bone marrow-derived mesenchymal stem cells (BMSCs) have long been employed in both preclinical and clinical research to treat osteoporosis. Even while new transplantation therapies using mesenchymal stem cells (MSCs) are promising, they are also expensive and urgent issues need to be resolved about their safety, transplantation effectiveness, and standardization of manufacturing techniques. Indeed, naturally occurring phytochemical substances (herbs) offer significant anti-inflammatory, pro-differentiation, and tissue regeneration potential, and the differentiation, migration, and immunomodulatory capabilities of MSCs treated with herbal extracts show promise in diseases like osteoporosis, neurological diseases, and other tissue degenerative disorders. In the creation of novel therapeutic approaches by MSCs for the treatment of osteoporosis illnesses, they have attracted a lot of interest. In this article, we summarize the most recent findings on herbal extracts' effects on MSCs differentiation, migration, immunosuppression, and epigenetic regulation as

well as potential mechanisms of action. Additionally, based on the yin-yang theory of Chinese traditional medicine, we did a thorough analysis of the molecular phenotypic variations between yin and yang in osteoporosis with the goal of improving guidance on the pathophysiology and clinical application of osteoporosis.

1. Introduction

Due to their enormous regeneration potential, human mesenchymal stem cells (MSCs) have gained popularity in the field of bioengineering and cell therapy[1]. MSCs were first demonstrated by Friedenstein and his associates in 1976[2]. Adult MSCs have been identified in a variety of tissues, including bone marrow, the umbilical cord, placental tissues, adipose tissues, synovial membrane and fluid, peripheral blood, dental pulp, and endometrial tissues[3]. Nevertheless, MSCs from each niche retain several features in common (like as marker expression) while differing in others (like as self-renewal and differentiation capacity). According to a recent study, perinatal niches (i.e., CPJ) present a more favorable environment for maintaining primitive MSCs than adult tissues do[4]. Additionally, Bone marrow is the putative source of various adult stem cells. Adipocytes, osteocytes, and chondrocytes are just a few of the connective tissues that mesenchymal stem cells (MSCs) obtained from the bone marrow can differentiate into[5]. MSCs are a promising cell source for regenerative medicine due to their flexible and controllable differentiation potential, ability to release a range of neurotrophins, and capacity to alter the immune system of the recipient[6].

As of 2022, a total number of 1902 clinical trials on stem cell therapy worldwide were recorded in the database of the U. S. National Library of Medicine. Of them, 499 of which are related to MSCs therapy accounting for nearly one- fourth[7]. Moreover, they provide a broad range of applications in tumors, immune disorders, neuroinflammation, and the replacement of damaged tissue due to accidents. Through their immunosuppressive or immunomodulatory characteristics in the tumor microenvironment, MSCs control immune response and accelerate tumor growth[8]. MSCs can be manipulated and transformed into effective drug carriers and transfected with anticancer genes for the therapeutic intervention of osteosarcoma due to their special properties[9]. In the context of treating liver illnesses, particularly acute liver failure, MSCs and their derivative exosome have emerged as a potential strategy[10]. Recent research shows that exosomes from MSCs improved functional recovery, encouraged neurogenesis, and decreased neuroinflammation in rats following traumatic brain injury (TBI) [11]. A novel therapeutic approach to prevent or treat sepsis and sepsis-induced liver injury has been

developed as a result of research into the potential of MSCs to increase macrophage polarization and alleviate sepsis in mice models. In order to restore damaged skeletal muscle, a novel ROS-scavenging hydrogel (Gel) containing mesenchymal stem cells (MSCs) was created (Gel@MSCs)[12-14]. MSCs have been used in investigations on diabetic nephropathy (DN) to convert 'Mφ' into an anti-inflammatory phenotype and to mitigate kidney damage in DN animals' besides mitochondrial transfer[13].

Osteoporosis (OP) is a metabolic bone disease typically characterized by low bone mass and deterioration of bone tissue microstructure, which leads to an increased risk of brittle fracture[15]. According to reports, osteoporosis and fractures brought on by the condition frequently cause morbidity and mortality in the elderly[16]. Researchers advise assessing the risk of osteoporosis in all postmenopausal women and men aged 50 and older[17]. Based on the American Association of Clinical Endocrinologists/American Society of Endocrinology Clinical Practice Guidance, osteoporosis is identified by the occurrence of fragility fractures in the absence of other metabolic bone disorders and even with a normal bone mineral density (T-score). It is also identified by T-scores of 2. 5 or less in the lumbar spine (anteroposterior), female neck, entire hip, or 1/3 radius (33% radius)[18]. The pathogenesis of osteoporosis is primarily influenced by homing disorder, decreased osteogenic differentiation ability, aging of mesenchymal stem cells, an unbalanced microenvironment, and disorders of immune control[19]. The chosen cell source for cell therapy is mesenchymal stem cells (MSCs), a kind of pluripotent cell that can transform into osteoblasts, adipocytes, or chondrocytes[20]. Recently, a large number of bone marrow mesenchymal stem cells have been applied to preclinical and clinical studies of osteoporosis. Up to now, the treatment of osteoporosis by MSCs mainly focuses on osteogenic and adipogenic differentiation, immune regulation, cell migration, and epigenetic regulation to improve the quality of life for patients. However, recombinant cytokines and growth factors, which are frequently utilized as proliferation and differentiation factors in the current stem cell therapy, have a high price tag and may have negative side effects[21]. Moreover, the efficacy of MSCs therapy is presently limited by low retention and survival ratio of transplanted cells, caused by oxidative stress, nutrient deprivation and inflammatory environment at injured sites. Because of these shortcomings, researchers have been searching for effective alternatives to the proteins and cytokines required for stem cell therapy.

Numerous herbal treatments for similar diseases have been made available by conventional medical systems since the dawn of time, herbal remedies are a promising alternative and supplementary scheme, which can significantly improve the patient's condition and significantly reduce the symptoms of the disease[7]. Although the majority of the time, the exact method by which individual and combined herbal plant extracts work is yet unknown. A deeper understanding of the therapeutic mechanism may be gained by examining the effects of various herbal extracts on stem cell differentiation, migration,

immunosuppression, and epigenetic regulation. In earlier investigations, herbal extracts were found to have significant potential for MSCs proliferation, differentiation, migration, anti-aging, and immune response management. More recently, due to its demonstrated osteogenic, anti-adipogenic, homing, anti-inflammatory, and medicinal effects, the utilization of herbal treatments and their extracts for the treatment of joint problems, involving OP, has also gained widespread acceptance in modern Western medicine[22-25]. The effectiveness of herbal components or herbal combinations and their application in the treatment of various ailments, including anti-inflammatory effects on chondrocytes and proliferation of cardiomyocytes, has really been the subject of numerous research[26,27]. The availability of herbal medications for intervention and treatment to a wide variety of people at a reasonable cost and with few adverse side-effects is an essential benefit[28]. Therefore, this literature review focuses on the potential of herbs as natural stimulants between MSCs and osteoporosis and their potential in maintaining bone homeostasis, as well as in the prevention and treatment of joint diseases, especially osteoporosis, with a macroscopic description of osteoporosis from a yin-yang perspective.

2. Effects of herbal extracts on the osteogenic differentiation and adipogenic differentiation of MSCs.

Apparently, bone loss is probably could be prevented by restoring the balance between bone-forming osteoblasts and bone-resorbing osteoclasts, as well as enhancing osteogenesis and reducing adipogenesis in MSCs. Much of the research in the following sections elaborate on such herbal remedies that showed great potential in the differentiation of MSCs.

2.1 Osteogenic effects of herbal extracts

First, Herba Epimedii has been used in traditional medicine to improve breastfeeding, encourage menstruation, ease delivery, and lessen the discomfort of dysmenorrhea, a disease involving estrogenic activity. According to estrogenic activity, BM-derived MSCs' ability to differentiate into osteoblasts was significantly enhanced by upregulating the gene expression of runt-related transcription factor 2 (RUNX2) and BMP-2[29], where in research on the total flavonoids of Herba Epimedii (HETF). Second, Curcumin, a kind of phenolic natural product isolated from the rhizome of turmeric, could promote the osteogenic differentiation of MSCs by increasing the mRNA expression of RUNX2 and osteocalcin specific to osteoblasts. In vivo studies have shown that the effect of curcumin on the osteogenic differentiation of MSCs is related to the expression of heme oxygenase (HO)-1, which is consistent with the role of ALP activity and RUNX2 mRNA on the osteoblast differentiation of MSCs[30]. Third, Berberine (BBR), known as a quaternary ammonium alkaloid isolated from Coptis coptidis. The canonical Wnt/β-catenin signaling pathway is activated by BBR, which also strongly increases the osteogenic differentiation of MSCs by

enhancing RUNX2 expression in general. In contrast, DKK-1, a specific inhibitor of Wnt signaling, can effectively inhibit the effect of BBR on osteogenesis, supporting the idea that Wnt/-catenin signaling is involved in BBR-induced osteogenesis[31]. Additionally, obtainable from Chinese medicine, cnidium lactone is a primary element having pharmacological action, which has the function of warming kidneys and strengthening Yang. Researchers suggested that cnidium lactone combined with ERα and other receptors, then activated the BMP-2/SMAD signaling pathway and ultimately stimulated BMSCs differentiation and mineralization[32]. Much more interesting, the traditional Chinese medicine compound Jiawei Yanghe soup (JWYHD) contains cooked Rehmannia, cinnamon, papaya, Jianji, caulis pathology, and other Chinese herbs, which can regulate bone homeostasis in BMSCs by activating the BMP-SMAD signaling pathway, restore the dynamic balance of osteogenic-lipogenic differentiation of MSCs, improve bone microstructure and reduce bone loss in ovariectomized PMOP rats[33].

2.2 Anti-adipogenic effects of herbal extracts

Several chemical compounds of herbal origin, including quercetin, Ligustrum lucidum, arginine, resveratrol, and Icariin were identified its anti-adipogenic activities, while restoring the balance between bone anabolism and catabolism.

Since, quercetin is a compound that exists in the form of glycosides in many plants, such as the leaves of Platycladus lateralis and Morus parasitis, and an inhibitory effect on adipocyte differentiation has been demonstrated when quercetin 3-O-β-D-galactopyranoside (Q3G) was used to induce MSCs for adipogenesis, while C/EBPα and PPARγ showed significantly lower levels, which in turn affected adipogenesis[34]. Besides, Ligustrum lucidum and psoralea (LP) are used in traditional medicine to strengthen the body and strengthen the bones, tighten the urine, and nourish the liver and kidney, which are all conditions involved in the effective promotion of bone health. The study based on the pairing of two herbs showed that the addition of LP to the osteogenic medium could significantly inhibit the proliferation and adipocyte differentiation of bone marrow derived human MSCs, and the number of adipocytes was significantly reduced[35]. Furthermore, arginine reduces triglyceride (TG) levels and exerts anti-lipid activity by inhibiting the adipose transcription factor peroxisome proliferator-activated receptor γ (PPARγ). This study provides the first experimental evidence of the bone-promoting and anti-fat effects of arginine[36], similar findings that were later confirmed in studies on resveratrol and Icariin [37] [38].

Together, these data suggest that herbs or herbal extracts have a significant modulating effect on osteogenic-lipogenic differentiation of MSCs. For instance, Icariin can, as was already mentioned, encourage MSCs development into osteoblasts[29,38], while suppress formation of adipocyte-like cells, and the ERK signaling pathway may play a critical role in the interaction between icariin and its main

metabolite, icariin II, on the osteogenesis and adipogenesis of MSCs[39]. These action mechanisms are consistent with osteoblast differentiation who have increased RUNX2 and Osterix (OSX), and reduced PPARγ and TNF-α. Numerous transcription factors and signaling pathways control the development of ubiquitous mesenchymal progenitor cells into distinct kinds of skeletal-associated cells, and several studies have shown that disturbances in the dynamic balance of bone formation and bone resorption are crucial to the pathogenesis of osteoporosis. Thus, in order to maintain bone homeostasis, which is essential for controlling the balance of MSCs during the process of osteogenic and adipogenic differentiation. Furthermore, it is known that bone marrow MSCs are effective in the treatment of osteoporosis. Whether transplantation of MSCs is clinically safe and effective for treatment remains unknown; however, in vitro data from multiple researches indicates that reactivation of the osteogenic differentiation capacity of MSCs by herbs, a natural and non-toxic in vitro activator, are a viable method.

3. Effects of herbal extracts on the immunological regulation of MSCs

It has been demonstrated that the inflammatory microenvironment interferes with MSCs function and blocks their osteogenic, lipogenic, and myogenic actions[40]. Recent studies in this area have discovered that specific herbal extracts can successfully lower inflammatory cytokine production and balance the helper T-cell population to enhance the immunomodulatory function of MSCs[41-43].

Immunomodulation of MSCs by herbs could be classified as cytokine modulation, which elevates or decreases the expression of inflammatory factors, or gene modulation, which alters gene expression to improve the performance of MSCs in the clinic. Total glucosides of paeony (TGP), for example, significantly enhanced MSCs immunomodulatory action by reducing IL-6 and TNF-α expression and upregulating TGF-β and IL-10 expression[44], while MSCs treated with phytosomal curcumin (PC) may influence the immune function of hDPSC by regulating the transcriptional levels of miR genes such as miR-23, miR-155[45]. Similarly, Ginkgo biloba extract can regulate oxidative stress-mediated bone homeostasis and inhibit the expression of inflammatory cytokines such as TNF-α, IL-6, IL-1β and IL-10 in different cells and animal models closely related to bone diseases[46-48]. In addition, it has been discovered that herbal extracts with immunomodulatory and anti-angiogenic properties, like Ganoderma lucidum polysaccharide (F3) and forsytha perforatum, can also be used in pharmaceutical formulations[49,50]. Herbs, as discussed and demonstrated above, hold great promise for MSCs-mediated immunomodulation in the treatment of diseases, particularly because of their anti-inflammatory and anti-oxidant properties[40].

Herbal-Stem Cell Combination therapies such as Astragalus and the mesenchymal stem cells, which derived from bone marrow and umbilical cord, has been applied clinically to patients who have suffered

skin and other tissue damage in order to speed up wound healing. Early vitro trials demonstrated that PG2 effectively promoted the proliferation of UCMSCs and their immunosuppressive effects, but did not clarify the precise mechanism[51]. A later vitro study, Lipopolysaccharide (LPS)-induced inflammation model in MSCs[52], confirmed that the co-treatment with astragaloside and baicalin could inhibit the expression of IL-1β, IL-8 and TNF-α more effectively, and further control‐group analysis revealed that they also have the capacity to suppress apoptosis, lessen inflammatory response, and encourage differentiation and proliferation of epithelial cells, findings that were later confirmed in another study[53]. The ability of MSCs to differentiate combined with their immunosuppressive effect makes them a prime option to move towards damaged tissue for healing and is considered to be an even more appealing choice for regenerative medicine; however, the majority of in vivo investigations revealed limited MSCs engraftment and trans-differentiation within diseased or damaged tissues[5], which may have an impact on the patient's healing efficiency and subsequent   maintenance. Wang *et al*.,[53]have demonstrated that Astragalus and human mese etabolism depends on the interplay of immune cells and MSCs, and abnormally high inflammatory factor levels cause excessive osteoclast activation, which causes pathological bone breakdown and bone loss. Thus, the new therapeutic options serve to improve the inflammatory microenvironment, inhibit the inflammatory response and promote the immunosuppressive role of MSCs in bone repair.

4. Effects of herbal extracts on the migration of MSCs.

Current cell-based therapeutic approaches have demonstrated efficacy and broad applicability in the treatment of degenerative and injurious diseases. Despite the significant regenerative potential of MSCs in tissue repair, they have shown a high degree of variability in therapeutic efficacy[54-56]. Recent studies suggest a strong correlation between the MSCs migration potential and their therapeutic efficacy in humans, and is proposed to use highly migratory subpopulations of stem cells in cell-based therapeutics. We enumerate several studies on the effects of herbal extracts on MSCs migration in recent years, and combined herbal-MSCs therapies have shown great potential in certain conditions[54].

This migration of MSCs is regulated by a number of factors. In essence, the process of seeking is based on specific molecular interactions rather than passive distribution. Thus, high levels of expression of appropriate adhesion molecules and chemotactic factors are required in the enhancement or inhibition of migration of MSCs by herbs. For instance, by activating CXCR4, tanshinone IIA and astragaloside IV encourage the migration and homing of mesenchymal stem cells in vitro and vivo[57]. Also, the results of the wound healing assay and gene expression analysis showed that eugenol increases BM-MSCs' capacity for migration by over-expressing c-Met[58,59]. Besides, Lin *et al*.,[60] found that naringin

activates the Ras signaling pathway to increase the production of cell chemokines and the migration of MSCs. It is worth noting that herbs may not only enhance the migratory homing ability of MSCs, but also inhibit it, which gives more possibilities for MSCs to treat diseases. Such as, Matrine inhibits Heterotopic ossification (HO) via inhibition of TGF-β-induced migration and osteogenic differentiation of MSCs in mice[61]. Agathis flavonoids also decreased the levels of STAT3 expression, which suppressed the migration and differentiation of heterogeneous glioblastoma (GBM) cells[62]. Furthermore, a lower quantity of curcumin might encourage osteogenic differentiation as well as immunomodulatory gene expression in BM-MSCs[63,64],while this has not been directly linked to cell migration. It has been shown that Higher concentrations of curcumin would induce BM-MSCs death and decrease cell proliferation and migration[65], suggesting that the migratory ability of MSCs may be related to the concentration of herbal extracts.

Salidroside could improve wound healing in diabetic patients by regulating paracrine function and proliferation of MSCs in a hyperglycemic environment and it was also found that salidroside pretreatment enhanced the migration capability of MSCs impaired under hyperglycemia, which may be an effective strategy to improve the survival and therapeutic efficacy of MSCs[66]. Additionally, Furumoto *et al*. found that Mallotus philippinensis bark extracts (EMPB) improved the wound healing status of the organism due to its effective mobilization and homing promotion ability of MSCs[67], indicating that herbal extracts with good properties can improve tissue regeneration rates and can be used for stem cell therapy and tissue engineering as an alternative treatment. Similar effects were seen in cyasterone[68] and Notoginsenoside R1[69], which cyasterone might encourage MSCs homing and osteogenic differentiation through related genes such as OPN, ALP, and BMP-2 as well as Notoginsenoside R1. Moreover, resveratrol was previously shown to increases the therapeutic efficacy of UC-MSCs by enhancing cell migration and reducing neuroinflammation mediated by MAPK signaling[70], suggesting that the migratory capabilities of MSCs manipulated with herbal extracts have potential in the treatment of disorders including diabetes, neuroinflammatory diseases, and other tissue-damaging conditions, and thus undoubtedly the combined herbal- mesenchymal stem cell therapy brings light to address this challenge despite the low rate and effectiveness of MSCs homing to damaged tissues remains a major challenge for regenerative medicine.

5. Effects of herbal extracts on the Epigenetic regulation of MSCs

Epigenetic mechanisms involved in the development of osteoporosis have long been the focus of researchers, and there is growing evidence that epigenetic modifications may represent the mechanism linking genetic and environmental factors to increased risk of osteoporosis and fracture, primarily

including DNA methylation, histone modifications and non-coding RNAs (lncRNA, microRNA and CircRNA)[71]. Gaining or losing of these epigenetic modifiers alters the epigenetic patterns of osteoblasts and the cells that are associated with them, which in turn impacts bone homeostasis, the bone immune microenvironment, and the pathological alterations implicated with osteoporosis[72]. In recent years, herbs or herbal extracts have been shown to be effective in modulating epigenetic mechanisms, especially in a range of diseases closely related to bone metabolism-related processes such as osteogenic differentiation, osteogenesis, and bone reconstruction, such as osteoporosis. In view of the significant role that epigenetic mechanisms play in controlling the metabolism of bones. We enumerate the research progress of related herbal epigenetic modulation MSCs in osteogenic lipogenic differentiation and osteoporosis pathogenesis to provide fresh directions for the treatment of diseases related to bone metabolism[73].

5.1. Resveratrol (RES)

Resveratrol (trans-3,4,5-trihydroxystilbene) is a natural polyphenol phytoestrogen found in rhubarb and other natural plants with osteogenic and osteoinductive properties[74,75] that can promote the osteogenic differentiation of adipose stem cells (ASC) and bone marrow mesenchymal stem cells (BMSCs) through epigenetic regulation. For BMSCs, resveratrol can stabilize the osteogenic/osteoclastic homeostasis of BMSCs by upregulating miR-146a expression levels, thereby inhibiting the transcription of β-catenin proteins by FOXO factors and exerting anti-osteoclastogenic effects through the Sirt1/NF-κB signaling pathway（Fig 1）[76]. Interestingly, it is the res-modulated miR-193a inhibition that appears to be responsible for the activation of Srit7/NF-κB signaling pathway in the process of promoting osteogenic differentiation of BMSCs[77]. What's more, RES could also enhance the expression of miR-92b and suppressing the expression of Nox4/NF-κB signaling pathway activity and osteoclast proliferation[78]. It's worth noting that RES could regulates miR-320c expression and thus promotes the differentiation of BMSCs to osteoblasts in a dose-dependent manner, while RUNX2 may play a direct target role in this process（Fig 1）[79]. These results suggest RES-mediated epigenetic regulation is critical for BMSCs osteogenic development.

5.2. Icariin

Icariin (ICA) is the main active ingredient of the traditional Chinese herb Epimedium, which is commonly used clinically for the treatment and prevention of many health disorders such as cardiovascular disease, osteoporosis, or sexual dysfunction[80]. It is reported that BMSCs treated with ICA in the patients with steroid-associated osteonecrosis exhibited significant osteogenesis-promoting and lipogenesis-inhibiting effects in patients with steroid-associated osteonecrosis, which may be attributed to ABCB1 promoter demethylation in BMSCs[81]. Additionally, miR-23a appears to be important in the epigenetic regulation

of osteogenic-lipogenic differentiation of bone marrow MSCs under the treatment of ICA[82], as ICA promotes the proliferation and osteogenic differentiation of BMSCs by regulating the miR-23a-mediated Wnt/β-catenin signaling pathway while inhibiting adipogenesis[83], while miR-21-5p may play a similar role[84].

5.3. Kaempferol and Zingerone

Both kaempferol and zingerone are active components isolated from Zingiber officinale[85,86]. The former can promote osteogenesis of BMSCs by mediating multiple signaling pathways such as PI3K / Aktand promote osteogenic differentiation of BMSCs and improve osteoporosis by reducing miR-10a-3p and increasing CXCL12 expression levels[87], while the latter's molecular mechanism for treating bone and bone-related disease was to target Smad7 via miR-590 resulting in Runx2 protection for osteoblast differentiation[88]. It was also found that gingerone contributes to differentiation of osteoblasts through the miR-200c-3p / smad7 regulatory axis in human bone mesenchymal stem cells (hBMSCs) [89].

5.4. Neohesperidin (NH)

NH could promote the osteogenic differentiation of human BMSCs, which in vitro studies suggest is likely to inhibit the histone modifications of LncRNA SNHG1 by regulating SNHG1 gene expression and occupancies of H3K4me3 and H3K27me3[90]. Similarly, NH was found to promote the proliferation of BMSCs, meanwhile bi-directionally regulating the occupancy of H3K27me3 and H3K4me3 in another study. Whereas LncRNA HOTAIR overexpression in particular has also been shown to inhibit osteogenic differentiation, but increase lipogenic differentiation[91].

5.5. Quercetin (QUE)

QUE could not activates the Wnt/β-catenin pathway and promotes hBMSCs osteogenic differentiation via the H19/miR-625-5p axis[92], but also partially modulates it by miR-206/Cx43 pathway, including increasing the expression of Cx43 and decreasing the expression of miR-206[93]. Significantly, QUE may regulate the osteogenic and adipocytic differentiation of ERα-deficient BMSCs to promote osteogenesis of BMSCs through circRNA–miR-326-5p–mRNA axis[94].

Majority of epigenetic pathways regulate the dynamic balance of bone formation and bone resorption, and numerous preclinical researches have shown that herbs play an important role in regulating the epigenetic mechanisms of MSCs. In recent years, extensive research has been conducted in this area (Table 1). For example, Cao *et al*[95] and Wu *et al*[96] found Astragaloside IV(AS-IV) improved tibial defects in rats through down-regulating miR-124-3p via miR-21/NGF/BMP2/Runx2 pathways. Li *et al*[97] reported that miR-671 is abundantly present in small extracellular vesicles derived from Rhizoma Drynariae-pretreated[98] bone mesenchymal stem cells and regulates osteogenesis by targeting TAK1 to mediate WNT signaling. Meanwhile, Huang *et al*[99] observed elevated cell viability and improved

osteogenic differentiation of BMSCs induced by psoralen[100,101]. Furthermore, Ferulic acid (FA)[102,103], artesunate (ART)[104,105], morinda officinalis polysaccharide[106,107] and puerarin[108-110] were similarly found to enhance osteogenic differentiation and inhibit lipogenic differentiation in BMSCs and to increase bone mass in bone grafted rats via epigenetic modulation.

While the epigenetic mechanisms involved in the development of osteoporosis remain unclear, epigenetic regulation of MSCs plays an integral role in the pathogenesis of osteoporosis. Supported by these findings, herbs are proposed to play an important role in regulating the epigenetics of MSCs, particularly through the regulation of non-coding RNAs, which in turn affects the proliferative activity and osteogenic differentiation of MSCs. Furthermore, herbs have been shown to mediate the expression of signaling pathways and cytokines through epigenetic regulation via histone modifications and DNA methylation. Interestingly, bone mineral density (BMD) is considered to be a common clinical measure of bone content and the gold standard for its diagnosis and treatment[111], yet most of the genome-wide association study hits for BMD were found to be in non-coding regions[112]. In summary, herbal modulation of epigenetic mechanisms of MSCs for estrogen deficiency and age-related osteoporosis is a feasible therapeutic strategy.

6. Molecular phenotypes of Yin-Yang in osteoporosis

In recent years, much has been accomplished in human research on osteoporosis, but most of these studies have focused on the microscopic rather than the systemic level. Therefore, gathering detailed information to fully describe the organism remains a major challenge[113]. Interestingly, recent cancer-related studies have increasingly invoked the ancient Chinese theory of yin-yang, and a variety of tumor-related genes and proteins have been reported to regulate various types of cancer in a yin-yang manner[114], and these studies have made the yin-yang theory popular in medical conditions worldwide[115]. The ancient Chinese theory of yin-yang is increasingly being invoked by modern researchers in an effort to move beyond the microscopic focus of disease research and to view biological phenomena at a macroscopic level[116]. Similarly, various genes, proteins and cells have been identified as having yin-yang effects by promoting or suppressing osteoporosis, which provide a more comprehensive and systematic understanding of this complex disease. The yin-yang relationship between osteoblasts and adipocytes or osteoblasts and osteoclasts in the bone marrow plays a key role in the development of osteoporosis. The balance between yin-yang has been considered as a cellular feature[117], and several yin-yang regulatory genes and proteins associated with osteoporosis have been identified in previous studies, such as mitogen-activated protein kinase, p38, PP5, RUNX2, PPARγ, and orexin, as well as cells such as T cells, B cells, macrophages, neutrophils, and mast cells[118].

The guided differentiation of MSCs into adipocytes or osteoblasts depends on the transcription factors PPARγ and RUNX2. It was discovered that serine phosphorylation controls the activity of PPARγ and RUNX2, but in different ways. RUNX2 activation and PPARγ inactivation are caused by the same p38MAPK that mediates serine phosphorylation, whereas PPAR activation and RUNX2 inactivation are caused by protein phosphatase 5 dephosphorylating both proteins[119]. The delicate yin-yang balance between the phosphorylation and dephosphorylation of the two proteins is thought to be the mechanism that keeps MSCs undifferentiated and sensitive to differentiation factors, which suggest a synchronized and reciprocal mechanism that regulates the quick transition of MSC differentiation to osteoblasts or adipocytes. Furthermore, Wei *et al*. also demonstrated that orexin is a dual yin-yang regulator, promoting bone production through primary OX2R and leptin-mediated neuroendocrine control and inhibiting bone formation through secondary OX1R and local regulation of osteoclast development[120]. Both p38 MAPK and PP5 signaling regulating the differentiation of MSCs and the dual regulation of skeletal homeostasis by orexins are paradigms of yin-yang regulation of osteoporosis pathogenesis. The confirmation of these mechanisms could identify pharmacological targets for the treatment of bone and related metabolic diseases[113].

Bone marrow MSCs and neighboring immune cells play an important role in the establishment of the bone marrow immune microenvironment and are the site of interaction between microenvironmental components and mesenchymal cells[117]. Various immune cells are involved in the bone homeostasis of osteogenic lipogenic differentiation and osteoclastogenesis in MSCs in a direct or indirect manner[121]. The pathophysiology of osteoporosis can actually be explained by the harmony between yin and yang. In a healthy host, the immune system's balance is maintained between Tregs and inhibitory cytokines and effector cells and pro-inflammatory cytokines; this is referred to as "yang," and when homeostasis is upset, osteoporosis is typically brought on, which is referred to as "yin." The Yin-Yang hypothesis has the potential to provide a very effective explanation for the pathology of osteoporosis[122]. Various inflammation-related cells, including T cells, B cells, macrophages, neutrophils and mast cells, have yin-yang effects on osteoporosis[123], for instance, certain T lymphocyte subtypes release tumor necrosis factor alpha[124], which raises osteoblast apoptosis and, through B cells' production of nuclear factor receptor activator B ligand (RANKL), indirectly induces osteoclastogenesis. Whereas the release of interleukin 17 (IL-17) by Th17 cells leads MSCs differentiation towards osteogenesis, it is this IL-17 that indirectly stimulates osteoclastogenesis, resulting in bone loss in osteoporosis. Macrophage polarization is modified as the disease progresses, which may be significant to the pathogenesis of osteoporosis[125]. The role of macrophages on osteoblasts may also vary depending on their polarization phenotype and the proteins and factors they produce[126].

In conclusion, recent advances in bioscience and research on osteoporosis have centered on cellular and molecular processes such cell proliferation and differentiation, apoptosis promotion and inhibition, cell migration, anti-inflammation and inflammation, and epigenetic regulatory mechanisms. As a result, the theoretical foundation is become increasingly intricate yet less coherent. Key ideas must be integrated into a macro theory or the framework would be incomplete or unstable[127]. The yin and yang hypothesis offers a macroscopic perspective of biological events (Fig 2). Additionally, Marilena *et al*. proposed a biochemical tool based on redox parameters (such as antioxidant capacity) that can be used to categorize and describe western drugs from a yin-yang perspective by fusing the yin-yang theory with contemporary antioxidant-oxidation theory[128]. However, by using LC-MS mapping, Huang *et al*. discovered that the yin-yang qualities of herbal remedies are closely related to the physical characteristics of the constituents, such as polarity and molecular mass, and that this classification has little to do with antioxidant qualities[129]. Whether the yin-yang phenotypes of osteoporosis have something in common with the yin-yang properties exhibited by herbs, and whether this could provide theoretical support for the combination of herbs with MSCs in the treatment of osteoporosis, is certainly an interesting point that we will also continue to follow and study.

7. Conclusion

The objective of this review is to assess the effect of phytochemicals (herbs) originating from plants on MSCs' capacity to treat osteoporosis while highlighting the contributions of these substances to MSCs migration, immunological control, osteogenic adipogenic differentiation, and epigenetic regulation. In aging civilizations, osteoporosis is a common occurrence that can result in acute discomfort, spine deformity, and fragility fractures. A very fascinating and insightful area of research, plant-derived phytochemicals as naturally powerful inducers and differentiation agents of MSCs have the ability to prevent bone disorders like osteoporosis and promise to produce new therapeutic approaches. Review of the literature indicates that herbal extracts have considerable effects on human bone marrow mesenchymal stem cells as stimulators of differentiation, immunological control, migration, and epigenetic regulation. There is a ton of evidence that several plants have beneficial pharmaceutical effects, such as anti-inflammatory, anti-adipogenic, and homing activities. These characteristics of MSCs treated with herb extracts could serve as a foundation for the therapy and replacement of tissue in the future for conditions like diabetes mellitus, myocardial infarction, neuropathy, and liver and brain injury.

Despite herbal medicines have been demonstrated to have anti-fat, migratory, and immunomodulatory characteristics, most of the current research concentrated on the control of MSC's osteogenic and proliferative capability by plant extracts. In addition, investigations of MSCs from unconventional sources,

such as placenta, umbilical cord, tooth pulp, and fat, are currently being examined due to the ethical considerations involved and the challenge of acquiring samples. We can find that plant sources of some compounds can be obtained through commercial gain, while others are obtained by extracting from plants, and some traditional region herbs such as traditional Chinese medicine, Indian Ayurvedic herb. Because most herbal medicines are not completely clear, in controlled clinical trials using the composition of the available components with the patient, there may be a potential difference between. Therefore, safety, toleration, and uniformity are serious considerations. Therefore, it is crucial for pharmaceutical businesses to evaluate and standardize the herbs and extracts they utilize to assure the security, effectiveness, and caliber of their pharmaceuticals before including Chinese herbal remedies in the normal treatment of osteoporosis. It is also anticipated. Once these fundamental obstacles are removed and handled, nutritional foods (herbal remedies) can be a highly beneficial replacement for hormonal medications (such selective estrogen receptor modulators), which have a number of adverse effects and are commonly used to treat osteoporosis in many parts of the world.

In osteoporosis treatment, therefore, MSCs treated with herbal extracts have the potential to induce differentiation, anti-inflammatory, pro-migration and epigenetic modulation, may produce high cost-effective, highly available, non-toxic alternative treatment application, thereby helping to control other degenerative and metabolic diseases. Though still in its infancy, the investigation of stimulants derived from natural plants has brought regenerative medicine fresh life.

Declaration

Ethics approval and consent to participate

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Availability of data and materials

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Acknowledgements

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Table 1. Effects of herbal extracts on the Epigenetic regulation of MSCs

Herbal extract	Epigenetic regulation	Study Type	Findings	References
Resveratrol	Resveratrol upregulated miR-146a while enhancing miR-92b-3p and BMP-2/Smad/Runx2, inhibiting Nox4/NF-κB.	in vitro/rat BMSCs	Stabilize osteogenic/osteogenic homeostasis in BMSCs, and stimulate proliferation and osteoblast differentiation	[76-78]
Icariin	ICA demethylated the ABCB1 promoter of BMSCs and mediate activation of Wnt/ β-catenin through miR-23a.	in vitro/human BMSCs	Promote BMSCs viability and osteogenic differentiation, weakened adipogenesis	[81-84]
Kaempferol and Zingerone	Kaempferol regulated the mediation of SOX2/miR-124-3p/PI3K/Akt/mTOR axis, while Zingerone provided Runx2 protection by targeting Smad7 with miR-590.	in vitro/human BMSCs, rat BMSCs	Promote osteogenic differentiation of BMSCs and improve osteoporosis	[87-89,130]
Neohesperidin	Neohesperidin (NH) inhibited histone modification of LncRNA SNHG1 by regulating occupation of H3K4me3 and H3K27me3.	in vitro/human BMSCs, rat BMSCs	Improve the activity of BMSC and promote the osteogenic differentiation of human BMSCs.	[90,91]
Quercetin	Quercetin regulated the H19 / miR-625-5p axis and circulates RNA-miR-326-5p-mRNA axis via miR-206/Cx43 pathway.	in vitro/rat BMSCs, human BMSCs,	Regulate osteogenic and adipocyte differentiation of ERα-deficient BMSCS.	[92-94]
Astragaloside IV	Astragaloside IV (AS-IV) increased STAT3 expression by down-regulating miR-124-3p.	in vitro/human BMSCs, rat BMSCs	Improve tibial defects and promotes the proliferation and osteogenic differentiation of BMSCs in rats.	[96]
Ferulic acid	Ferulic acid (FA) induced β-catenin expression by inhibiting miR-340-5p.	in vitro/human BMSCs	Enhance osteogenic differentiation and promotes proliferation of human BMSCs.	[103]
Rhizoma Drynariae	Rhizoma Drynariae regulated the generation of miR-671 and mediates WnT signaling.	in vitro/ BMSCs	Dry core nodules (Gu-Sui-Bu) are often used to regulate osteogenesis.	[97]
Artesunate	Artesunate (ART) modulated miR-34a/DKK1 / Wnt pathway.	in vitro/human BMSCs	Accelerate osteoblast differentiation of hBMSCs.	[105]
Psoralen	Psoralen induced negative regulation of miR-488 by targeting Runx2.	in vitro/rat BMSCs	Increase cell viability and improve osteogenic differentiation of BMSCs.	[99]
Morinda officinalis polysaccharide	Molinda polysaccharide regulated miR-21/PTEN/PI3K/AKT axis.	in vitro/rat BMSCs	strengthening bone and improving immunological function through osteogenesis and lipogenesis inhibition	[107]
Puerarin	Puerarin regulated Mir-155-3p-mediated p53 / TNF-α / STAT1 signaling.	in vitro/rat BMSCs	Promotes BMSCs differentiation and bone formation as well as bone mass increase in bone graft rats.	[110]
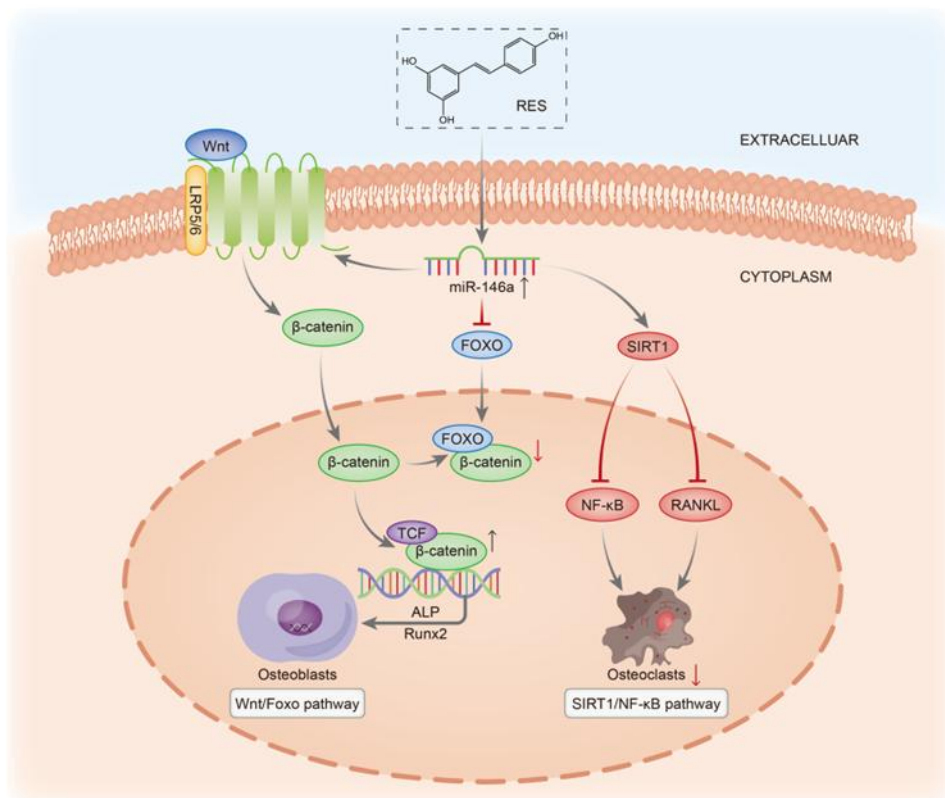
Figure 1. RES stabilizes the dynamic balance of osteogenesis/osteoclastogenesis through Wnt/Foxo and SIRT1/NF-κB pathways. RES upregulates miR-146a exp miR-146a sion levels, promotes SIRT1 expression, inhibits RANKL-induced NF-κB signaling pathway in bone marrow mesenchymal cells (BMSCs), and reduces levels of nuclear transcription factor κB (NF-κB) and the receptor activator of nuclear factor kappa‐B ligand (RANKL) to suppress osteoclastogenesis. RES inhibits the expression of FOXO protein, which causes β-catenin from Wnt/TCF to FOXO-mediated transcription. RES increases the expression levels of β-catenin and Runt-related transcription factor 2 (Runx2) by attenuating the sequestration of β-catenin protein by FOXO transcription factors and promotes osteoblastogenesis by upregulating Wnt signaling.
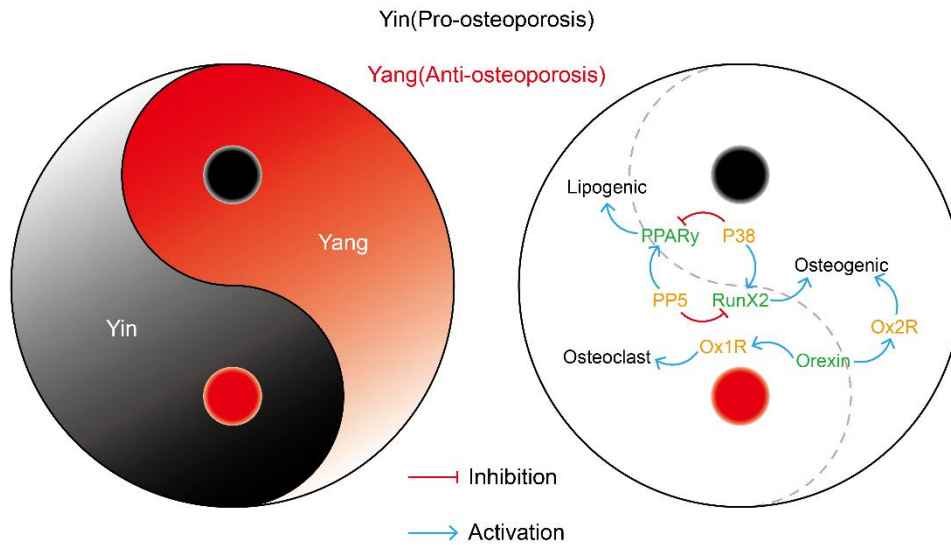
Figure 2. Yin and Yang effects of osteoporosis-related genes and proteins. Yin represents the pathological mechanism that promotes osteoporosis; Yang represents the regulatory mechanism that inhibits osteoporosis. Various genes, proteins and cells have been identified as having yin and yang effects by promoting or inhibiting the eradication of osteoporosis. Mitogen-activated protein kinase, p38, PP5, RUNX2, PPARγ, and appetitin all play an important role in osteoporosis.