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Review

Bioactivity and Delivery Strategies of Phytochemical Compounds in Bone Tissue Regeneration

Anna Valentino [1,2,†], Francesca Di Cristo [3,†], Michela Bosetti [1], Amal Amaghnouje [4], Dalila Bousta [4], Raffaele Conte [5,*] and Anna Calarco [2,*]

1 Dipartimento di Scienze del Farmaco, Università del Piemonte Orientale "A. Avogadro", Largo Donegani, 2, 28100 Novara, Italy; anna.valentino@uniupo.it (A.V.); michela.bosetti@uniupo.it (M.B.)
2 Research Institute on Terrestrial Ecosystems (IRET)-CNR, Via Pietro Castellino 111, 80131 Naples, Italy
3 Elleva Pharma S.R.L. via Pietro Castellino 111, 80131 Naples, Italy; francesca.dicristo@ellevapharma.com
4 Laboratory of Biotechnology, Environment, Agrifood, and Health, University of Sidi Mohamed Ben Abdellah, 30000 Fez, Morocco; Amal.amaghnouje@usmba.ac.ma (A.A.); Boustadalila@usmba.ac.ma (D.B.)
5 AMES Group Polydiagnostic Center, via Padre Carmine Fico, 24, 80013 Casalnuovo di Napoli, Italy
* Correspondence: raffaele.conte86@tiscali.it (R.C.); anna.calarco@cnr.it (A.C.)
† These authors contributed equally to this work.

Abstract: Plant-derived secondary metabolites represent a reservoir of phytochemicals for regenerative medicine application because of their varied assortment of biological properties including anti-oxidant, anti-inflammatory, antibacterial, and tissue remodeling properties. In addition, bioactive phytochemicals can be easily available, are often more cost-effective in large-scale industrialization, and can be better tolerated compared to conventional treatments mitigating the long-lasting side effects of synthetic compounds. Unfortunately, their poor bioavailability and lack of long-term stability limit their clinical impact. Nanotechnology-based delivery systems can overcome these limitations increasing bioactive molecules' local effectiveness with reduction of the possible side effects on healthy bone. This review explores new and promising strategies in the area of delivery systems with particular emphasis on solutions that enhance bioavailability and/or health effects of plant-derived phytochemicals such as resveratrol, quercetin, epigallocatechin-3-gallate, and curcumin in bone tissue regeneration.

Keywords: bone regeneration; phyto-bioactive compounds; molecular signaling pathways; bone-devices

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1. Introduction

Bone defect, due to traumatic injury, congenital disease, or tumor resection, represents a severe ailment affecting millions of people. However, bone regeneration is a complex and dynamic process that involves several actors including osteoprogenitor cells that respond to intracellular and extracellular molecular signaling pathways to ensure bone functional recovery [1,2]. Although the bone tissue is capable of self-repair and renew, regenerative medicine approaches are essential to promote and speed up the healing of bone defects recovering the normal and healthy function of the skeletal system [3]. The conventionally therapeutic approaches have demonstrated a limited efficacy due, for example, to graft rejection, pathogen transmission, and invasive surgical procedures [4]. Owing to the drawbacks and limitations of many bone grafts, bioactive materials that integrate various delivery vehicles, bioactive molecules, stem cells, or demineralized bone matrix may help bone repair creating microenvironments that favor and guide bone regeneration [5,6]. An engineering bone substitute should operate as a proper template for new bone ingrowth showing osteogenic properties (osteoinductive and/or osteoconductive) and being biocompatible with the host tissue. In the last decades, the nanotechnological approach has made great strides in the design of materials able to mimic the natural characteristics of the bone. To improve bone formation/regeneration, phytochemicals such as curcumin,

resveratrol, oleuropein, quercetin, etc., have often been incorporated into biomaterials as a natural and non-toxic therapeutic alternative to traditional treatments [7,8]. Phytobioactive substances, defined as non-nutritive plant secondary metabolites, could interact with enzymes, proteins, and membrane receptors modulating cell-signal transduction cascade and specific molecular pathways leading to bone anabolic effects and decreasing bone resorption [9,10]. In addition, epidemiological studies have reported a correlation between a diet rich in biologically active factors such as fruits, vegetables, and olive oil and the reduced risk of bone loss and bone-related trauma [11,12]. However, these compounds present in vivo limited biological activity, lack long-term stability, and are subject to oxidation overtime under exposure to oxygen, light, moisture, and heat [13,14]. Therefore, a nanotechnological approach that involves controlled drug delivery systems for natural bioactive molecules could be a solution to avoid invasive procedures and minimize off-target cell behaviors. In addition, these alternative strategies could provide phytochemicals better performance, enhance their low water solubility or very short circulating half-life, improving the functionality and clinical utility [3,15]. This review attempts to summarize the recent works involving delivery systems (i.e., synthetic ceramic, scaffolds, nanoparticles) and phytochemicals to guarantee the protection of natural biomolecules from environmental degradation, to modulate compounds release, and to prolong delivery at localized injury sites. A short chapter on the structure of bone tissue, its functional activities, and the regulatory mechanisms of bone remodeling/regeneration will help in understanding the results discussed.

2. Bone Structure and Function

Bone is a metabolically active tissue with self-healing capability, in constant renewal, adapting its structure to mechanical stimuli, stress, hormonal changes, and repairing structural injuries through a process of remodeling [16]. Bone homeostasis is preserved by the coordinated action between osteoblasts (bone-generating cells derived from mesenchymal stem cells, MSCs) responsible for bone growth and osteoclasts (multinucleated bone-resorbing cells differentiated from the hematopoietic stem) involved in bone resorption [17]. During bone matrix synthesis, first osteoblasts secrete the organic matrix: collagen proteins, mainly collagen type I and non-collagen proteins, such as osteonectin (ON), osteocalcin (OCN), bone sialoprotein (BSPI/II), and osteopontin (OPN), and proteoglycan [18–20]. Secondly, deposition and mineralization of the bone matrix take place through the production of a protein mixing called osteoid that promotes calcium and phosphate adhesion, resulting in the organization and mineralization of new bone [21,22]. Mature osteocytes (derived from MSCs through osteoblastic differentiation) are completely trapped inside the mineralized bone matrix. Due to their strategic location, osteocytes maintain the connections to other osteocytes and osteoblasts and react to several biochemical signaling paths and mechanical stimuli contributing to the regulation of calcium and phosphate homeostasis [23]. When bone resorption should not take place, lining cells avoid direct interface among osteoclasts and bone matrix, playing a significant role in calcium homeostasis and osteoclast differentiation [24–27]. Osteoclasts resorb bone through the release of enzymes and acids capable of dissolving and digesting minerals in the bone, but they also secrete cytokines that affect the activity of surrounding cells inducing mesenchymal stem cells and osteoblasts to initiate osteogenesis in resorption lacuna (remodeling) or another non resorbed site (modeling) [28–30]. The RANKL/RANK/OPG system is a crucial mediator of osteoclastogenesis. In particular, the interaction of RANK with RANKL is required for osteoclast formation, differentiation, activation, and survival. On the contrary, OPG can block RANK/RANKL interaction, thus preventing osteoclast differentiation and activation [31,32]. Irregularities in osteoclastic activity lead to disorders such as osteoporosis and osteopetrosis [33].

3. Bone Regeneration Process

The bone healing process is a complex mechanism of bone regeneration, which involves inflammation, bone production, and bone remodeling phases [34]. Inflammation is usually observed immediately following the fracture at the injury site since tissues swell, bone cells die, and blood vessels break, with consequent formation of hematoma, a source of hematopoietic cells capable of secreting growth factors. The injury to bone leads to the secretion of pro-inflammatory factors like tumor necrosis factor-alpha (TNF-α), bone morphogenetic proteins (BMPs), and interleukins (IL-1, IL-6, IL-11, IL-23). These molecules attract, at the fracture site, macrophages, monocytes, and lymphocytes able to take out damaged necrotic tissue and secrete factors (i.e., vascular endothelial growth factor, VEGF) to stimulate angiogenesis and healing [35]. MSCs migrate to the fracture site and, under BMPs control, start to differentiate into fibroblasts, osteoblasts, and chondroblasts. As a result, chondrogenesis begins to occur, and a fibrocartilaginous callus (also called "soft callus") forms within two weeks. The soft callus undergoes endochondral ossification, which converts fibrocartilaginous callus to bony callus (also identified as "hard callus"). The expression of RANKL promotes further differentiation of chondroblasts, osteoblasts, and osteoclasts [36–38]. Bone regeneration is thinly modulated by several signaling pathways and transcriptional factors. During the early stages of bone healing, the Wnt pathway suppresses the differentiation of mesenchymal stem cells into osteoblasts, while in the later stages it controls the commitment of the undifferentiated cells to the osteoblasts [39]. Notch signaling is another potential pathway with osteoinductive properties. Notch receptors, through their ligand (Jag-1), increase the expression of genes related to osteoblasts as ALP and BSP, inducing osteoclastogenesis [40]. An interesting study demonstrates that the functionalization of titanium implant surface with Jag-1 contributes to the enhancement of osteoblast differentiation, improving osteogenic properties [41]. Indeed, the activation of the Notch pathway leads to an increase of osteogenic differentiation, as highlighted by an upregulation of osteogenic markers, in particular BSP and OCN; bone differentiation proteins as BMP2 and BMP6; and growth/differentiation factor 15 (GDF15) [42]. Several other factors are implicated in bone regeneration processes, such as mitogen-activated protein kinase (MAPK) associated pathways, phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K)/Akt, growth factors as fibroblast growth factors (FGFs), insulin-like growth factors (IGFs), and VEGF [43]. MAPKs pathway takes part in bone formation and bone healing post-fracture through the transduction of signals induced by numerous growth factors or adhesion molecules. The (PI3K)/Akt signaling pathway promotes the expression of OPG, Runx2, *p*-Akt, and BMP-2 proteins, as well as the proliferation, differentiation, and osteogenesis of osteoblasts [44]. Devi and Dixit demonstrated that the release of rh-VEGF, rh-IGF-I from a polylactide-polyglycolide acid membrane and β-tricalcium phosphate bone graft led to better clinical results such as bone pocket reduction and bone filling simultaneously with respect to growth factors used alone [45]. Furthermore, FGF signaling plays a pivotal role in the intramembranous and endochondral signaling pathway regulating process in osteoprogenitor cells [46]. It has been reported that treatment with hydrogel-bFGF after a fracture has a higher rate of mineralization, as well as an upregulation of Runx2 and osteocalcin in mice [47,48]. Normal bone development requires the downregulation of Runx2 to form mature bone [49].

4. Bioactive Phytochemicals and Bone Signaling Pathways

Phyto-bioactive compounds (i.e., polyphenolic compounds, carotenoids, tocopherols, and phytosterols) are defined as natural secondary metabolites available in fruits, vegetables, grains, and other plant-based foods which provide health benefits and reduce the risk of major chronic diseases [50–53]. In addition to health benefits, bioactive molecules of natural origin are being used as prominent alternatives to chemical preservatives and additives [54–56] as well as in the green synthesis of nanomaterials (i.e., graphene nanosheets, gold nanoparticles, etc.) [57–61]. In bone regenerative medicine, their antioxidant and anti-inflammatory beneficial properties can regulate bone regeneration signaling pathways,

offering an innovative potential therapeutic strategy [62]. Notably, phytochemicals target several critical molecular pathways involved in bone metabolism, such as estrogen signaling pathway, MAPK cascade, Wnt/β-catenin, sirtuin 1 (Sirt1), TGF-β/BMP, PI3K/Akt, and adenosine monophosphate protein kinase (AMPK) [63]. These pathways can be split into three main classes based on their activity: anti-inflammatory, antioxidants, and bone cell differentiation activity (Figure 1).

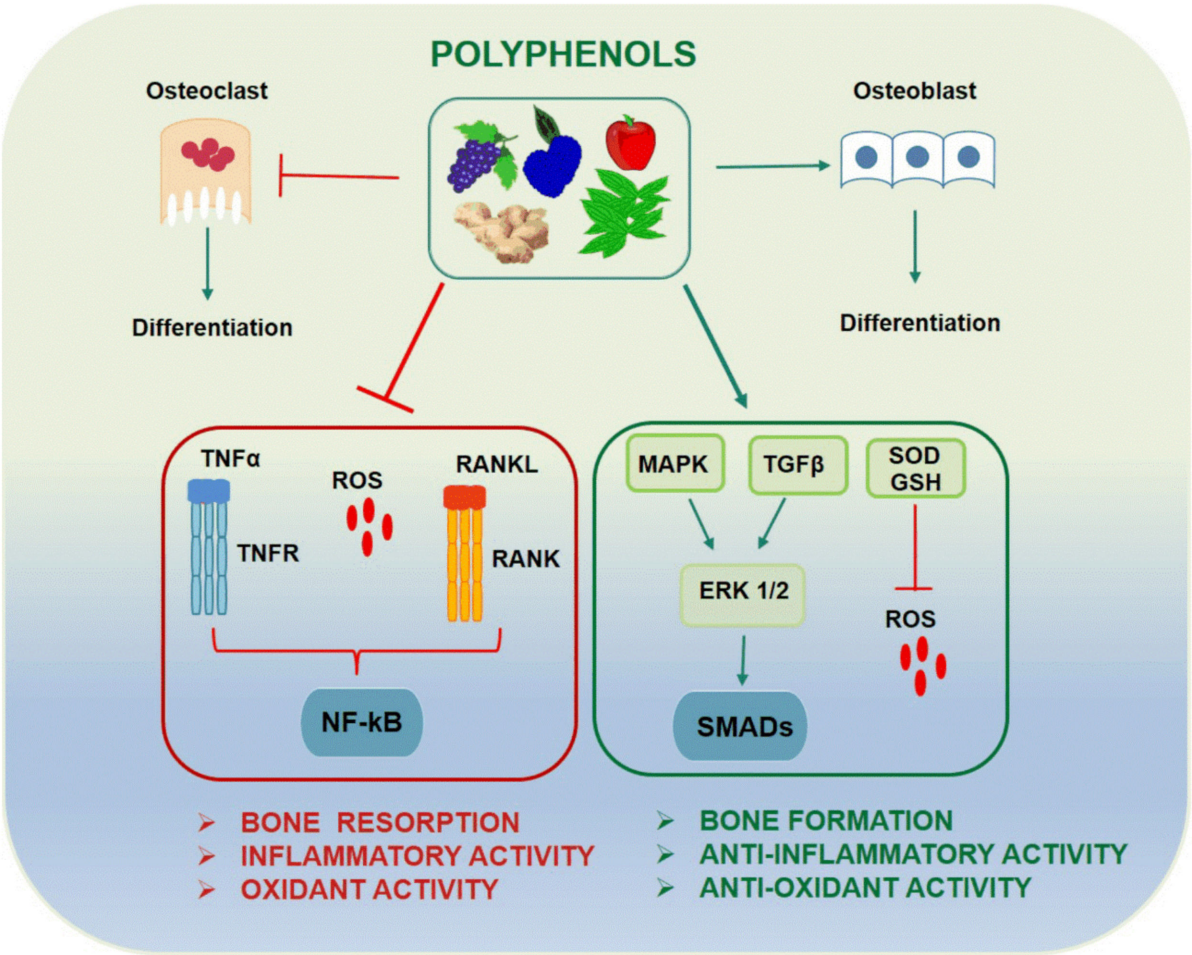

Figure 1. Signaling pathways involved in bone formation (green box) and bone resorption (red box). Polyphenols positively regulate MAPKs/TGFβ/ERK1-2 pathway that activates and translocate Smads complex into the nucleus. Activated Smads regulate the expression of transcriptional factors and coactivators important in osteoblasts differentiation and bone formation process including Dlx5, Runx2, and Osx. Polyphenols also up-regulate genes involved in antioxidant activity such as superoxide dismutase (SOD) and glutathione synthetase (GSH). At the same time, polyphenols down-regulate RANKL and TNFα, two master gene regulators of osteoclasts differentiation and inflammatory pathways, respectively.

4.1. Anti-Inflammatory Activity

The anti-inflammatory activity of phyto-molecules is related to the inhibition of genes expression such as TNF-α, [64] monocyte chemotactic protein (MCP)-1, [65] and matrix metalloproteinases (MMPs) [66], and the decrease of pro-inflammatory molecules, such as IL-6, IL-10, and IL-1β [67–69]. For example, curcumin, an extract from *Curcuma longa*, has been extensively studied due to its ability to inhibit NF-kB and the activation of the activator protein 1 (AP-1) after an inflammatory stimulus [70]. This bioactive molecule suppresses the transcription of pro-inflammatory genes, such as TNFα, IL-6, [64] cyclooxygenase 2 (COX2), and inducible nitric oxide synthase iNOS [71], and contributes to inhibition of MMPs synthesis [72]. Similarly, dried plum polyphenols and tannins indirectly suppress osteoclast differentiation and activity via lowering TNF-α and NO production [73,74] and down-regulating RANKL expression. Epigallocatechin gallate (EGCG),

the most abundant catechin in green tea, exerts an anti-inflammatory effect through MAPKs pathway. Moreover, EGCG reduces the phosphorylation levels of MEK1/2and Raf-1 upstream of ERK1/2 MAPK cascade, [75] promoting bone anabolism, enhancing osteoblasts proliferation, differentiation, and mineralization, and decreasing inflammatory mediators [76,77]. Flavonoids, polyphenols present at relatively low concentrations in most fruit and vegetables, are known as food-based anti-inflammatory agents. Important flavonoids such as quercetin, quercitrin, icaritin, and phloridzin, through downregulation of COX-2 and hypoxia-inducible factor 1-alpha (HIF-1α) pathways, help to reduce the production of prostaglandin E2 (PGE2), [78] exerting anti-inflammatory and antioxidant actions simultaneously [79].

4.2. Antioxidants Activity

Phytochemicals that operate as direct antioxidant substances are able to activate and regulate antioxidant enzymes, with simultaneous action on the inhibition of oxidases, cyclooxygenases, and other enzymes such as iNOS, involved in radical generation [80]. In general, polyphenols, thanks to their B-ring hydroxyl configuration, display a significant antioxidant action that enhances with the increasing of the total number of OH groups and the attendance of the 3,4-catechol structure [81]. By decreasing the oxidative state, bioactive molecules provide for osteoblasts proliferation, activity, and differentiation through the involvement of crucial molecular signaling pathways.

The ROS-scavenging activity is particularly visible in icaritin (a flavonoid isolated from *Epimedium pubescens*), which can reduce superoxide generation in osteoclasts by indirect action on NFATc1 [82] and in naringin, a flavanone with effects on lipid peroxidation, glutathione (GSH) oxidation, and DNA cleavage [83]. Through the same mechanism of action, curcumin and resveratrol (a polyphenolic compound found in grapes and wine) upregulate in the osteoclast the antioxidant enzymes like glutathione peroxidase (Gpx)-1 and superoxide dismutase (SOD), thus modulating ROS levels [84,85]. Curcumin acts on osteoclastogenesis contributing to mitigate bone loss during osteoclast formation and function, preventing ROS and cytokine production. Myricitrin, a glycoside from myricetin, is able to inhibit bone-resorbing cytokines production under oxidative conditions, displaying protective effects against osteoblast cytotoxicity [86]. On the other hand, polyphenols can exert their antioxidant activity through a mechanism of chelation interacting with metals, in particular, Fe and Zn [87,88]. The EGCG shows cytotoxic properties on osteoclasts thanks to its reductive action on Fe (III) catalyzed by the Fenton reaction, leading to hydroxyl radical's generation [89,90].

4.3. Bone Cells Differentiation Activity

Phytomolecules are not only responsible for bone resorption inhibition, but also promote bone formation by aiming at osteoblasts differentiation. For example, EGCG positively acts on osteoblast differentiation and MSC proliferation by upregulating BMP2 and Runx2 expression [91]. Likewise, myricetin can promote osteoblast differentiation and activity, by targeting SMAD-1/5/8, downstream of BMP signaling [92]. It has been demonstrated that myricetin and Baicalin affect osteoblast and osteoclast differentiation and function also through Wnt/β-catenin pathway [93,94]. Additionally, due to structural similarity to mammalian estrogens, some polyphenols can bind estrogen receptors (Ers) that are called phytoestrogens [95]. Among them, vanillic acid upregulates the expression of osteoblastic differentiation markers, i.e., Runx2, OCN, and OPG, by activating ERs pathway [96]. Rutin, instead, downregulates the RUNX suppressor genes [97] and exerts its osteogenic effect through an ER-mediated mechanism [98]. In addition, phyto-derived neurotransmitters such as dopamine, commonly found in fruit and vegetables (in particular bananas), promote VEGF and bFGF expression, leading to enhanced angiogenesis and osteogenesis [99]. Furthermore, several studies have highlighted the crucial role of polyphenols in regulating gene activation or silencing through epigenetic modifications such as DNA methylation and histone modification [100]. Resveratrol is one of the main

activators of Sirt, a known NAD-dependent deacetylase, which induces a conformational change in proteins, translating into an increase in enzymatic activity [101]. Resveratrol induces the MSC differentiation into osteoblasts via a very complex mechanism, which could be direct or indirect. Indirectly, resveratrol, through the interaction of Sirt1 with nuclear receptor co-repressor (NcoR), inhibits peroxisome proliferator-activated receptor gamma (PPARγ) [102], while directly activating RUNX2 transcription factor by forming a Sirt1-Runx2 complex [103]. Resveratrol-mediated activation of Sirt1 enhances phosphorylation of downstream kinases involved in osteoblastic differentiation, such as PKB/Akt, SMAD1/5/8, AMPK, and MAPKs [104,105]. Furthermore, quercetin stimulates osteoblast differentiation through the stimulation of the expression of TGF-β1, BMP-2, and Runx2, via activation of ERK1/2, p38, and JNK MAPKs [106]. Finally, curcumin regulates the expression of genes implicated in RANKL-induced osteoclast differentiation through the suppression of NF-kB [107]. Table 1 recaps the phytochemical-related bone regeneration signaling pathways.

Table 1. Summary of phytochemical signaling pathways for bone regeneration.

Phytochemical	Signaling Pathway	Reference
Curcumin	NF-kB pathways, Redox-sensitive signaling pathways	[75,89,90]
EGCG	MAPKs signaling pathways	[82]
Quercetin	COX2/HIF1αsignaling ERK1-2/MAPKs signaling	[83,84,108]
Resveratrol	Redox-sensitive signaling pathways Sirt/RUNX2 signaling MAPKs pathways	[89,90,109]
Incaritin	NFATc signaling	[87]
Naringin	*Glutathione Pathway (GSH)*	[88]
Myricetin	SMAD/BMP signaling Wnt/β-catenin signaling	[97]
Vanillic acid	ERs pathways	[101]
Rutin	ERs pathways	[102,103]

The cellular responses resulting from the activation of different biological pathways underline the importance of natural bioactive molecules and their ability to modulate inflammatory processes, oxidative stress, and cellular differentiation.

5. Phytochemical-Delivery Vehicles in Bone Tissue Regeneration

To date, the most effective treatment for bone-defect restoration is represented by living tissue transplantation (autologous bone) and/or devitalized donor bone (allograft) because of their notable osteoconductive and osteoinductive properties [108,109]. However, the potential for disease transmission, the limited amount of donor tissue, and postoperative pain at the donor site represent some of drawbacks related to these approaches. To overcome these challenges, new and promising strategies involving delivery systems and phytochemicals have been developed in bone tissue regeneration [110–113]. A successful delivery system should be able to protect phytochemicals from degradation, enhancing their poor bioavailability and minimizing off-target tissue effects [114,115]. These constructs, determining a localized delivery of the natural bioactive molecules, should promote the normal process of bone regeneration and minimize tissue toxicity caused by systemic drug administration (Figure 2) [116].

5.1. Ceramics

Synthetic ceramic materials are inorganic material favorably used in dentistry that proved excellent mechanical properties and osteo-conduciveness owing to their good biocompatibility, reproducibility, non-immunogenicity [117,118]. Ceramic nanocomposites in the form of particles or nanofibers could mimic the hierarchical arrangement of native bone mineral phase, providing a functional scaffold for cell adhesion [119–122], but are

not able to prevent the cause of bone resorption, to control specific anti-osteoclastogenic actions, or to counteract the damage related to oxidative stress. To overcome these disadvantages, polyphenols are widely used to enhance periodontal regeneration or to remineralize bone tissue, due to their antioxidant, free-radical scavenging, and antimicrobial properties [123–125]. The preparation of these composites is often optimized to form nanopores (pore diameter < 0.1 μm) to increase the specific surface area of the scaffolds, allowing for better drug loading and higher bioactivity [125]. For example, Iviglia G et al. patented a polyphenol-based collagen gel with granular ceramic fillers to fill the peri-implant bone defects. Such material, characterized by strong mechanical scaffolding properties, combines the pro-osteogenic action of collagen with the anti-inflammatory, antioxidant, and anti-osteoclastogenic activity of a polyphenolic mixture extracted from the pomace of the *Croatina* grape variety [126]. In vitro and in vivo results demonstrated that both the control of inflammation and oxidative stress and the enhancement of early bone matrix deposition are necessary in the case of oral disease. Cazzola M et al. produced a silica-based bioactive glass coupled with gallic acid and polyphenols extracted from red grape skins and green tea leaves. These modified bioactive glasses showed enhanced free radical scavenging activity [127]. Zhou et al. proposed a simple protocol to functionalize porous calcium phosphate ceramics (PCPC) using dietetic tea polyphenols (TP). TP molecules modulated the nucleation and crystallization of calcium phosphate nanorods and promoted bone mesenchymal stem cell (BMSC) proliferation and differentiation, increasing BMP2, ErK/MAPK, and JNK/MAPK levels and cell mineralization capacity [128].

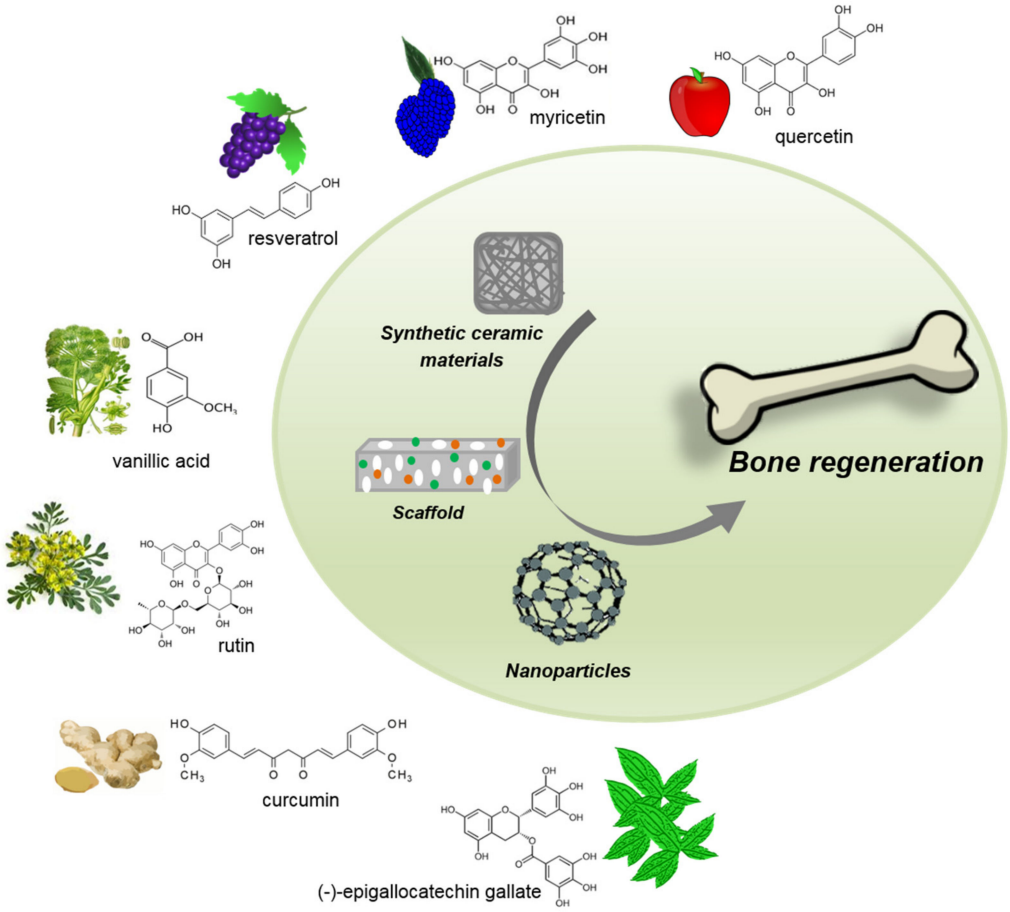

Figure 2. Schematic representation of the main phyto-bioactive nano delivery systems involved in bone regeneration.

5.2. Scaffolds

Since the scaffold surface functionalization with polyphenols increases the bone regeneration capacity, the use of enriched scaffolds is considered a promising tool for bone bioengineering [129–131]. Ideally, a scaffold should mimic the extracellular matrix characteristics of the organ of interest to form cell/tissue-specific combination, pattern/topology, and mechanical properties able to support tissue formation [131]. The combination of scaffolds and phytochemicals is used to improve adhesion, growth, or differentiation of cells through the action of the bioactive compound for which the release can be controlled through three methods. When drugs are incorporated into the matrix of the scaffold, the release kinetics are regulated by the degradation of the polymer. Similarly, when scaffold surfaces are coated with a polymer/drug layer, the release is controlled by diffusion and degradation of the coating polymer. Conversely, the integration of micro-nano spheres into scaffolds offers a third mechanism of release based on the degradation of the scaffold and the consequent diffusion of the particle [132]. For example, Santin M et al. used biodegradable antioxidant scaffolds based on soybean (SB), as bone filler. This material showed an in vitro block of osteoclast activation succeeding incubation with SB, with a parallel inhibitory effect on monocyte/macrophage activity and an improved ability to induce mineralization in osteoblasts [133]. In another study, the SB granules implanted in rabbits led to bone repair with distinctive morphology from non-treated defects [134].

Wang W et al. produced scaffolds loaded with resveratrol by grafting the polyphenol to polyacrylic acid (PAA) and integrating this molecular drug into atelocollagen (Coll) hydrogels (Coll/PAA-RSV) [135]. These scaffolds supported the growth of chondrocytes and BMSCs protecting cells against reactive oxygen species. Moreover, the in vivo implantation on rabbits led to the disappearance of osteochondral defects and the integration of the newly formed tissue with surrounding tissue and subchondral bone. Li et al. functionalized a poly-ε-caprolactone (PCL) surface with resveratrol, obtaining an osteogenic porous material. The presence of polyphenol on a scaffold surface increases the mineralization in stromal cells with an improvement in bone regenerating capacity [136]. Kamath MS et al. formulated a porous composite scaffold integrating PLC with resveratrol-loaded albumin nanoparticles. This 3D material produced a significant increment in cell proliferation, ALP activity, and mineralization imparting osteogenic properties to PCL scaffold [137]. Riccitiello et al. synthesized a PLA electrospinning membrane able to release resveratrol in a tunable manner for the preservation of the alveolar socket after tooth extraction. The controlled release of resveratrol influenced in vitro osteoblast and osteoclast differentiation [138]. In another work, the resveratrol released form PLA membrane presents a significant antibacterial and antibiofilm activity versus *Pseudomonas aeruginosa* and *Streptococcus mutans*, becoming a promising solution for the prevention of implant-associated infections [51]. For cranio-facial tissue-engineering applications, Wang et al. combine a collagen scaffold loaded with resveratrol with human adipose stem cells (hASCs). This composite promotes epidermal wound healing and bone mineralization [139]. Wang et al. introduced dopamine (D) onto strontium-doped calcium polyphosphate (SCPP) scaffolds with silk fibroin (SF). SCPP/D/SF stimulated angiogenic factor secretion, osteogenesis, and had great biocompatibility (Figure 3). Then, SCPP/D/SF could fulfill a role as a potential scaffold for bone tissue engineering with the ability to speed up bone regeneration and vascularization. (Figure 4) [140]. Dhand et al. reported the synthesis by electrospinning of bone-like composite structures containing catecholamines and Ca(2+). Human fetal osteoblasts seeded on these collagen scaffolds exhibited enhanced cell adhesion, penetration, proliferation, and differentiation as well as increased osteogenic expression of osteocalcin, osteopontin, and bone matrix elements [141]. Lee et al. reported an easy, multifunctional surface modification using catechin to enhance the polymeric scaffolds functionality for bone regeneration by stem cells. These catechin-functionalized polymer nanofiber scaffolds, in a critical-sized calvarial bone defect, markedly supported bone formation by hADSC transplantation [142].

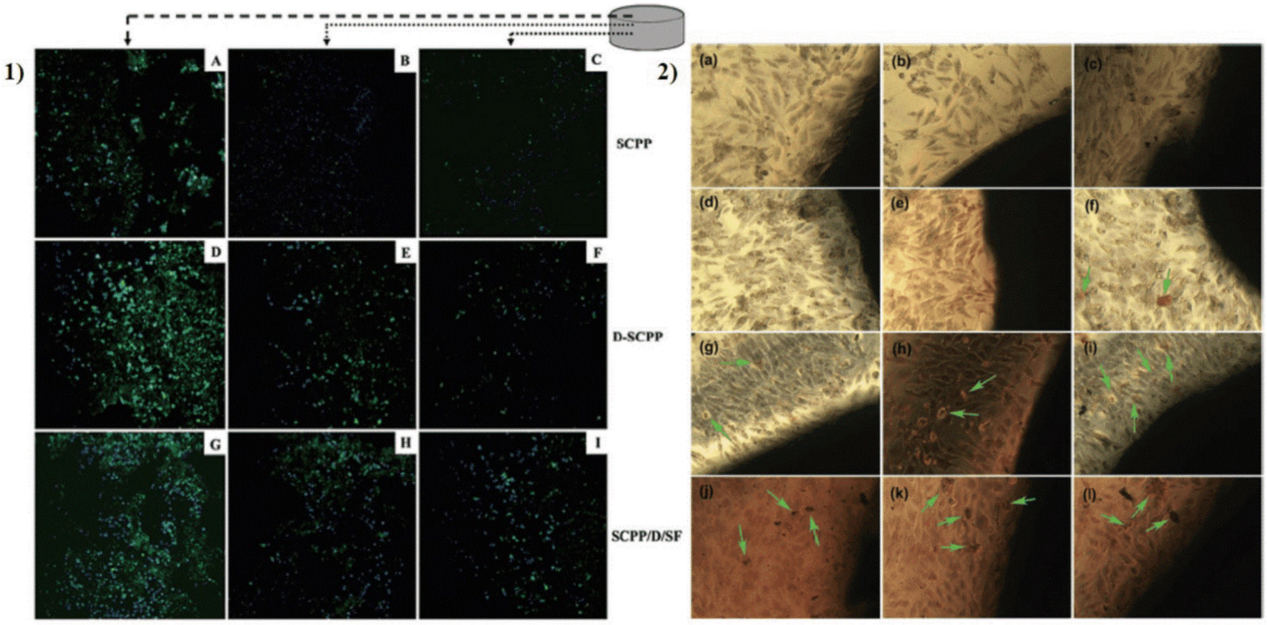

Figure 3. Image (**1**) represents cells cultured with different scaffolds. Image (**2**) shows scaffolds alizarin red staining on day 4 (**a**–**c**), day 7 (**d**–**f**), day 10 (**g**–**i**), day 14 (**j**–**l**); SCPP (**a**,**d**,**g**,**j**), D-SCPP (**b**,**e**,**h**,**k**), SCPP/D/SF (**c**,**f**,**i**,**l**), respectively. Green arrows: calcium nodules. Courtesy of: Wang X, Gu Z, Jiang B, Li L, Yu X. Surface modification of strontium-doped porous bioactive ceramic scaffolds via poly(DOPA) coating and immobilizing silk fibroin for excellent angiogenic and osteogenic properties. Biomater Sci. April 2016;4(4):678–88. doi: 10.1039/c5bm00482a. Epub 12 February 2016. PMID: 26870855.

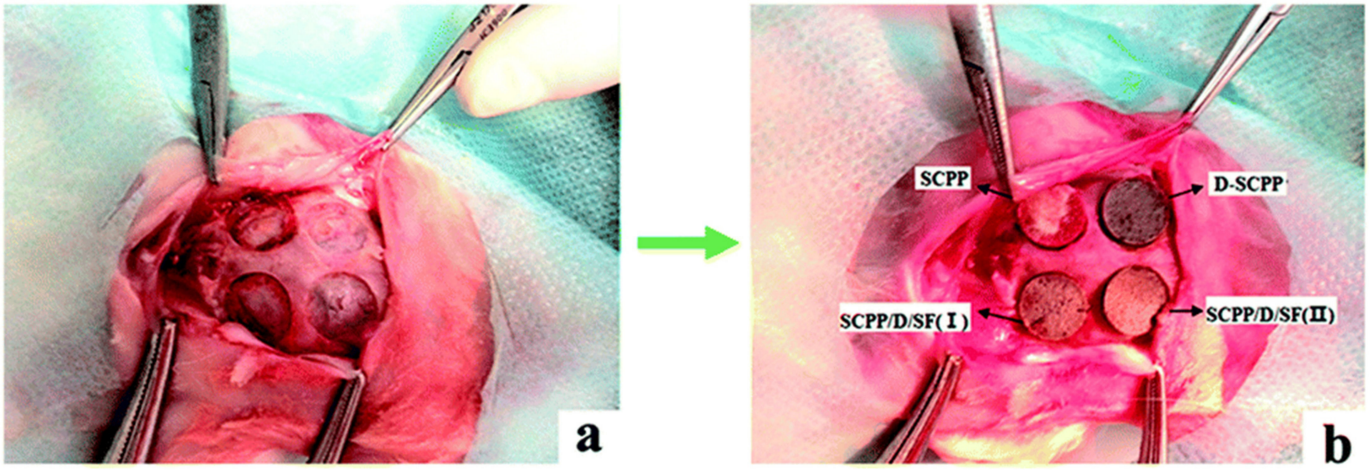

Figure 4. Photographs of animal modeling in vivo. Defects on the cranial bone (**a**,**b**) materials implanted. Courtesy of: Wang X, Gu Z, Jiang B, Li L, Yu X. Surface modification of strontium-doped porous bioactive ceramic scaffolds via poly(DOPA) coating and immobilizing silk fibroin for excellent angiogenic and osteogenic properties. Biomater Sci. April 2016;4(4):678–88. doi: 10.1039/c5bm00482a. Epub 12 February 2016. PMID: 26870855.

5.3. Nanoparticles

The therapeutic efficacy of natural bioactive molecules can be improved by nanotechnological approaches. The design of drug delivery systems with pre-determined physico-chemical properties permits an increase of phytochemical bioavailability and reduces their toxic side effects [53]. For example, positive surface charges could facilitate the transport of nanoparticles through small intestinal epithelial cells improving the oral bioavailability, while the introduction of polyethylene glycol chains limits opsonization prolonging circulation times [143–145]. Moreover, the modulation of structure-property

relationships (i.e., size, geometry or shape, material composition, etc.) of nanoparticles can influence the transport mechanism, facilitating their internalization into the target cells.

He L et al. produced tea polyphenol-modified calcium phosphate nanoparticles (TP-CaP) able to enhance remineralization of preformed enamel lesions on bovine incisors. Moreover, the released tea polyphenols inhibited bacterial growth and enzyme activities [146]. Wang produced gold nanoparticles (Au-NPs) formed using Anogeissus latifolia (A. latifolia) phytochemicals. Such nano-vehicles showed great osteoinductive potential and analgesic properties and were characterized by exceptional blood compatibility and cytocompatibility [147]. Felice et al. synthesized polyphenol-based mucoadhesive polymeric nanoparticles (GSE-NP) able to protect endothelial progenitor cells (EPCs) from oxidative stress. These vehicles demonstrated strong antioxidant capacity thanks to their high content in total polyphenols [148]. Del Prado Audelo et al. synthesized nanoparticles of PCL and Pluronic® F-68, loaded with curcumin. These nanoparticles were able to reduce cell proliferation without affecting cell migration and adhesion, and decrease the oxidative stress induced by hydrogen peroxide exhibiting a cytoprotective effect [149]. Finally, Malathy S and Priya R Iyer used chitosan to prepare Naringin-loaded chitosan nanoparticles (NCN). The NCN had strong anti-inflammatory, anti-coagulant, antioxidant, and anti-cancerous effects. Furthermore, these nanoparticles promoted osteoblast differentiation, so they could be considered an efficient model for bone tissue regeneration [150]. All described delivery systems are summarized in Table 2.

Table 2. Summary of bioactive compounds-based devices system and their effects on bone regeneration.

Bioactive Compound	Device	Effect	Ref
- Gallic acid - Tea polyphenols	Synthetic ceramic materials	- pro-osteogenic - anti-inflammatory - antioxidant	[128,134]
- Resveratrol - Phlorotannins - Catechins	Scaffolds -hydrogel - PLGA - PCL and PLA	- antioxidant - pro-differentiating - pro-osteogenic - wound healing	[135–137,142]
- EGCG - Catechin - Pro-anthocyanidins - Curcumin - Naringin	Nanoparticles - TP-CaP - Au-NPs - GSE-NP - Cur–PCL	- osteopromotive - osteoblast differentiation - osteoblast proliferation - cytoprotective - remineralization - antioxidant - anti - inflammatory	[147–150]

6. Conclusions

In this review paper, recent developments in delivery systems for phytochemicals release for bone tissue regeneration were discussed. Despite the updates reviewed in this paper, more work is required to develop materials that can present controlled release kinetics and degradation, and that directly influence the rate of new bone formation. Soon, researchers, in accordance with clinicians, might be able to design and develop new delivery systems with improved characteristics that mimic bone microenvironment at the site of implantation, promoting the inflammation, angiogenesis, and osteogenesis phases of new bone formation. The interaction between a nanotechnological approach and natural-derived compounds with osteogenic, anti-oxidant, antimicrobial, and anti-inflammatory activities will open up a new era of advanced treatment and solutions to prevent and/or treat bone-related complications.

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