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Review article

Curcumin-loaded scaffolds in bone regeneration

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ABSTRACT

In recent years, there has been a notable surge in the development of engineered bone scaffolds intended for the repair of bone defects. While autografts and allografts have traditionally served as the primary methods in bone tissue engineering, their inherent limitations have spurred the exploration of novel avenues in biomedical implant development. The emergence of bone scaffolds not only facilitates bone reconstruction but also offers a platform for the targeted delivery of therapeutic agents. There exists a pervasive interest in leveraging various drugs, proteins, growth factors, and biomolecules with osteogenic properties to augment bone formation, as the enduring side effects associated with current clinical modalities necessitate the pursuit of safer alternatives. Curcumin, the principal bioactive compound found in turmeric, has demonstrated notable efficacy in regulating the proliferation and differentiation of bone cells while promoting bone formation. Nevertheless, its utility is hindered by restricted water solubility and poor bioavailability. Strategies aimed at enhancing the solubility, stability, and bioavailability of curcumin, including formulation techniques such as liposomes and nanoparticles or its complexation with metals, have been explored. This investigation is dedicated to exploring the impact of curcumin on the proliferation, differentiation, and migration of osteocytes, osteoblasts, and osteoclasts.

1. Introduction

In recent years, a diverse array of engineered bone grafts has emerged aimed at addressing bone defects arising from surgical procedures or traumatic injuries. The utilization of scaffold grafting for bone defect repair is imperative given the inherent limitations of the human body in regenerating substantial volumes of bone [1,2]. Presently, autografts represent the preferred choice for bone grafting due to their tissue compatibility and lack of immunogenicity. However, they are encumbered by several drawbacks, including the necessity for secondary surgery, donor site morbidity, elevated procedural expenses, heightened risks of infection and inflammation, as well as associated bleeding and pain. Conversely, allografts, procured typically from cadaveric sources, serve as the secondary option in tissue engineering grafting. Despite their cost-effectiveness relative to autografts, allografts exhibit diminished bone formation owing to their reduced cellular content and heightened susceptibility to infection. The convergence of technological innovations and burgeoning clinical demand for biomedical grafts has catalyzed notable advancements, resulting in the Food and Drug Administration (FDA) approval of a variety of bone substitutes [2,3].

Tissue engineering endeavors to pioneer novel approaches in the creation of bone grafts tailored for tissue regeneration. This

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method holds promise in the revitalization of hard tissues through the introduction of functional bone grafts. The evolution of innovative bone grafts facilitates the fabrication of apt constructs not solely for bone mending but also for the targeted dissemination of therapeutic agents. Forecasts indicate that with the progression of biomaterials research, porous biomaterials of this nature are poised to assume a pivotal role in hard tissue engineering, particularly in the realm of bone tissue reconstruction [4].

Presently, there exists considerable interest in harnessing biomolecules with osteogenic potential to enhance bone formation, driven by the imperative to mitigate the long-term side effects associated with conventional clinical treatments. The quest for safer alternatives has spurred exploration into natural compounds sourced from the environment and their bioactive constituents, which have demonstrated promise in attenuating the enduring adverse effects induced by synthetic drugs used in osteoporosis management. The multifaceted biological activities and physiological intricacies inherent in natural compounds distinguish them from their synthetic counterparts. Moreover, the utilization of natural compounds in addressing bone disorders presents a cost-effective and relatively low side-effect prophylactic option compared to contemporary pharmaceutical interventions [5].

Curcumin, the principal bioactive constituent derived from the turmeric root (Curcuma longa) of the Zingiberaceae family, has garnered extensive research attention due to its therapeutic potential. Numerous investigations have explored its antimicrobial, anti-inflammatory, anti-arthritic, and anti-cancer properties [6,7]. Notably, several studies have elucidated curcumin's role in modulating the proliferation and differentiation of bone cells, thereby enhancing bone formation [8–10]. Despite its broad therapeutic spectrum, curcumin's bioavailability remains a challenge, primarily attributed to its poor solubility in water. Research indicates rapid intestinal and hepatic metabolism, resulting in substantial elimination through the intestines [11,12]. Various strategies have been proposed to address this limitation, including the utilization of formulations such as liposomes, nanoparticles, and micelles, as well as the complexation of curcumin with metals, aiming to enhance its solubility, stability, and overall bioavailability [13–18]. This review endeavors to synthesize extant literature concerning the integration of curcumin into scaffolds utilized for bone repair, with the overarching aim of enhancing their efficacy. Initially, an exhaustive analysis of curcumin's mechanism of action is undertaken, with particular emphasis placed on its impact on the proliferation, differentiation, and migration dynamics of osteoblasts, osteocytes, and osteoclasts, the principal cellular constituents governing bone regeneration. Subsequently, attention is directed towards strategies aimed at bolstering the bioavailability of curcumin within these scaffolds. Moreover, diverse methodologies pertaining to scaffold synthesis are scrutinized, with a focus on augmenting crucial parameters such as cell adhesion, proliferation, biocompatibility, biodegradability, and mechanical strength. Through this comprehensive exploration, the review endeavors to offer insights into the potential synergistic benefits of curcumin-incorporated scaffolds for advancing bone tissue engineering applications.

2. Bone formation mechanisms

Bone tissue undergoes development through two discernible mechanisms: intramembranous ossification and endochondral ossification. In the intricate process of intramembranous bone formation, which primarily manifests in flat bones like those comprising the craniofacial skeleton and the clavicle, a cascade of cellular events orchestrates the transition from undifferentiated pluripotent stem cells to fully functional osteocytes within a mineralized matrix. Commencing with the proliferation of pluripotent stem cells, a critical step ensues as these cells migrate and aggregate, thereby initiating the formation of osteogenic centers. Within these burgeoning aggregates, a milieu conducive to osteogenic differentiation emerges, facilitated by the action of cytokines such as bone morphogenetic proteins (BMPs) which incite the upregulation of Runx2 expression, a pivotal transcription factor driving the commitment of stem cells to the osteoblastic lineage. Subsequent to this priming, osteoblast precursors mature and commence the secretion of osteoids, characterized by their abundant type 1 collagen content, thus laying the groundwork for subsequent mineralization. Concurrently, angiogenesis is stimulated within the mineralized osteoids through the action of angiogenic factors like vascular endothelial growth factor (VEGF), facilitating the ingress of vasculature into the nascent bone tissue. As the extracellular matrix becomes mineralized, osteoblasts become encapsulated within this matrix and undergo terminal differentiation into osteocytes, effectively embedding themselves within the developing bone tissue. Meanwhile, surrounding the mineralized matrix, a cohort of angiogenic stem cells orchestrates the formation of the periosteum membrane, a crucial contributor to bone development and repair. Subsequent to this stage, a dual process ensues, wherein the bone subjacent to the periosteum undergoes compression, culminating in the formation of compact bone, while the osteogenic center, marked by its heightened vascularity, gives rise to cancellous bone, thus completing the intricate orchestration of intramembranous bone formation [19,20].

Endochondral ossification, a fundamental process primarily observed in the development of long bones, constitutes a nuanced cascade of events distinct from its intramembranous counterpart. Commencing with the compression of stem cells, a pivotal departure from intramembranous ossification emerges as these cells undergo initial differentiation into chondrocytes, thus initiating the formation of a cartilaginous template. Orchestrated by a repertoire of signaling molecules including transforming growth factor-beta (TGF-β) and bone morphogenetic proteins (BMPs), stem cells within the developing cartilage undergo a coordinated upregulation of SOX9 expression, instigating their aggregation and subsequent differentiation into chondrocytes. The perichondrium, a specialized membrane enveloping the cartilage, assumes a pivotal role in this process, fostering the proliferation of chondrocytes within localized regions through the release of parathyroid hormone-related protein (PTHrP) and facilitating the secretion of type II collagen, thereby contributing to the expanding cartilaginous matrix. Concomitantly, the orchestrated action of factors like fibroblast growth factor (FGF) serves to arrest the growth of chondrocytes at the center of these aggregations, promoting their hypertrophy and the secretion of a distinct matrix enriched in type X collagen and calcium phosphate granules, pivotal precursors for the subsequent formation of apatite crystals. At the periphery of these hypertrophic zones, a dynamic interplay ensues, culminating in the differentiation of perichondrial cells into osteoblasts, thereby initiating the formation of the bone collar, a precursor to the ossification process. Concurrently, hypertrophic chondrocytes secrete angiogenic factors, instigating the invasion of blood vessels from the perichondrium into the

developing bone matrix, ultimately establishing a highly vascularized ossification center. As hypertrophic chondrocytes undergo programmed cell death, the ensuing resorption paves the way for the invasion of osteoblasts, precipitating the formation of the primary spongiosa, an intermediate tissue bridging the gap between cartilage and bone. In parallel, at the extremities of long bones, secondary ossification centers emerge, characterized by heightened osteogenic activity and vascular ingrowth. Meanwhile, the intervening region delineated by the primary and secondary ossification centers assumes the guise of the growth plate, serving as a reservoir for longitudinal growth during the postnatal period. Thus, the intricate orchestration of endochondral ossification underpins the foundational architecture of long bones, epitomizing the exquisite interplay between cellular signaling, matrix remodeling, and vascular ingrowth in skeletal development [19–21].

3. Challenges and innovations in addressing defects in bone regeneration

Bone possesses an intrinsic ability to undergo regeneration following injury, a process intricately orchestrated by a cascade of biological events mediated through molecular pathways involving diverse cellular component [22,23]. Predominantly observed during fractures, bone regeneration mirrors the embryonic pathways of bone formation, encompassing both intramembranous and endochondral ossification. Notably, unlike many other tissues, bone injuries typically heal without the formation of scar tissue, resulting in seamless integration with surrounding undamaged bone [24,25]. However, in a subset of cases such as severe fractures or certain surgical procedures involving extensive bone defects, the natural capacity for self-healing may prove insufficient, necessitating interventions to augment bone regeneration beyond its intrinsic capabilities.

At present, a variety of therapeutic interventions exist for the treatment of this particular medical condition. Among these options, surgical interventions utilizing autograft or allograft bone tissues emerge as potential courses of action. Autologous bone grafting involves the extraction of bone tissue from another anatomical site within the same patient, representing the gold standard approach in treatment modalities. This method stands out as the most efficacious means of bone regeneration, eliciting differentiation of local stem cells without provoking an immune reaction. Despite demonstrating a relatively favorable success rate, its applicability is circumscribed by constraints such as the finite availability of autologous grafts and attendant complications at the donor site [26,27]. In instances where autologous bone resources are limited, allografts or even xenografts may serve as viable alternatives. Allografts, sourced from donors, present an alternative to autograft deployment; however, they exhibit diminished integration with the host bone and may engender immune-mediated rejection and pathogen transmission risks [26,28]. Xenograft bone substitutes, derived from non-human species, were first introduced utilizing bovine bones in 1957. Although offering osteoconductive properties at a lower cost, xenografts bear the caveat of potential transmission of animal-borne diseases [29,30]. Notably, contemporary treatment strategies have embraced the induction membrane technique, notably the Masquelet technique, for addressing substantial bone defects. Comprising a two-phase process, this approach involves initial debridement of soft tissue and bone, followed by insertion of a polymethyl methacrylate (PMMA) cement spacer, secured with an external fixator, to impede fibrous tissue infiltration into the defect. Subsequently, the surrounding membrane fosters vascular proliferation within the bone graft. After a designated interval of 6–8 weeks, the induced membrane is meticulously incised, the spacer extracted, and cancellous bone from the iliac crest implanted, with subsequent closure of the membrane utilizing primary fixation. Despite the promise of this method, attendant side effects necessitate thorough investigation and optimization of surgical protocols for its optimal utilization [31].

Numerous contemporary approaches to bone regeneration yield outcomes of reasonable efficacy. Nonetheless, inherent drawbacks and constraints impede their widespread application, coupled with contentious findings concerning their efficacy and cost-efficiency. Moreover, the absence of heterologous or synthetic bone substitutes possessing comparable biological and mechanical attributes to native bone compounds the challenge. Consequently, in pursuit of surmounting these hurdles, a longstanding objective, there arises a pressing imperative to innovate novel therapeutics as either substitutes or adjuncts to conventional bone regeneration modalities [27].

4. Biological properties of curcumin in tissue engineering

In the contemporary scientific landscape, a burgeoning body of research has unveiled a myriad of pharmacological potentials inherent in curcumin, the bioactive compound found in turmeric. Of particular intrigue is its burgeoning application within the realm of regenerative medicine, where a surge of interest has coalesced around its therapeutic efficacy. While much of the current investigative fervor revolves around its capacity to facilitate wound healing, the multifaceted attributes of curcumin, including its antioxidative, anti-inflammatory, antimicrobial, and anti-apoptotic properties, have engendered an expansive exploration into its utility across diverse tissue repair modalities. This burgeoning interest underscores a promising avenue for further inquiry into the therapeutic potential of curcumin within the broader scope of regenerative medicine [6,7].

Numerous investigations have elucidated the antioxidant properties inherent in curcumin. This compound demonstrates a capacity to afford cytoprotective benefits against oxidative stress induced by H2O2 within fibroblast cells, primarily through its ability to scavenge reactive oxygen species [7]. Moreover, curcumin manifests its antioxidant prowess by not only neutralizing these reactive entities but also by instigating an up-regulation of antioxidant proteins [32,33]. Its multifaceted action has been documented to counteract diverse forms of physiological damage, including but not limited to hepatic, cerebral, and renal impairment, hyperglycemia, lipid peroxidation, inflammatory processes, and oxidative stress within biological systems [34,35].

The extensive exploration of curcumin's capacities as an inhibitor of inflammatory cytokines has yielded rich insights. Numerous mechanisms underpinning its anti-inflammatory actions have been proposed, chief among them being its purported ability to mitigate oxidative stress and inflammation in chronic pathologies through modulation of the Nrf2-keap1 signaling cascade [36,37]. Furthermore, curcumin exhibits a remarkable capability to dampen pro-inflammatory pathways implicated across a spectrum of chronic

diseases, concurrently attenuating the production of tumor necrosis factor (TNF) and impeding TNF-mediated cell signaling in various cellular contexts [38]. Notably, curcumin's impact extends to the reduction of interleukin release via its scavenging of endogenous free radicals, thereby curtailing the amplitude of immune responses orchestrated by NF-κB [39,40].

The multifaceted realm of curcumin's antibacterial efficacy has been meticulously examined, revealing intricate interplays with the protein FtsZ, instrumental in orchestrating bacterial cell division. FtsZ, a cytoskeletal protein analogous in function to eukaryotic tubulin yet divergent in structural composition, assumes a pivotal role in the intricate choreography of cellular division. Studies elucidate that curcumin's impact on bacterial proliferation extends beyond mere inhibition, intricately altering the dynamics of FtsZ-mediated cellular processes. By intricately modulating the assembly dynamics of cellular division machinery orchestrated by FtsZ, curcumin intervenes at a molecular level, impeding the seamless progression of bacterial cell division and thus underscoring its significance as a potential agent in combating bacterial infections [41,42].

5. Curcumin effects on bone cells

5.1. Osteocyte

5.1.1. Apoptosis inhibition

Osteocytes constitute the predominant cellular population within bone tissue, thereby underscoring their critical role in maintaining bone health through the secretion of signaling molecules and cytokines [43]. Apoptosis of osteocytes emerges as a significant contributor to bone cell demise and diminished osteocyte viability, particularly evident in individuals afflicted with glucocorticoid-induced osteonecrosis [44,45]. Inflammation emerges as a key instigator of osteocyte apoptosis, with pro-inflammatory cytokines disrupting bone homeostasis and triggering osteocyte cell death [46]. Notably, specific phenotypes of macrophages serve as primary sources of proinflammatory cytokines, with the ability to transition between pro-inflammatory (M1) and anti-inflammatory (M2) states under certain conditions [47]. Investigations highlight a notable proportion of femoral head macrophages in patients with glucocorticoid-induced osteonecrosis adopting the M1 phenotype, thereby escalating the secretion of pro-inflammatory mediators such as TNF-a and IL-1b. Jin et al. demonstrated that dietary supplementation of curcumin in a murine model of glucocorticoid-induced osteonecrosis attenuated the inflammatory response by impeding the transition of macrophages to the M1 phenotype. Furthermore, cellular studies have elucidated curcumin's ability to mitigate macrophage polarization towards the M1 phenotype and suppress inflammation via the JAK-STAT pathway. Consequently, curcumin emerges as a promising anti-inflammatory agent in the management of glucocorticoid-induced osteonecrosis, concurrently alleviating osteocyte apoptosis within the femoral head [48].

5.2. Osteoblast

5.2.1. Apoptosis inhibition

Apoptosis of osteoblasts assumes a pivotal role in both bone development and maintenance, as well as in the pathogenesis of conditions such as osteoporosis and steroid-induced sexual dysfunction [49]. Numerous investigations have implicated oxidative stress in these pathological contexts, elucidating its role in impeding osteoblast differentiation, proliferation, and ultimately triggering apoptosis. Consequently, mitigating osteoblast apoptosis instigated by oxidative stress emerges as a crucial determinant in averting or postponing the decline in bone density observed in osteoporosis [50,51]. Curcumin has been demonstrated to attenuate apoptosis induced by oxidative stress in osteoblasts, potentially attributed to its modulation of mitochondrial function and activation of the Akt/GSK3β pathway [52]. Mitochondria, recognized as principal sites of reactive oxygen species (ROS) production, assume a central role in orchestrating osteoblast apoptosis through ROS-mediated damage [53]. Akt, a pivotal kinase regulating cell proliferation, exerts its anti-apoptotic effects by phosphorylating and inactivating GSK3β. Conversely, GSK3β activation, facilitated by oxidative stress, promotes apoptosis by activating caspase3 and facilitating the release of cytochrome C from mitochondria [52].

Possessing anti-inflammatory and immune-modulatory properties, glucocorticoids are commonly employed in the management of numerous autoimmune disorders. Nonetheless, prolonged administration of these medications is associated with a decline in bone mineral density and bone strength [54,55]. Curcumin exhibits significant protective effects against dexamethasone-induced apoptosis in osteoblasts and ameliorates osteoporosis both in vitro and in vivo by modulating apoptotic proteins such as Bax and Bcl2, as well as the ERK pathway. The activation of ERK signaling is crucial for cell viability, characterized by the phosphorylation and nuclear translocation of ERK1/2 to initiate downstream processes [56].

Previous research has demonstrated that varying doses of curcumin exert notable effects as apoptotic or necrotic agents in osteoblast cells, with this mechanism intricately regulated by intracellular ATP levels. Enhanced energy reserves prompt apoptosis, whereas diminished energy reserves precipitate necrosis. Specifically, doses ranging from 12.5 to 25 μM of curcumin trigger apoptosis in osteoblasts through the generation of reactive oxygen species (ROS), the activation of JNK signaling, and subsequent induction of mitochondrial membrane depolarization and caspase activation. In contrast, exposure to higher concentrations of curcumin, ranging from 50 to 200 μM, diminishes intracellular ATP levels, directing the cells towards the necrotic pathway [57].

Additional investigations have indicated that lower concentrations of curcumin hinder osteoblast proliferation. Moran et al. observed that at a dose of 10 μM, curcumin suppressed both the proliferation and mineralization of osteoblasts by downregulating the expression of inducible nitric oxide synthase (iNOS) and reducing nitric oxide (NO) production. Nitric oxide, synthesized by NOS through the catalysis of L-arginine, plays pivotal roles in various physiological systems including the nervous, cardiovascular, and immune systems. It has been proposed that NO, either directly or by inducing the production of prostaglandin E2 (PGE2), promotes

osteoblast proliferation, and serves as a signaling molecule involved in extracellular matrix (ECM) maturation and osteoblast differentiation [58]. Moreover, Notoya et al. demonstrated that curcumin at doses ranging from 5 to 10 μM arrests rat calvarial osteoblastic cells (ROB) in the G1 phase of the cell cycle by upregulating the expression of p21WAF1/CIP1, thus impeding their proliferation. Collectively, these investigations underscore the significance of curcumin in modulating both apoptosis and proliferation in osteoblast cells, with the specific effects contingent upon the administered dose [59]. The mechanisms underlying curcumin's role in mitigating apoptosis in osteocyte and osteoblast cells are elucidated in Fig. 1.

5.2.2. Differentiation stimulation

Bone marrow harbors multipotent mesenchymal stem cells (MSCs), which have garnered considerable attention in the realm of tissue engineering [60,61]. Studies have elucidated the pivotal role of curcumin in orchestrating the differentiation of MSCs into osteoblasts and their subsequent mineralization. MSCs possess the capacity to differentiate into both osteoblasts and adipocytes, with factors promoting adipocyte accumulation ultimately culminating in decreased bone density [62,63]. Notably, upregulation of the expression and enzymatic activity of heme oxygenase-1 (HO-1) has been identified as pivotal in guiding the differentiation of bone marrow mesenchymal stem cells (BMSCs) towards osteoblast lineage. Curcumin demonstrates the ability to augment osteoblast differentiation from MSCs while concurrently suppressing adipocyte differentiation by enhancing HO-1 expression [64]. Additionally, curcumin exerts regulatory effects on endoplasmic reticulum stress-associated genes, such as ATF6, by upregulating the expression of Runx2 in C3H10T1/2 osteoblasts in a time and concentration-dependent manner. Augmented expression of these genes fosters the upregulation of osteoblast differentiation-related genes, including osteocalcin [9].

Oxidative stress poses a significant impediment to osteoblast differentiation, proliferation, and may induce apoptosis. Among the key regulatory elements implicated in apoptosis, inflammation, and oxidative stress-related disorders is glycogen synthase kinase-3 beta (GSK3β). Notably, GSK3β diminishes the expression of Erythroid-derived 2-like 2 (Nrf2), a transcription factor crucial for

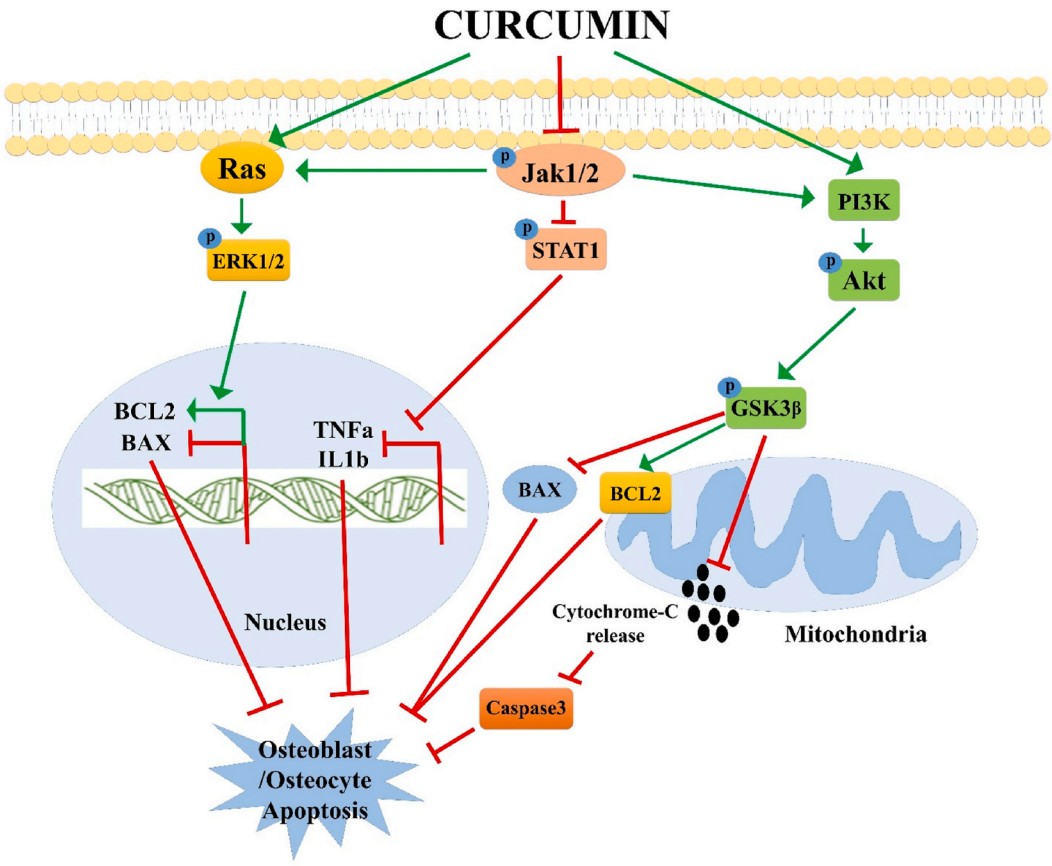

Fig. 1. The mechanisms underlying curcumin's role in mitigating apoptosis in osteocyte and osteoblast cells can be delineated as follows: Firstly, curcumin exerts its effects by suppressing the expression of inflammatory genes IL-1b and TNF-a via the JAK-STAT pathway. Secondly, curcumin mitigates oxidative stress-induced apoptosis in osteoblasts by activating the Akt/GSK3β pathway. Activation of Akt results in the phosphorylation and subsequent inactivation of GSK3β, which in turn impedes apoptosis induction by activating caspase3 and facilitating the release of cytochrome C from the mitochondria. Thirdly, curcumin shields osteoblasts from apoptosis through activation of the ERK pathway, leading to increased expression of pro-apoptotic protein Bax and decreased expression of anti-apoptotic protein Bcl2. Green arrows signify pathway activation, while red arrows denote pathway suppression mediated by curcumin.

orchestrating the expression of antioxidant-related genes [65]. Li et al. demonstrated that curcumin possesses the capacity to promote the differentiation of MC3T3-E1 cells into osteoblasts by activating the GSK3β/Nrf2 pathway under conditions of oxidative stress [8].

The Wnt/β-catenin signaling pathway stands as a pivotal regulatory axis governing the growth, development, and maintenance of bone tissue [66]. Wang et al. elucidated that curcumin exhibits the capacity to safeguard the viability and foster osteogenic differentiation of human adipose-derived mesenchymal stem cells (hADMSCs) against oxidative stress induced by H2O2 at low concentrations. Their findings underscored curcumin's role in mitigating oxidative stress by upregulating the expression of proteins within the Wnt/β-catenin signaling pathway [10]. Furthermore, curcumin demonstrates efficacy in attenuating glucocorticoid-induced osteoporosis through the activation of the Wnt/β-catenin pathway [67,68]. The mechanisms through which curcumin facilitates the differentiation of mesenchymal cells into osteoblasts are depicted in Fig. 2.

5.3. Osteoclast

5.3.1. Stimulation of apoptosis

Osteoclasts, essential for bone resorption and the maintenance of bone homeostasis, represent a crucial cellular component [69]. Multiple signaling pathways, notably the AP-1 and NF-κB pathways, intricately regulate osteoclast viability. AP-1, an Activator Protein-1 transcription factor, governs a spectrum of cellular processes encompassing apoptosis, proliferation, and differentiation. Similarly, Nuclear Factor-Kappa B (NF-κB) acts as another pivotal transcription factor, modulating diverse cellular processes such as inflammation, immune response, and cell survival. Activation of both the AP-1 and NF-κB pathways is instrumental in promoting osteoclast survival, underscoring their significance in bone physiology. Consequently, targeting these pathways holds promise as a

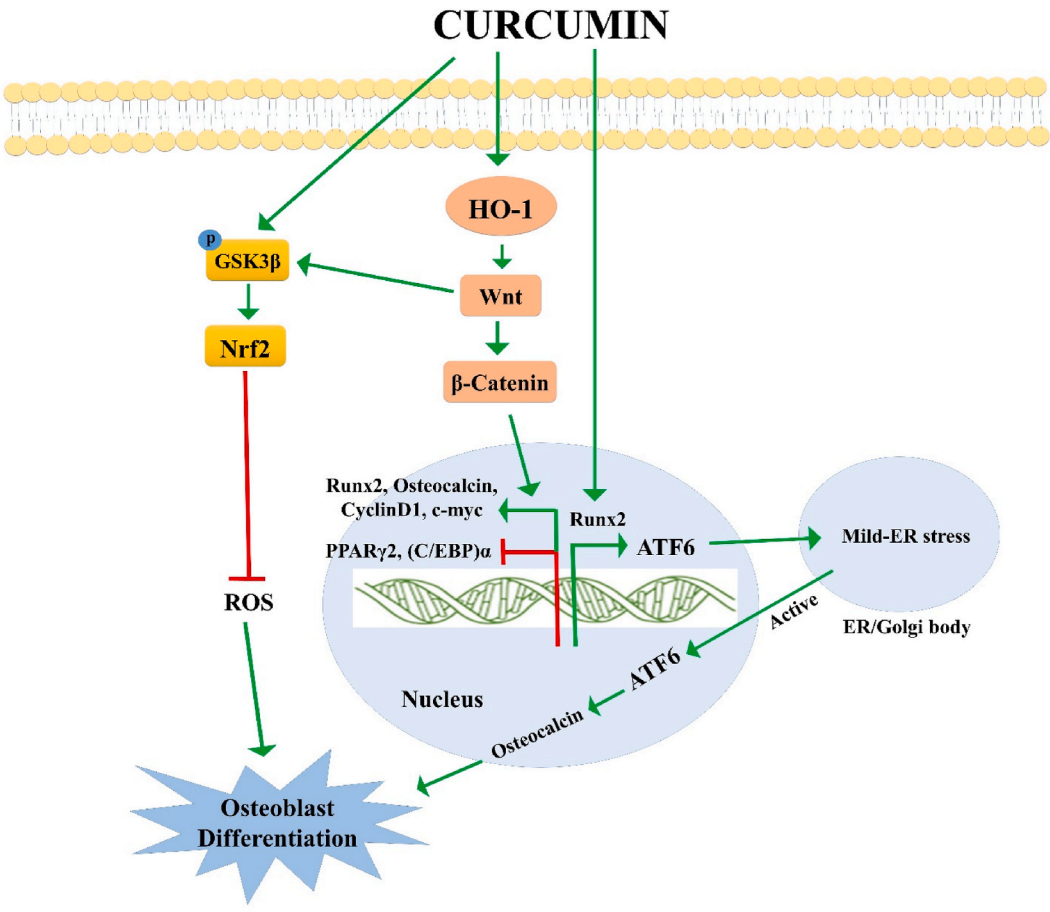

Fig. 2. The mechanisms by which curcumin facilitates the differentiation of mesenchymal cells into osteoblasts are multifaceted: Firstly, curcumin enhances osteoblast differentiation from mesenchymal stem cells (MSC) while concurrently suppressing adipocyte differentiation by upregulating the expression of heme oxygenase-1 (HO-1). Secondly, curcumin modulates the expression of endoplasmic reticulum stress-related genes, such as ATF6, within osteoblasts by elevating the expression of Runx2. Augmented expression of these genes culminates in heightened expression of osteoblast differentiation-related genes, including osteocalcin. Thirdly, under conditions of oxidative damage, curcumin prompts osteoblast differentiation by activating the GSK3β/Nrf2 pathway and scavenging reactive oxygen species (ROS). Lastly, curcumin mitigates oxidative stress and fosters osteoblast differentiation by augmenting the expression of proteins within the Wnt/β-catenin signaling pathway. Green arrows signify pathway activation, while red arrows denote pathway suppression mediated by curcumin.

potential therapeutic strategy for addressing bone disorders characterized by excessive bone resorption [70,71].

Osteoclast apoptosis serves as a critical regulatory mechanism in maintaining bone homeostasis, as excessive osteoclast activity can precipitate bone loss and osteoporosis. Numerous investigations have highlighted curcumin's capacity to induce osteoclast apoptosis through diverse signaling pathways implicated in cell survival. Several studies have underscored curcumin's potential as a stimulator of apoptosis in osteoclasts, demonstrating its ability to hinder the expression of transcription factors such as NFkB and AP-1 in a manner contingent upon both dosage and duration [72,73].

5.3.2. *Inhibition of differentiation*

Bone undergoes continual remodeling, characterized by the removal of old or damaged bone tissue and its replacement with new bone. This dynamic process is meticulously regulated to maintain a delicate balance between bone formation and resorption. Any disruption in this equilibrium can precipitate the onset of bone-related ailments such as rheumatoid arthritis and osteoporosis [74,75]. Osteoporosis, a debilitating condition, is marked by a decrease in bone mineral density (BMD) and an elevated risk of fractures, commonly afflicting elderly individuals, particularly women. Bisphosphonates represent a widely employed therapeutic intervention aimed at mitigating bone damage and fracture risk. Nonetheless, prolonged administration of these drugs is associated with severe complications, including jaw osteonecrosis [76].

Osteoclasts represent large, specialized cells unique to bone tissue, arising from hematopoietic precursor cells [77]. Their

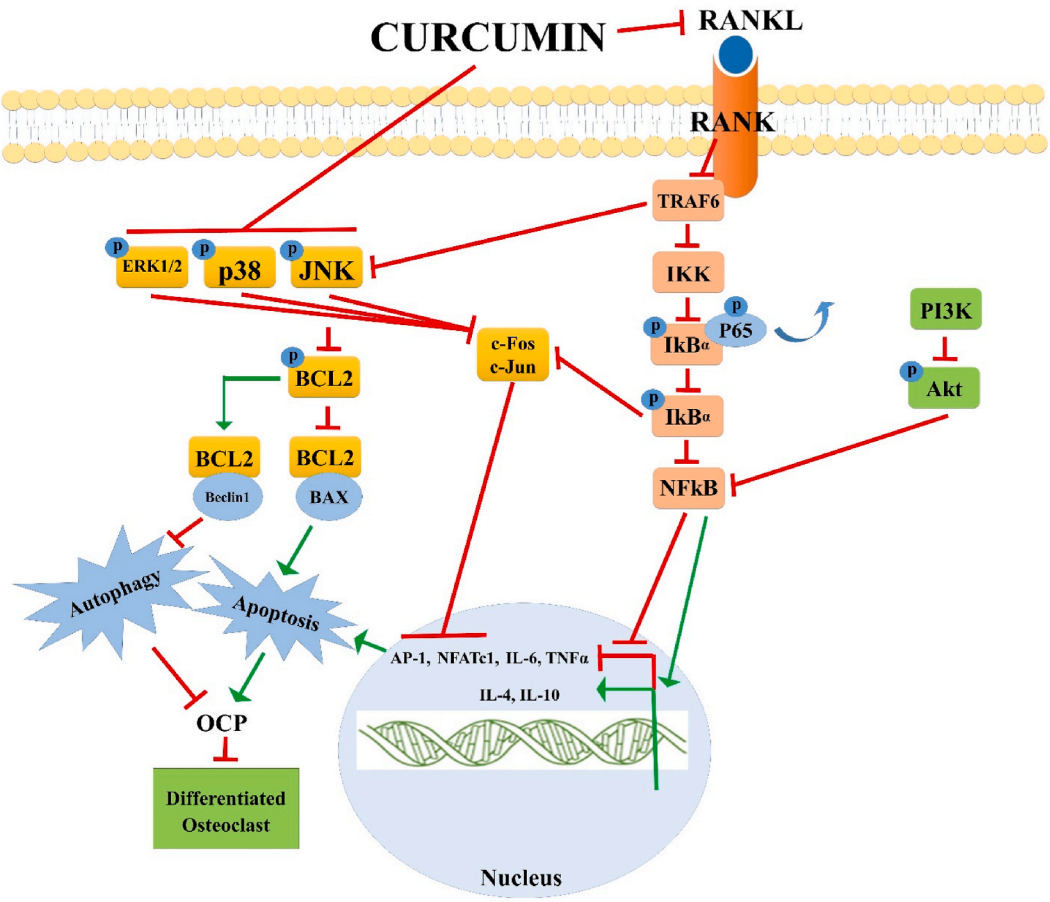

Fig. 3. Curcumin employs various mechanisms to induce apoptosis and impede osteoclast cell differentiation. Firstly, it prompts apoptosis in osteoclasts by inhibiting the expression of transcription factors AP-1 and NF-κB. Secondly, curcumin diminishes NF-κB activity, thereby curtailing RANKL-induced osteoclastogenesis. Thirdly, it suppresses osteoclastogenesis by reducing the expression of the dimeric transcription factor AP-1 (composed of c-Fos and c-Jun). Additionally, curcumin attenuates the activity of IkB kinase (IKK) via the RANKL pathway, resulting in decreased IkBα activity and subsequently reduced osteoclastogenesis. Moreover, curcumin hampers osteoclast precursor cell (OCP) differentiation and autophagy through modulation of the RANK/TRAF6/JNK/BCL2/Beclin1 signaling pathway, while inducing apoptosis in OCP cells by hindering the interaction between BAX and BCL2. Furthermore, curcumin inhibits osteoclastogenesis by phosphorylating components of the MAPK signaling pathway (ERK1/2, p38, and JNK), thereby reducing the expression of c-Fos and NFATc1. Lastly, it prevents osteoclastogenesis by suppressing the Akt pathway and decreasing NF-κB expression, consequently augmenting the expression of anti-inflammatory genes IL-4 and IL-10 while diminishing pro-inflammatory genes IL-6 and TNFa, as well as the NFATc1 gene. Green arrows signify pathway activation, while red arrows denote pathway suppression mediated by curcumin.

differentiation is governed by two receptor activators: NF-kB (RANKL) and macrophage-colony stimulating factor (M-CSF). RANKL engages its receptor, RANK, a pivotal mediator of bone resorption essential for osteoclast maturation. Activation of this pathway triggers the activation of several regulatory transcription factors, including AP-1 and NF-kB, orchestrating the differentiation, activation, and survival of osteoclasts [78,79]. AP-1, a dimeric transcription factor comprising c-Fos and c-Jun subunits, plays a pivotal role in regulating the expression of specific osteoclast genes. Notably, curcumin has emerged as a potent inhibitor of AP-1, capable of impeding osteoclastogenesis by downregulating the expression of c-Fos and c-Jun in diabetic bone marrow cells [80].

Curcumin exhibits the capability to mitigate NF-kB activity and RANKL-induced osteoclastogenesis [81]. Free radicals serve as vital secondary messengers and regulators within signal transduction pathways. In the context of bone remodeling, intracellular reactive oxygen species (ROS) induced by RANKL activation contribute to pathway stimulation, thereby augmenting osteoclast activity, survival, and differentiation [82]. Moon et al. demonstrated curcumin's efficacy as a suppressor of RANKL-induced osteoclastogenesis, attributing this effect to its ability to attenuate intracellular ROS production and reduce IkBα activity [83]. Furthermore, curcumin hampers osteoclast differentiation by curtailing NFkB activity and inhibiting IkB phosphorylation, chiefly through the suppression of IkB kinase (IKK) in a dose-dependent manner [84].

Autophagy stands as a profoundly conserved cellular safeguarding mechanism crucial for osteoclastogenesis and bone resorption [85]. A wealth of studies has elucidated curcumin's role as an autophagy regulator across diverse cultured cell types. For instance, Ke et al. demonstrated curcumin's capacity to inhibit autophagy and the differentiation of osteoclast progenitor cells by modulating the autophagy-signaling pathway RANK/TRAF6/JNK/BCL2/Beclin1 [86].

NFATc1 emerges as a pivotal transcription factor expressed in osteoclast progenitor cells in response to RANKL stimulation mediated by calcium ion oscillations, MAPKs, c-Fos, and RAN [87,88]. Curcumin exhibits a capacity to diminish the osteoclastogenic potential of peripheral blood mononuclear cells (PBMCs) sourced from rheumatoid arthritis (RA) patients by phosphorylating ERK1/2, p38, and JNK, components of the MAPK signaling pathway, while concurrently suppressing the expression of c-Fos and NFATc1 [89]. Additionally, Yang et al. elucidated the protective effect of curcumin against osteoclastogenesis in macrophages treated with titanium nanoparticles, attributing this effect to the downregulation of Akt expression and its downstream transcription factor, NFATc1 [90]. The mechanisms underlying curcumin's induction of apoptosis and inhibition of osteoclast cell differentiation are delineated in Fig. 3.

5.3.3. Inhibition of migration

The migration and mobilization of osteoclast precursor cells (OCP) are pivotal processes in osteoclast fusion and differentiation, orchestrated in part by various chemokines such as CCL2, CCL3, and CX3CL1 [91]. Liang et al. conducted a study revealing curcumin's inhibitory effect specifically on the production of CCL3, while leaving CCL2 and CX3CL1 unaffected in osteoclast cells. Interestingly, they found that despite curcumin's presence, the inhibition of OCP migration and the reduction in CCL3 production had minimal impact, even in the face of heightened expression of the CCL3 receptor (CCR1) through lentivirus transduction. Prior research has indicated that RANKL stimulation prompts the production of CCL3, a factor pivotal in early cellular differentiation. However, Liang et al. provided evidence suggesting that curcumin dampened CCL3 production in OCPs both in the presence and absence of RANK [92].

5.3.3.1. Dual target of developing osteoblast survival and osteosarcoma prevention. Osteosarcoma represents a primary malignant bone cancer characterized by a notably high fatality rate among children and adolescents [93]. While tumor removal stands as a common therapeutic approach, its efficacy is hindered by the persistence of untreated tumor cells within bone lesions, consequently fostering cancer recurrence and metastasis [94]. Addressing the imperative to impede tumor resurgence during bone defect reconstruction underscores the importance of developing a biomaterial with anticancer properties capable of effectively filling bone defects. Curcumin has emerged for its robust anticancer activity against various tumor types [95], demonstrating the capacity to impede tumor progression and induce cellular apoptosis by modulating diverse cellular and molecular pathways. Moreover, curcumin exhibits biocompatibility across a wide dosage range with normal cells due to its minimal nonspecific toxicity. In a study by Chang et al., osteosarcoma cells displayed significantly greater cytotoxicity to curcumin compared to normal human osteoblast cells, particularly highlighting its selective elimination of bone cancer cells within the concentration range of 5–25 μM [96].

Zhang et al. investigated the anti-cancer properties of curcumin when immobilized on TiO2 nanorods, aiming to eradicate residual tumor cells while ensuring acceptable biocompatibility to facilitate the growth of natural bone tissue. Their study revealed that MG63 cells cultured on TiO2 and TiO2/pDA/pCD substrates maintained their native morphologies, whereas the introduction of curcumin to TiO2/pDA/pCD/curcumin (CUR) notably reduced cell numbers and induced morphological changes. While the precise mechanism of curcumin-induced apoptosis in cancer cells remains elusive, evidence suggests the involvement of free radicals. Curcumin has been observed to trigger ROS production in tumor cells, ultimately inducing apoptosis through the mitochondrial-dependent pathway. Given its potential as an adaptable biomaterial for impeding osteosarcoma growth, biocompatibility stands as a crucial requirement alongside its anti-tumor effects. Zhang and colleagues demonstrated that curcumin-containing synthesized substrates facilitated the proliferation of MC3T3-E1 cells in a manner dependent on both time and concentration, while maintaining their typical phenotype. Notably, the study's use of a high concentration of curcumin (1.6 mg/ml) significantly impacted cell morphology and proliferation rates. Upon evaluating morphological alterations in normal and tumor cells post-curcumin treatment, it was concluded that curcumin exhibited a preference for eliminating sarcoma cells over osteoblast cells, possibly attributed to its preferential absorption by cancerous cells owing to differences in membrane structure, protein composition, and tumor cell content. This selective absorption mitigates adverse effects on normal cells [97].

Table 1
Curcumin-loaded scaffolds in bone regeneration.

Scaffold synthesis method	Bioactive molecule	Scaffold	Stage/Model	Results	References
Electrospinning	Curcumin powder	PCL nanofiber	In vitro/MC3T3-E1 mouse pre-osteoblasts	The scaffold containing 1 % CU compared to that containing 5 % CU increased the adhesion, proliferation, and differentiation of osteoblasts.	[102]
	graphene oxide (GO) and Zn-Curcumin complex (Zn-CUR)	Core-shell nanofibers	In vitro/MG63 osteoblastic cells	Nanofibers containing the Zn-CUR complex increase the adhesion, proliferation, biocompatibility, and differentiation of osteoblasts.	[17]
	Curcumin powder	poly (3-hydroxybutyrate)/ poly (ι-lactic acid) nanofibers (PHB/PLLA)	In vitro/Adipose-derived stem cells	The combination of curcumin with the PHB/PLLA nanofibers improved the differentiation, adhesion, and biocompatibility of ADSCs.	[103]
	Curcumin powder	Hydroxyapatite–gelatin nanofibers	In vitro/*Staphylococcus aureus*, *Escherichia coli*, and Streptococcus mutans	Microbial evaluation of the curcumin-containing composite showed significant antimicrobial effects.	[104]
	Curcumin powder and aspirin nanoparticles	Asymmetric membrane	In vitro/*Staphylococcus aureus* (*S. aureus*), *Escherichia coli* (*E. coli*) and *Enterococcus faecalis* (*E. faecalis*) In vivo/adult mongrel dogs	Microbial evaluation of the composite containing curcumin showed significant antimicrobial effects. The presence of curcumin in the asymmetric membrane not only improved osteogenesis and new bone formation at the lesion site for 28 days but also had significant anti-inflammatory properties.	[105]
	Curcumin powder	poly (3-hydroxybutyrate) (P3HB)-multiwalled carbon nanotubes (MCNTs)	In vitro/Synovial mesenchymal stem cells (SMSCs) In vivo/male Sprague-Dawley rats	The addition of up to 20 wt% curcumin to the scaffolds significantly increased their mechanical properties. It showed excellent biocompatibility and adhesion to SMSCs. In addition, curcumin strongly reduced the inflammatory response after eight weeks of in vivo implantation.	[106]
	MCNTs and CUR	P3HB	In vitro/Mesenchymal stem cells (MSCs) In vivo/rat animal model	The fabricated scaffold containing curcumin showed biocompatibility, proliferation, differentiation, and excellent adhesion of MSCs compared with curcumin-free scaffolds. Moreover, curcumin strongly reduced inflammatory reactions in tissues.	[107]
3D printer	Curcumin-encapsulated liposomes	3D printed tricalcium phosphate (CaP)	In vitro/Human osteosarcoma cell line (MG-63) and Human fetal osteoblast cell (hFOB) line	Scaffolds containing curcumin increased the adhesion, proliferation, survival, and differentiation of osteoblasts.	[16]
	Curcumin-PCL-PEG	3D printed scaffolds	In vitro/Human osteoblast cell line hFOB In vivo/Sprague-Dawley rats	The presence of curcumin in the scaffold caused a significant increase in the survival, proliferation, and differentiation of osteoblasts and increased bone formation after 6 weeks. It also showed anti-inflammatory, antioxidant, and tissue biocompatibility properties compared to those of curcumin-free scaffolds.	[13]
	Curcumin powder	HA/β-TCP/PCL	In vitro/BMSCs In vivo/Male Sprague-Dawley rats	The fabricated scaffolds containing curcumin showed excellent biocompatibility, proliferation, differentiation, and migration of osteoblast cells compared to curcumin-free scaffolds. In addition, it is tissue-compatible and has the ability to induce ossification and	[108]

(*continued on next page*)

Table 1 (*continued*)

Scaffold synthesis method	Bioactive molecule	Scaffold	Stage/Model	Results	References
				migration of BMSCs to the bone defect site.	
Freeze drying	Curcumin loaded PLGA microspheres	Fish collagen/nano-hydroxyapatite	In vitro/bone marrow mesenchymal stem cells of type 2 diabetic rat model	The release of curcumin from composite scaffolds reduced the negative effects of diabetic serum on proliferation, migration, and osteogenic differentiation of BMSCs compared to curcumin-free scaffolds.	[15]
	Curcumin powder	Collagen-hydroxyapatite (COL-HA)	In vitro/Synovial membrane mesenchymal stem cells (SM-MSCs) In vivo/Male Sprague-Dawley rats	Five and 10 %wt showed a significant increase in the mechanical strength. They also showed excellent biocompatibility and improved survival and differentiation of mesenchymal cells. In addition, it is tissue biocompatible and has anti-inflammatory properties.	[109]
	Curcumin powder	Chitosan, cellulose nanocrystals, and halloysite nanotubes (CS/CNC/HNT)	In vitro/NIH3T3 fibroblast cells In vitro: *E. coli* and *S. aureus*	The nanocomposite scaffold containing curcumin exhibited acceptable cell proliferation and antibacterial properties.	[14]
	Curcumin and MWCNTs	Type I Collagen	In vitro/synovial membrane mesenchymal stem cells (SM-MSCs) In vivo/Male Sprague-Dawley rats	Ten wt% curcumin-loaded scaffolds showed better mechanical properties than scaffolds containing 5 and 15 wt% curcumin. This scaffold is superior in terms of biocompatibility, cell adhesion, proliferation, and differentiation. Moreover, it exhibited tissue biocompatibility and greatly reduced the inflammatory reaction after 6 weeks of in vivo implantation.	[110]
Hydrogel	Curcumin coated iron oxide nanoparticles	Hyaluronic acid hydrogel	In vitro/Bone marrow stem cells	Scaffolds containing curcumin increased cell adhesion and proliferation of BMSCs.	[111]
	TiO2 and curcumin	Bovine femur ECM hydrogel	In vitro/ADMSCs	The curcumin-loaded composite scaffold promoted the biocompatibility, proliferation, and differentiation of ADMSCs. In addition, it is tissue compatible and has the ability to create osteogenic cells.	[112]
Powder metallurgy techniques	Curcumin/ β-cyclodextrin comlex	Biphasic calcium phosphate (BCP)	In vitro In vivo/male Wistar rats	The presence of curcumin in the scaffold induced proliferation and differentiation of osteoblasts and increased the density of bone minerals.	[18]
	Curcumin Spiroborate Ester	Hydroxyapatite/β-Tri calcium phosphate (HA/β-TCP)	In vitro/L929 fibroblasts In vitro/*Staphylococcus aureus* and *Escherichia coli*	Antibacterial evaluation showed superiority against the studied bacteria in the scaffold containing curcumin and excellent biocompatibility, cell adhesion, and proliferation of mouse fibroblast cells.	[113]
	Curcumin nanoparticles	Type I collagen, demineralized bone matrix, olive leaves extract	In vitro/Osteoblast cell line (MG-63)	The incorporation of curcumin into the composite increased its mechanical properties. In addition, it showed biocompatibility and proliferation of osteoblasts.	[100]
	Zn2+–curcumin complex	a fluoride doped hydroxyapatite matrix	In vitro/Human fetal osteoblast (hFOB 1.19 and Human osteosarcoma cell line (MG-63) In vitro/*S. aureus*	Curcumin increased the proliferation and survival of normal osteoblasts and inhibited osteosarcoma cells by four times compared to the curcumin-free group. Moreover, curcumin exhibits significant antibacterial properties.	[98]

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Table 1 (*continued*)

Scaffold synthesis method	Bioactive molecule	Scaffold	Stage/Model	Results	References
Precipitation/Co-precipitation	Curcumin powder	d-MWCNT-SrHAP	In vitro/human osteoblast-like MG-63 cells	The curcumin-loaded composite increased biocompatibility, proliferation, and differentiation of osteoblasts.	[114]
	Curcumin powder	calcium polyphosphate composite	In vitro/MC3T3-E1 cells	The curcumin-containing composite exhibited significant antioxidant properties and promoted cell proliferation and differentiation.	[115]
	Curcumin powder	Low quaternized Chitosan-hydroxyapatite (LQC-HAP) High quaternized Chitosan-hydroxyapatite (HQC-HAP)	In vitro/Human osteoblast-like MG-63 cells	Composites containing curcumin were biocompatible and enhanced the proliferation and differentiation of osteoblasts.	[116]
	Curcumin powder	Chitosan/hydroxyapatite (CS/HA)	In vitro/MG63	The curcumin-containing scaffolds showed excellent biocompatibility and osteoblast proliferation.	[117]
	Curcumin powder	Hydroxyapatite (HA) and polylactic acid (PLA)	Synthesis and charactrization	Curcumin increased the mineralization and nucleation of apatite crystals in the composites.	[118]
Casting	Curcumin powder	Hydroxyapatite/cellulose nanofibers	In vitro/*Escherichia coli* (*E. coli*) and *Staphylococcus aureus* (*S. aureus*) In vitro/HOS MG63 cells	Curcumin-containing scaffolds exhibited better mechanical properties than curcumin-free scaffolds. In addition, it has demonstrated biocompatibility, cell survival, and antibacterial properties.	[119]
	hydroxyapatite nanoparticles (nHA) and curcumin	Poly (glycerol sebacate urethane)s (PGSU)	In vitro/mouse fibroblast L929 cells In vitro: *P. aeruginosa* & *S. aureus*	Scaffolds loaded with curcumin exhibit better mechanical properties than curcumin-free scaffolds. It also improved the survival and differentiation of fibroblasts and exhibited significant antimicrobial activity.	[120]
Hydrothermal method	Curcumin-Modified TiO2 Nanorods	TiO2/pDA/pCD/CUR constructs	In vitro/MG-63 cells. In vivo/Osteosarcoma nude mice	Scaffolds containing curcumin supported the attachment and proliferation of osteoblasts.	[97]
Template method	Curcumin powder	Mesoporous calcium silicate	In vitro/hMSCs	The composites showed better biocompatibility, morphology, migration, and anti-inflammatory properties after addition of curcumin at a higher dose of 10 mg/ml. A lower dose of curcumin (2 mg/ml) increased cell proliferation.	[121]

6. Bioavailability increase of curcumin in bone scaffolds

Curcumin, a polyphenolic compound renowned for its diverse health advantages, including anti-inflammatory and antioxidant properties, faces challenges in maximizing its therapeutic potential due to its limited bioavailability resulting from rapid metabolism in the liver and intestines [11,12]. To address this limitation, several strategies have been devised to enhance curcumin's bioavailability. One approach involves the utilization of formulations aimed at improving its stability and solubility, such as liposomes, nanoparticles, or micelles. Alternatively, combining or complexing curcumin with various compounds or metals has been explored to augment its absorption and bioavailability. These strategies represent promising avenues for enhancing the efficacy of curcumin-based therapeutics [13–18].

In order to harness the therapeutic potential of curcumin in bone regeneration, Sedghi et al. engineered a nanofiber incorporating a zinc-curcumin complex to enhance curcumin's bioavailability. Their findings demonstrated that fibroblast cells exhibited enhanced adhesion to nanofibers containing Zn-CUR compared to drug-free scaffolds. Moreover, proliferation and mineralization of osteoblasts were notably increased within the drug-loaded scaffolds. Additionally, Zn-CUR-infused nanofibers exhibited concentration and time-dependent antibacterial activity against *S. aureus* and *E. coli* bacteria [17]. In a separate investigation by Bhattacharjee et al., this complex was integrated into fluoride-doped disks, resulting in a 2.5-fold increase in curcumin release. This scaffold not only sustained the viability of normal osteoblast cells but also induced apoptosis in osteosarcoma cells compared to controls. Furthermore, the antibacterial efficacy of the scaffold against *S. aureus* was augmented due to the presence of zinc and curcumin [98]. Truite et al. explored a different approach by complexing curcumin with beta-cyclodextrin to enhance its bioavailability. Beta-cyclodextrins, characterized by hydrophobic ring-shaped oligosaccharides, possess a hydrophobic cavity capable of forming complexes with

fat-soluble molecules like curcumin, thereby improving its pharmacological properties and facilitating controlled release to enhance its biological effects [18].

Another category of approaches involves utilizing formulations such as liposomes, nanoparticles, micelles, and coatings to enhance the solubility and stability of curcumin. Among these, liposomes stand out as one of the most prevalent, extensively studied, and promising drug delivery systems. Liposomes, spherical vesicles composed of biocompatible, biodegradable, and non-toxic phospholipids, exhibit highly efficient drug delivery capabilities, enhancing cellular absorption and promoting drug release at the target site. These nano-sized vesicles have the capacity to encapsulate both hydrophilic and hydrophobic drugs [99]. Sarkar et al. employed a liposomal nanocarrier to encapsulate curcumin, integrating it into a 3D calcium phosphate scaffold. Their findings demonstrated that this scaffold exerted significant toxicity against osteosarcoma cells while fostering the survival and proliferation of healthy bone osteoblasts [16]. Similarly, Doustdar et al. utilized a halloysite nanotube delivery system to incorporate curcumin into a chitosan/nanocellulose composite. Their results indicated that curcumin release from the scaffold occurred in a controlled manner over an extended period, and the addition of curcumin to this nanocomposite enhanced the adhesion and proliferation of fibroblast cells compared to other groups [14]. Furthermore, Senthil et al. investigated the use of curcumin nanoparticles within a collagen/demineralized bone matrix and olive bark extract composite. This biocomposite exhibited excellent mechanical properties suitable for bone scaffold applications, along with favorable biocompatibility with osteoblast cell lines and notable antibacterial activity [100].

Polymer coatings represent another class of materials explored to enhance the bioavailability of curcumin. Bose et al. employed water-soluble polymers like PEG alongside biocompatible and biodegradable polymers such as PCL or PLGA to mitigate tissue absorption, rapid metabolism, and achieve controlled and stable delivery of curcumin. Their study demonstrated that a hydroxyapatite matrix containing the PEG/PCL/PLGA/CUR polymer system could sustain curcumin release over 22 days, showcasing high viability in human normal osteoblast cells and promoting bone formation after a six-week period [13]. Additionally, Li et al. synthesized a curcumin-containing PLGA microsphere-loaded collagen/nanohydroxyapatite scaffold for bone tissue engineering. Utilizing PLGA microspheres known for their stability, low cytotoxicity, and high encapsulation efficiency for hydrophobic drugs, their scaffold achieved controlled curcumin release for 30 days. The released curcumin effectively countered the overproduction of ROS in mesenchymal cells cultured in diabetic serum, enhancing their proliferation, differentiation, and migration [15]. Moreover, Nogueira et al. employed a sulfated polysaccharide, kappa-carrageenan, to fabricate curcumin nanoparticles, derived naturally from certain types of red seaweed and resembling some ECM components like sulfated glycosaminoglycans. Their research demonstrated the non-toxicity of these nanoparticles to osteoblast cells at concentrations exceeding 1 μM, along with their ability to upregulate bone-related genes [101]. Nonetheless, while these studies underscore the potential of curcumin-based formulations in bone tissue engineering, further investigation is warranted to comprehensively assess their efficacy and safety for clinical applications.

6.1. *Curcumin-loaded scaffolds*

Every day, a multitude of surgeries are conducted globally to alter or restore damaged tissues. The field of tissue engineering has emerged with the aim of repairing injured tissues or fostering the regeneration of new ones. Various scaffolds composed of diverse biomaterials have been engineered using synthetic approaches to reconstruct various tissues and organs. Curcumin has garnered attention for its potential in treating damaged tissues, particularly in wound healing [6]. Several scaffolds incorporating curcumin have been developed for medical and tissue engineering applications. The advancement of controlled and targeted drug delivery methods for curcumin to specific tissues or organs holds significant importance. Various techniques have been explored for constructing bone tissue engineering scaffolds, including electrospinning, 3D scaffolds, freeze-drying, and hydrogels, all of which have been investigated for curcumin delivery purposes (see Table 1).

Electrospinning has emerged as a widely utilized technique due to its simplicity, adaptability, and capacity to fabricate diverse nanofibers [6,7,122]. Three-dimensional (3D) nanofiber scaffolds closely mimic the structural characteristics of the extracellular matrix found in bone tissue. The architecture of these nanofibers has demonstrated the ability to stimulate the differentiation of progenitor cells into osteogenic lineage cells, even in the absence of specific bone-inducing factors. Incorporating curcumin into electrospun scaffolds has been explored to enhance bone healing outcomes. Jain et al. developed polycaprolactone (PCL) nanofibers loaded with curcumin, demonstrating successful entrapment of the drug within the fibers. This scaffold exhibited sustained release kinetics, with approximately 60 % of the curcumin released over a span of 9 days. Furthermore, a scaffold containing a 1 % curcumin concentration demonstrated enhanced cell viability, osteogenic differentiation, and mineralization in pre-osteoblast cells compared to control counterparts [102].

It is imperative for polymer scaffolds to possess a spectrum of properties including cell adhesion, proliferation, biocompatibility, biodegradability, and mechanical strength. However, individual polymers often lack some of these critical attributes, prompting researchers to combine multiple polymers to attain desired outcomes. Core-shell nanofibers synthesized via coaxial electrospinning offer a versatile platform for integrating diverse polymers and bioactive materials tailored for tissue engineering applications. Sedghi et al. engineered core-shell nanofiber scaffolds incorporating a zinc-curcumin complex and graphene oxide as bioactive components, revealing that Zn-CUR nanofibers exhibited superior cell adhesion, proliferation, and osteogenic activity compared to blank nanofibers. The incorporation of Zn-CUR conferred antibacterial properties against *S. aureus* and *E. coli*, promising a reduction in infection rates [17]. Despite variations in cell wall composition, multiple studies have elucidated the primary mechanism by which curcumin eradicates *S. aureus* and *E. coli*, attributed to its interaction with bacterial membranes. This interaction, likely facilitated by curcumin's phenolic groups, induces membrane instability, culminating in bacterial cell death [41,123].

Biopolymers synthesized by bacteria, such as poly (3-hydroxybutyrate) (P3HB), present a promising option for fabricating 3D scaffolds in tissue engineering due to their biocompatibility, excellent solubility in organic solvents, and facile conversion into

extracellular matrix (ECM)-like fibers through electrospinning. However, their application in hard tissue engineering advancements is constrained by their insufficient mechanical strength [124,125]. To address this limitation, Tanideh et al. augmented the mechanical and biological properties of electrospun nanofiber scaffolds by incorporating multi-walled carbon nanotubes (MCNTs) into P3HB. Additionally, they loaded curcumin, serving as an anti-inflammatory agent, into the scaffold to mitigate inflammatory reactions. Integration of 20%wt of curcumin into the scaffold resulted in enhanced mechanical properties, bioactivity, biodegradability, in vitro and in vivo biocompatibility, and notably, a reduction in inflammatory response [106].

One challenge reported with bone grafts is the migration of fibroblasts to the fracture site, which can impede efficient angiogenesis and hinder osteoblast growth by forming a fibrous capsule, ultimately resulting in non-union. Guided bone regeneration (GBR) techniques employing a barrier membrane offer a solution by preventing rapid fibrous capsule migration, thereby promoting osteoblast retention at the defect site and creating an inner surface conducive to bone absorption and regeneration [90]. Ghavimi et al. developed an asymmetric GBR membrane loaded with aspirin and curcumin through electrospinning with a collagen polymer. These nanofibers demonstrated antibacterial activity against *S. aureus*, *E. coli*, and *E. faecalis*. The inclusion of curcumin in the asymmetric membrane prompted the differentiation of dental pulp stem cells into osteogenic cells. Animal studies revealed that the scaffold effectively filled the defect with new bone within approximately a month [105].

Three-dimensional printed scaffolds offer unique advantages, including precise control over pore shape, connectivity, and chemical composition, rendering them highly suitable for bone graft substitutes. The interconnected pores facilitate crucial processes such as nutrient transfer, continuous growth, vascularization, and waste removal. Moreover, 3D printing stands out as the sole technique capable of producing an accurate structure mirroring the defect in the patient's bone [126,127]. Sarkar et al. devised a calcium phosphate 3D scaffold infused with liposome-encapsulated curcumin. The released curcumin demonstrated dual effects on both healthy and cancerous bone cells, exhibiting substantial toxicity against human osteosarcoma cells while promoting proliferation and survival in human fetal osteoblast (hFOB) cells. Furthermore, the curcumin-loaded 3D scaffold enhanced the osteogenic differentiation of stem cells. The multifaceted action of this scaffold against cancerous and normal cells presents a promising avenue for addressing bone defects following tumor removal [16].

The precise differentiation of stem cells stands as a pivotal initial stage in osteogenesis, prompting the exploration of bone defect tissue engineering's potential with BMSCs possessing multi-lineage differentiation and self-renewal capabilities. Previous research has delved into transcription factors like PPAR-γ and Runx2, along with the biological and pathological components pivotal for stem cell differentiation [128,129]. However, recent investigations have unveiled alterations in glucose absorption as an alternative pathway for osteoblast differentiation and the stimulation of bone remodeling. Glucose transporter 1 (GLUT1), a key mediator of glucose absorption, has emerged as a crucial player, with reduced Glut1 expression and low glucose absorption inhibiting the expression of osteogenic differentiation genes such as alkaline phosphatase (ALP), osteopontin (OPN), and osteocalcin (OCN) [130]. GLUT1 serves as an upstream marker for RUNX2 and partakes in osteoblast differentiation and bone regeneration. The regulation of GLUT channels is governed by specific lipid rafts, with cholesterol being the most significant. Wei et al. engineered a 3D HA/b-TCP/PCL scaffold loaded with gelatin microspheres containing curcumin, capable of triggering the Cho/LR sensor and GLUT1 activation while preserving cholesterol's spatial structure. Enhanced glucose absorption consequently activates the osteogenic differentiation marker RUNX2, substantiated by increased expression of osteogenic markers like Runx2, Alp, Col1-1a, Opn, and Ocn [108].

Type 2 diabetes, characterized by impaired carbohydrate metabolism due to insulin resistance or insufficiency, often presents with aberrant bone remodeling and an increased susceptibility to fractures compared to non-diabetic counterparts [131]. Previous research indicates that heightened levels of free radicals in type 2 diabetes may be primarily responsible for irregular bone formation. Glycated products under diabetic hyperglycemic conditions trigger an immune response and stimulate the mitochondrial electron transport chain, leading to excessive production of free radicals [132]. Elevated oxidative stress results in the degradation of macromolecules like lipids and nucleic acids, apoptosis of MSCs, and hindered osteogenic differentiation [133]. Consequently, mitigating abnormal ROS levels with antioxidants significantly shields MSCs from free radicals and counteracts the adverse effects of type 2 diabetes on bone regeneration. Recent studies highlight curcumin's potent antioxidant properties, increasing HO-1 levels in endothelial microvascular cells and safeguarding human ADMSCs from oxidative damage, thereby enhancing proliferation and osteogenic differentiation [129]. Li et al. showcased that functionalizing a chitosan-hydroxyapatite (CHA) scaffold with curcumin-loaded microspheres notably reduced free radical production in BMSCs treated with diabetic media, enhancing their proliferation, migration, and osteogenic differentiation. Moreover, curcumin release from the scaffold substantially upregulated Nrf2 and HO-1 expression in BMSCs treated with diabetic media. The Keap1/Nrf2/HO1 signaling pathway plays a pivotal role in cellular defense against oxidative stress, with Keap1 sequestering Nrf2 in the cytoplasm under basal conditions. However, in the presence of free radicals, Nrf2 dissociates from Keap1, inducing the expression of antioxidant genes such as HO-1 [15].

Hydrogel scaffolds have garnered significant attention in bone tissue engineering due to their unique characteristics, such as high water content, biocompatibility, and adjustable mechanical properties. These scaffolds, composed of polymeric chains in a three-dimensional structure, possess the ability to retain large amounts of water, mimicking the extracellular matrix (ECM) found in natural organs. In bone tissue engineering applications, hydrogel scaffolds offer a conducive environment for cellular growth, differentiation, and tissue formation. Their mechanical properties can be tailored to match those of natural bone, crucial for effective tissue regeneration. Additionally, hydrogel scaffolds can be functionalized with bioactive molecules to enhance cell adhesion, proliferation, and differentiation [134,135]. Amirazad et al. demonstrated that a hydrogel scaffold derived from demineralized and decellularized bovine femur, loaded with TiO2 and curcumin, enhanced the viability of ADMSCs compared to the control group. Furthermore, they showed that the combined effects of curcumin and TiO2 promoted the expression of bone differentiation markers in cultured cells under both normal and osteogenic conditions [112].

Angiogenesis, the formation of new capillaries, is crucial for the metabolic activity of active tissues and is driven by growth factors

such as vascular endothelial growth factor (VEGF). In the realm of bone tissue engineering, angiogenesis plays a vital role in tissue repair [136]. Curcumin demonstrates a dual role in angiogenesis; while it has been shown to possess anti-angiogenic properties in cancer treatment, it also exhibits the ability to enhance neovascularization in anticancer wound healing. Specifically, curcumin has been found to boost VEGF secretion in endothelial progenitor cells, thereby promoting blood vessel formation [137–140]. Daya et al. demonstrated that a hyaluronic acid hydrogel scaffold incorporating curcumin-coated magnetic nanoparticles elicited a significantly higher concentration of VEGF secretion from BMSCs compared to other groups. This scaffold thus facilitates adequate nutrition and oxygen supply for the formation of new bone tissue, supporting the flow of nutrients and removal of waste products [111].

7. Conclusion

This review endeavors to comprehensively assess the diverse range of studies that have explored the multifaceted properties of curcumin, encompassing its anti-inflammatory, antioxidant, antimicrobial, and angiogenic effects, within the context of bone tissue. Accumulating evidence suggests that curcumin holds significant promise in enhancing and preserving bone tissue health. Specifically, curcumin has been found to facilitate the proliferation and differentiation of osteoblasts by modulating various signaling pathways, thereby promoting bone formation and regeneration. Moreover, curcumin demonstrates the capacity to impede the proliferation, differentiation, and migration of osteoclasts, crucial in preventing excessive bone resorption and maintaining bone density. Through its multifunctional properties, curcumin emerges as a potential therapeutic agent for addressing various aspects of bone tissue homeostasis and pathology.

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Data availability statement

The authors confirm that the data supporting the findings of this study are available within the article.

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