Orthopedic Research and Reviews

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REVIEW

β-Caryophyllene and Statins in Bone Fracture Healing – A Narrative Review

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Abstract: Bone fractures are a leading cause of morbidity and healthcare expenditure globally. The complex healing process involves inflammation, cartilage formation, mineralization, and bone remodeling. Current treatments like immobilization, surgery, and bone grafting, though effective, pose significant challenges, such as prolonged recovery and high costs. Emerging therapies such as biological agents, pharmacological treatments, and physical stimulation techniques are also associated with high costs, side effects, and practical applicability limitations. There is a critical need for alternative therapies that are cost-effective, safe, and easy to use. Recent studies suggest the potential of β-caryophyllene (BCP) and statins in promoting bone healing. BCP, a naturally occurring anti-inflammatory and antioxidant compound found in essential oils, enhances osteoblast activity and inhibits osteoclastogenesis. Statins, known for their cholesterol-lowering effects, also promote bone formation and reduce bone resorption through multiple biochemical pathways. Both BCP and statins have shown promising results in preclinical studies, enhancing bone density and promoting fracture healing. This review explores the individual and potential synergistic effects of BCP and statins on bone fracture healing. It highlights the complementary mechanisms of these agents: BCP's anti-inflammatory and osteogenic properties and statins' ability to inhibit osteoclast activity and promote angiogenesis. Combining BCP and statins could offer a multifaceted approach to enhance fracture healing, reduce complications, and improve patient outcomes. While individual effects are supported preclinically, further studies investigating synergies, formulations, and clinical translation are needed to develop this promising novel therapeutic approach for improving fracture repair outcomes.

Keywords: bone regeneration, fracture repair, osteoblast, osteogenesis, piezoelectric effect

Introduction

Bone fractures are among the most prevalent musculoskeletal injuries globally, contributing significantly to healthcare costs, with an estimated 178 million new cases annually.[1] Fracture healing is a complex process involving, inter alia, inflammation, cartilage formation, mineralization, and bone remodeling.[2–4] Impairments in this process can lead to delayed healing, nonunion, or malunion, resulting in morbidity, disability, and reduced quality of life.[5] Standard treatments for fracture healing include immobilization, surgical interventions, and bone grafting; however, these methods face challenges such as prolonged immobilization, surgical risks, donor site morbidity, and high costs.[6,7] Additional treatments, such as biological therapies, pharmacological treatments, shock wave therapy, low-intensity pulsed ultrasound (LIPUS), and electrical bone growth stimulation, offer various benefits but also present challenges like high costs, side effects, and the need for long-term commitment and specialized equipment.[6]

Biological therapies, such as growth factors, stem cells, or osteoinductive agents, enhance healing at the cellular level but are expensive, complex to administer, and have uncertain long-term outcomes.[8] Often used off-label,

Received: 13 November 2024
Accepted: 9 January 2025
Published: 23 January 2025

pharmacological treatments pose risks of side effects, long-term adverse effects, and potential contraindications with other medications.[9] These include gastrointestinal issues, jaw osteonecrosis, femur fractures, renal toxicity, flu-like symptoms with bisphosphonates; hypercalcemia, dizziness, leg cramps, unclear cancer risk with teriparatide; hypocalcemia, infections, jaw osteonecrosis with denosumab; renal and gastrointestinal anomalies, cardiovascular risks, delayed bone healing with non-steroidal anti-inflammatory drugs; osteoporosis, infections, hyperglycemia, wound healing issues with corticosteroids; and hepatic toxicity, cardiovascular problems, mood swings, hormone suppression with anabolic steroids.[9–11]

Hormone replacement therapy is associated with an increased risk of breast cancer, thromboembolic events, cardiovascular disease, and stroke, and is contraindicated in patients with a history of hormone-sensitive cancers.[12] Calcitonin nasal sprays tend to cause nausea, flushing, injection reactions, cancer risk, and allergies.[11] Shock wave therapy can be uncomfortable and variably effective, depending on the fracture type.[13] LIPUS offers a non-invasive option but requires daily use for several months, and its effectiveness is debated.[14] Electrical bone growth stimulation, while useful, can cause skin irritation, is inconvenient for continuous use, and is unsuitable for patients with electronic medical devices like pacemakers.[15] These considerations must be carefully weighed for clinical decision-making. Certain populations, including the elderly and individuals with comorbidities like diabetes and osteoporosis, are at higher risk for impaired fracture healing.[16] Thus, there is an urgent need for alternative or adjuvant therapies that are cost-effective, easy to use, patient-friendly, safe, have a long shelf-life, and can enhance and accelerate the fracture healing process, reduce complications, and improve patient outcomes.

Recent studies highlight the possibilities of β-caryophyllene (BCP) and statins in promoting bone formation and fracture healing.[17,18] BCP is a naturally occurring bicyclic sesquiterpene found in various essential oils, spices, and plants, known for its anti-inflammatory and antioxidant properties.[19] Statins, on the other hand, are widely used cholesterol-lowering drugs that have been found to exert pleiotropic effects, including bone anabolic actions.[17,20] BCP has been shown to protect against bone defects caused by Vitamin D deficiency through the upregulation of klotho expression.[21] It also demonstrates anticancer potential by inducing apoptosis in osteosarcoma cells via ROS and the JAK1/STAT3 pathway,[22] and enhances wound healing when incorporated into a hydrogel with nano-emulsified BCP.[23] Meanwhile, statins play a significant role in bone metabolism by promoting osteoblast activity and reducing bone resorption, making them effective for treating bone diseases.[24,25] Local delivery methods further improve their efficacy.[26] Together, both BCP and statins hold promise for advancing bone health treatments. This review aims to provide a comprehensive overview of the current literature on the potential roles and mechanisms of action of BCP and statins in bone fracture healing, highlighting their therapeutic potential and future research directions, which could ultimately lead to improved outcomes for patients suffering from fractures and other conditions that compromise bone integrity.

A thorough literature search for scholarly articles published in English was conducted in PubMed and Google Scholar databases, using combinations of the medical subject heading (MeSH) terms "β-caryophyllene", "statins", "bone fracture", "fracture healing", "osteoblasts", "osteoclasts", "bone formation", and "bone resorption", separated by suitable Boolean operators. Relevant articles published between the years 2000 and 2022 were included. Studies before 2000, review articles, case reports, and articles not available in English were excluded (Figure 1).

Overview of BCP and Statins

BCP is a bicyclic sesquiterpene with the chemical formula alpha-zingiberene ($C_{15}H_{24}$). It occurs naturally in two isomeric forms: α-caryophyllene (α-humulene) and iso-caryophyllene (Z-BCP), often in a mixture with its oxidation product, BCP oxide.[27] Widely distributed in the plant kingdom, BCP is found in various essential oils, spices, and herbs, including clove oil (*Syzygium aromaticum*), black pepper (*Piper nigrum*), and cannabis (*Cannabis sativa*).[27] BCP is known for its volatile nature and distinctive woody, spicy aroma, contributing to the characteristic scent of numerous plants and spices. BCP exhibits various biological activities, including anti-inflammatory, antioxidant, antimicrobial, and analgesic properties (Figure 2).[28] In terms of bone metabolism, BCP promotes osteoblast differentiation and mineralization while inhibiting osteoclast formation and bone resorption, potentially through modulation of the Wnt/β-catenin pathway.[18,29] Beyond its effects on bone metabolism, BCP protects against seizures.[30] It also shows promise in

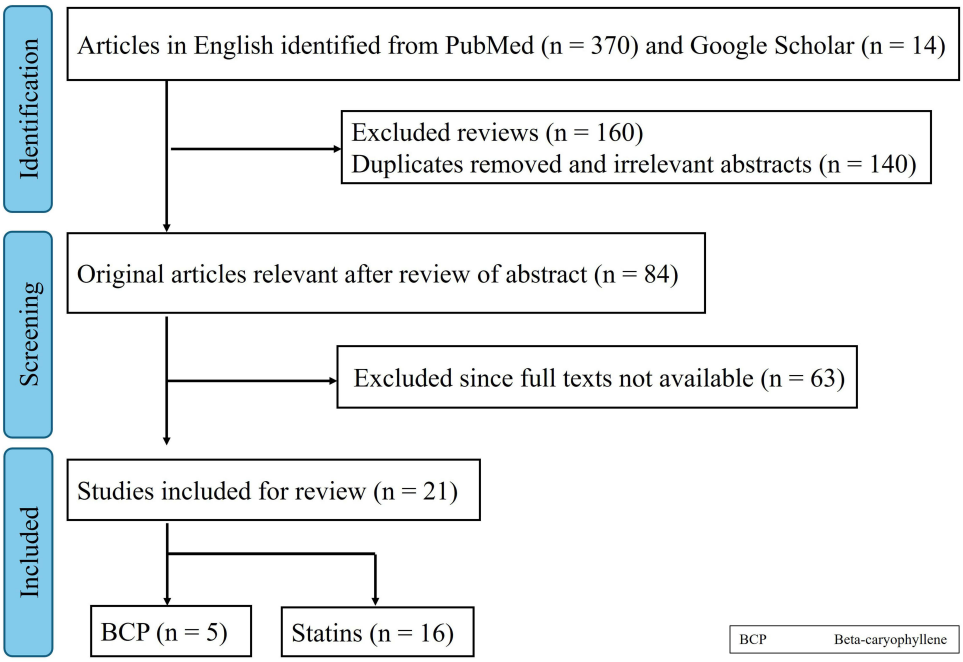

Figure 1 Flow diagram depicting literature search and study selection.

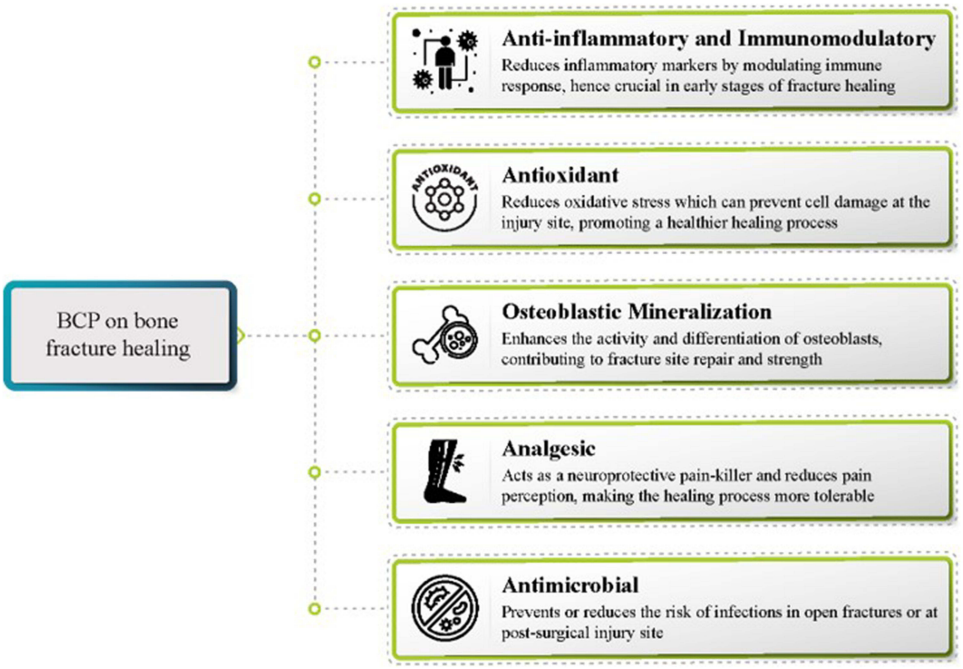

Figure 2 Effect of BCP on bone fracture healing. BCP offers multiple benefits, including significant anti-inflammatory, immunomodulatory, and antioxidant effects, and enhanced osteoblastic mineralization, crucial for fracture healing. Additionally, BCP's analgesic and antimicrobial activities reduce pain perception and risk of infection.

preventing the development of neurodegenerative diseases like Alzheimer's.[31] Additionally, BCP inhibits cytochrome P450 isoforms, particularly cytochrome P450 3A4 (CYP3A4), mitigating adverse effects from excessive drug levels.[32]

Numerous studies have demonstrated BCP's low toxicity profile, with no significant adverse effects observed in animal models even at relatively high doses.[33] Additionally, BCP is widely present in many foods and food products and has been granted Generally Recognized as Safe status by the US Food and Drug Administration.[34] BCP has exhibited

Table 1 Summary of the Studies on BCP and Bone Fracture Healing

Reference	Study type	Outcomes
Chang et al[35]	In vivo (animal)	BCP showed neuroprotective effects against cerebral ischemic injury by reducing inflammation and oxidative stress.
Mahmoud et al[36]	In vivo (animal)	BCP exhibited protective effects against hepatic fibrosis and apoptosis associated with bile duct ligation in rats, potentially through cannabinoid receptor modulation.
Yamaguchi and Levy[18]	In vitro	BCP promoted osteoblastic mineralization and suppressed osteoclastogenesis and adipogenesis in mouse bone marrow cultures, suggesting its potential for enhancing bone formation.
Yang et al[38]	In vivo (animal) and in vitro	BCP exhibited neuroprotective effects against cerebral ischemia-reperfusion injury by regulating necroptotic neuronal death and inflammation.
Koyama et al[37]	In vitro and in vivo (animal)	BCP enhanced wound healing through multiple mechanisms, including promoting cell migration, angiogenesis, and collagen deposition.

Abbreviation: BCP, Beta-caryophyllene.

diverse therapeutic effects, such as neuroprotective properties against cerebral ischemic injury through the reduction of inflammation and oxidative stress,[35] protective effects against hepatic fibrosis and apoptosis in animal models,[36] and the potential to promote osteoblastic mineralization while inhibiting osteoclastogenesis and adipogenesis, suggesting its utility in enhancing bone formation.[18] Furthermore, BCP has been shown to enhance cell migration, angiogenesis, and collagen deposition, contributing to wound healing.[37] It has also demonstrated neuroprotective effects against cerebral ischemia-reperfusion injury by regulating necroptotic neuronal death and inflammation (Table 1).[38]

Statins, widely known as cholesterol-lowering medications, have garnered significant interest due to their pleiotropic effects beyond lipid regulation, particularly in promoting bone regeneration and enhancing fracture healing.[39] These effects are mediated through multiple mechanisms that modulate osteoblast and osteoclast activity, angiogenesis, and inflammatory responses.[40] At the molecular level, statins inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, a key enzyme in the mevalonate pathway.[41] This inhibition reduces downstream metabolites, such as farnesyl pyrophosphate (FPP) and geranylgeranyl pyrophosphate (GGPP), consequently impairing protein prenylation of small GTPases. Disruption of these signaling pathways affects cytoskeletal organization and impedes osteoclast formation and function.[17,40,41]

Role of BCP in Bone Fracture Healing

After a bone fracture, the body initiates an inflammatory response characterized by hematoma formation and the recruitment of polymorphonuclear neutrophils to clear debris.[42] Chemokines such as monocyte chemoattractant protein-1 and interleukin-6 (IL-6) attract macrophages crucial for subsequent bone healing. Additionally, macrophages and osteoMacs play a pivotal role in the adaptive immune response initiated by lymphocytes, ultimately promoting bone regeneration.[42] Disruption in this inflammatory phase can hinder proper bone healing and increase the risk of non-union. Due to its potential therapeutic effects, BCP is gaining attention, including its anti-inflammatory and bone-healing properties.[36,43] Macrophages also play a crucial role in osteogenesis, with both M1 and M2 macrophages being essential for ensuring proper formation and recovery during the inflammatory and remodeling phases.[44] Acting as a selective agonist of cannabinoid receptor type 2 (CB2), BCP exhibits potent anti-inflammatory properties by inhibiting various cytokines and factors involved in inflammation, such as IL-1β and IL-6.[36] Its engagement with peroxisome proliferator-activated receptors alpha and gamma contributes to its anti-arthritic effects.[45]

Several preclinical investigations have shed light on the potential benefits of BCP in bone fracture healing. BCP stimulates osteoblastic mineralization while suppressing adipogenesis and osteoclastogenesis. By selectively activating CB2 receptors, BCP promotes bone formation and inhibits bone resorption, enhancing bone mineral density.[46,47] The distinctive expression patterns of CB2 in osteoclasts from menopausal women highlight its role in inhibiting osteoclast activity, with reductions in CB2 signaling efficacy associated with lower bone density and the onset of osteoporosis.[47,48]

Despite its widespread use and generally recognized safety, interactions with other compounds or medications, as well as potential effects in specific populations, warrant further investigation and consideration.

Statins and Bone Fracture Healing

Statins stimulate osteoblast differentiation by enhancing the expression of bone morphogenetic protein-2 (BMP-2) and osteocalcin while suppressing the activation of Rho and Rho kinase.[40,49] This dual action promotes bone formation and mineralization. Moreover, statins activate Smad3, a critical mediator of transforming growth factor-beta (TGF-β) signaling, pivotal for maintaining bone mass by inhibiting osteoblast apoptosis and fostering bone formation.[50,51] Additionally, statins modulate the osteoprotegerin (OPG)/receptor activator of nuclear factor-kappa beta ligand (RANKL)/RANK system, a key regulator of osteoclastogenesis, by upregulating OPG expression and downregulating RANKL expression, consequently inhibiting osteoclast formation and activity.[52] This anti-osteoclastogenic effect is complemented by the promotion of osteoblastogenesis through the induction of estrogen receptor-alpha (ER-α) expression, leading to reduced RANKL expression and further hindering osteoclast formation.[53]

Statins also exhibit pro-angiogenic properties, promoting neovascularization and enhancing collateral blood flow.[54] This angiogenic activity is mediated through the Akt/phosphatidylinositol 3-kinase (Akt/PI3K) pathway, resulting in increased endothelial cell proliferation and secretion of angiogenic factors such as vascular endothelial growth factor (VEGF).[55] Additionally, statins possess anti-inflammatory properties, contributing to their beneficial role in fracture healing. They promote the polarization of macrophages toward the anti-inflammatory M2 phenotype and upregulate the expression of anti-inflammatory cytokines like interleukin-13 (IL-13) and growth factors.[56] These foster an environment conducive to tissue repair and regeneration (Figure 3).

Preclinical investigations strongly support the beneficial impact of statins on fracture healing. Early research showed that compactin inhibited bone resorption by blocking the fusion of osteoclasts and disrupting their actin ring.[41] Subsequent studies suggested that statins differentially regulated VEGF synthesis in endothelial and vascular smooth muscle cells.[57] In vitro studies

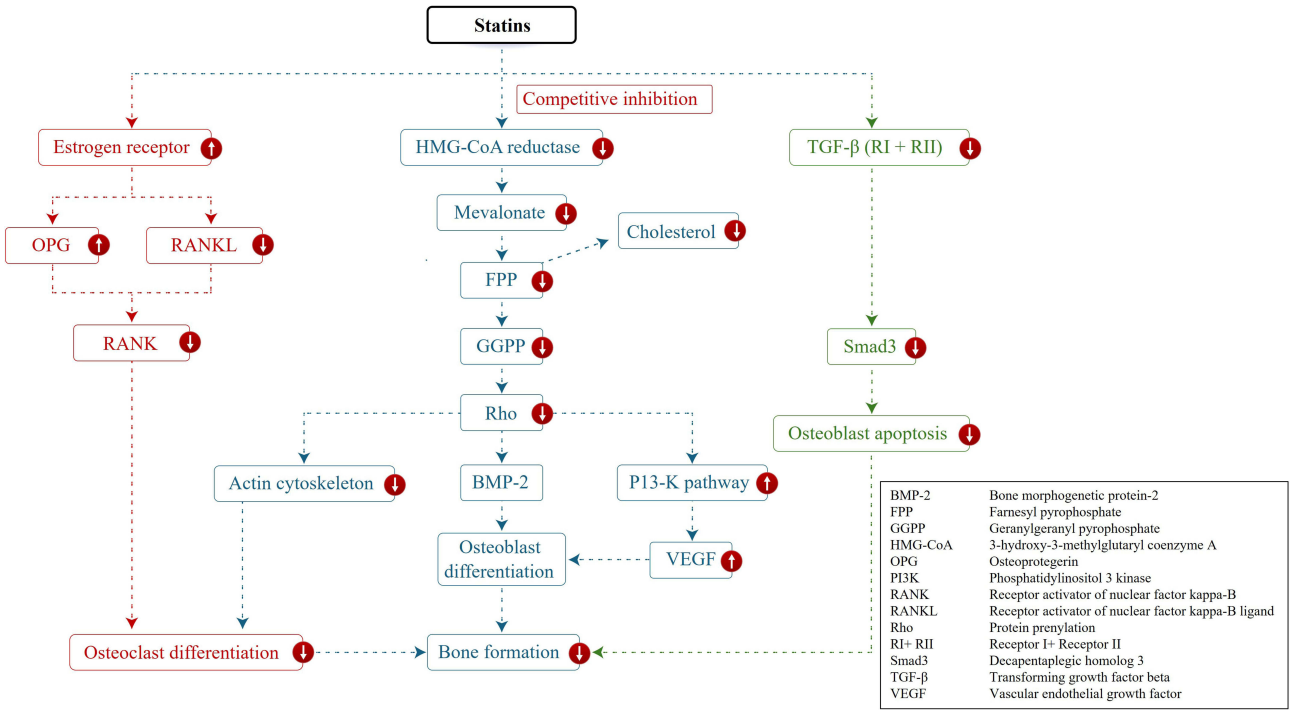

Figure 3 Statins exhibit pro-angiogenic properties. They modulate various pathways. They enhance estrogen receptor expression, inhibit osteoclast differentiation by modulating the OPG/RANKL/RANK signaling pathway, and promote bone formation (depicted in red). They inhibit actin depolymerization and enhance osteoblast differentiation leading to bone formation via the FPP/GGPP/Rho/BMP-2/P13-K pathway and VEGF (depicted in blue). They also activate TGF-β signaling by activating Smad3, essential for maintaining bone mass. Deletion of Smad3 decreases bone formation due to increased osteoblast apoptosis. Statins induce Smad3 expression, promoting bone formation (depicted in green).

https://doi.org/10.2147/ORR.S506427

demonstrated that simvastatin induced the expression of ER-α in murine bone marrow stromal cells and suppressed apoptosis in osteoblastic cells through the TGF-β Smad3 pathway.[58,59] Simvastatin also induces ER-α expression in bone, restoring bone loss and reducing ER-α expression and uterine wet weight in ovariectomized rats.[60] Additionally, inhibiting actin depolymerization enhances osteoblast differentiation and bone formation in human stromal stem cells.[61] Further exploration revealed that accumulation of FPP inhibited calvarial osteoblast differentiation, while direct inhibition of GGPP synthase affected osteoblast differentiation.[62] Also, GGPP synthase was found to be downregulated during osteoblast differentiation,[49] while another study indicated that pitavastatin enhanced BMP-2 and osteocalcin expression in human osteoblasts by inhibiting Rho-associated kinase.[40] Animal model studies have further substantiated these findings, showing that statin administration enhances callus formation, increases bone density, and improves the biomechanical properties of the healing bone (Table 2).[17,63]

Studies also demonstrate that topical simvastatin accelerates wound healing in diabetes by enhancing angiogenesis and lymphangiogenesis.[64] Recently, an exploration into the potential of simvastatin-loaded lyophilized wafers as a dressing for chronic wounds yielded positive outcomes.[65] An in vitro study has illustrated that simvastatin activates Akt and promotes angiogenesis in normocholesterolemic animals.[55] Ex vivo studies have further supported these findings suggesting that statins promote angiogenesis (Table 3).[66]

The Promise of Combinatorial Therapy

Combinatorial therapies offer an advanced approach to bone fracture healing, leveraging multiple biological pathways. Utilizing therapeutic agents with complementary mechanisms offers several key advantages, such as reducing the likelihood of resistance, lowering individual drug doses, and minimizing potential side effects.[67] Combining statins

Table 2 Summary of the Studies on Statins and Bone Fracture Healing

Reference	Study type	Outcomes
Woo et al[41]	In vitro	Compactin suppresses bone resorption by inhibiting the fusion of perfusion osteoclasts and disrupting the actin ring in osteoclasts.
Borton et al[50]	In vivo (animal)	Loss of Smad3 resulted in lower bone formation and osteopenia due to dysregulation of osteoblast differentiation and apoptosis.
Ohnaka et al[40]	In vitro	Pitavastatin enhanced BMP-2 and osteocalcin expression in human osteoblasts by inhibiting Rho-associated kinase.
Frick et al[57]	In vitro	Statins differentially regulated VEGF synthesis in endothelial and vascular smooth muscle cells.
Kaji et al[52]	In vitro	Statins modulated the levels of osteoprotegerin/receptor activator of NF-κB ligand mRNA in mouse bone cell cultures.
Yoshida et al[49]	In vitro	GGPP synthase was downregulated during osteoblast differentiation.
Song et al[58]	In vitro	Simvastatin-induced ER-α expression in murine bone marrow stromal cells.
Kaji et al[59]	In vitro	Statins suppressed apoptosis in osteoblastic cells through the TGF-β Smad3 pathway.
Masuzaki et al[63]	In vivo (animal)	A single remote injection of statin-impregnated PLGA microspheres enhanced osteogenesis around titanium implants in rat tibia.
Weivoda and Hohl[62]	In vitro	Accumulation of FPP inhibited calvarial osteoblast differentiation; direct inhibition of GGPP synthase affected osteoblast differentiation.
Li et al[60]	In vivo (animal)	Simvastatin induced ER-α expression in bone, restored bone loss, and decreased ER-α expression and uterine wet weight in ovariectomized rats.
Li et al[61]	In vitro	Inhibiting actin depolymerization enhanced osteoblast differentiation and bone formation in human stromal stem cells.

Abbreviations: BMP-2, Bone morphogenetic protein 2; ER-α, Estrogen receptor alpha; FPP, Farnesyl pyrophosphate; GGPP, Geranylgeranyl pyrophosphate; NF-κB, Nuclear factor kappa B; PLGA, Poly (lactic-co-glycolic acid); TGF-β, Transforming growth factor beta; VEGF, Vascular endothelial growth factor.

Table 3 Effect of Statins on Bone Regeneration

Reference	Study type	Outcomes
Kureishi et al[55]	In vitro	Simvastatin activates Akt and promotes angiogenesis in normocholesterolemic animals.
Khaidakov et al[66]	Ex vivo	Statins promote angiogenesis.
Asai et al[64]	In vitro	Topical simvastatin accelerates wound healing in diabetes by enhancing angiogenesis and lymphangiogenesis.
Rezvanian et al[65]	In vitro	Simvastatin-loaded lyophilized wafers show potential as dressing for chronic wounds.

and BCP may enhance the therapeutic impact beyond their individual capabilities. Statins inhibit osteoclast differentiation via the RANK/RANKL pathway,[52,68] while BCP promotes osteoblast differentiation and exerts anti-inflammatory effects.[27,69,70] This complementary targeting fosters an environment conducive to accelerated fracture repair. Statins and BCP also modulate inflammation by inhibiting cytochrome P450 isoforms like CYP3A4, thereby balancing inflammation and cytotoxicity.[36,71] The combination can also mimic the piezoelectric effect in bone, where mechanical loading generates electrical potentials that govern bone remodeling.[72,73] Statins reduce osteoclastogenesis, favoring bone formation,[52] while BCP promotes osteoblast differentiation.[69] This duality echoes bone's natural response to mechanical strains and electrical signals.[74–76] A controlled-release formulation of statins and BCP could provide a multi-faceted approach to bone repair, enhancing therapeutic efficacy (Figure 4).

While preclinical studies specifically investigating the combinatorial effects of BCP and statins on bone fracture healing are limited, several studies have examined the individual effects of these compounds in animal models. Research findings indicate that the administration of BCP can promote callus formation in rodent fracture healing models.[37,77] Similarly, numerous studies have reported that statin administration can accelerate fracture healing, improve callus formation, and enhance the biomechanical properties of the healing bone in various animal models, including rodents.[17,63] While these studies provide valuable insights into the individual effects of BCP and statins on bone fracture healing, further preclinical investigations are needed to evaluate their potential synergistic effects when combined.

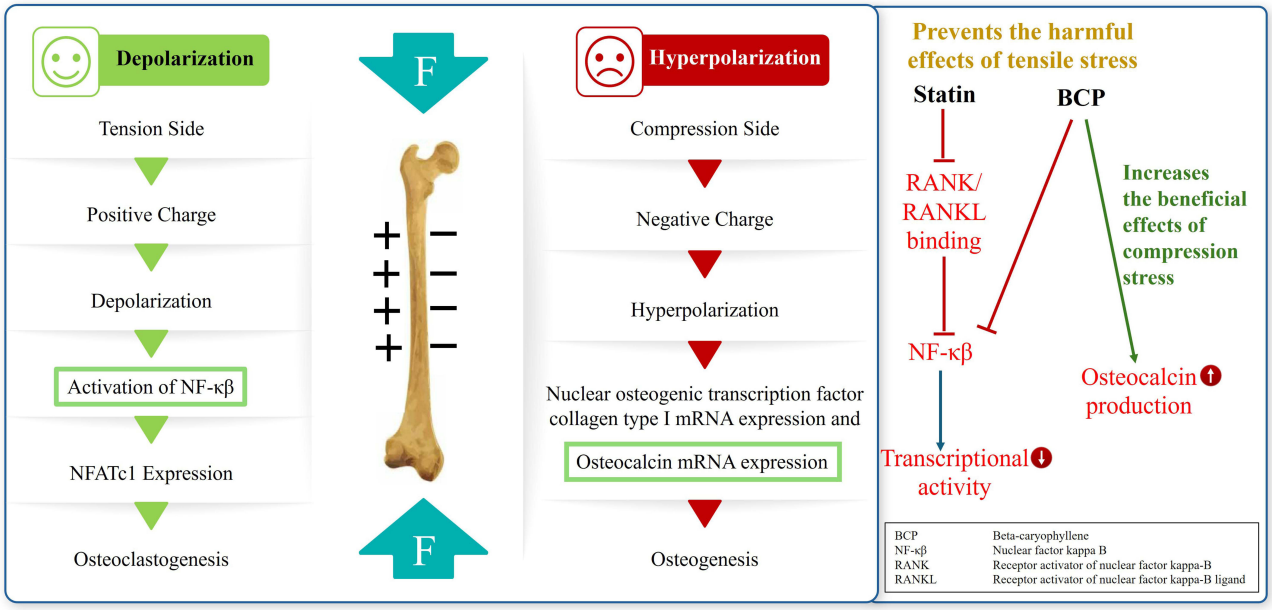

Figure 4 Potential combined effect of BCP and statins on bone fracture healing. Bone remodeling involves osteoblast and osteoclast activity regulated by cytokines and the piezoelectric effect, with mechanical deformation generating negative charges in compressed areas and positive charges in tension areas. These changes influence osteocyte activity, leading to osteogenesis and osteoclastogenesis via NF-κB signaling, NFATc1, and osteocalcin mRNA expressions. Statins and BCP together counteract tensile stress by inhibiting RANK/RANKL binding and NF-κB activation (depicted in red blunt arrow), while enhancing compression stress effects by increasing osteocalcin production and inhibiting NF-κB (depicted in green sharp arrow and red blunt arrow).

https://doi.org/10.2147/ORR.S506427

The synergy between BCP and statins, particularly lovastatin, can prevent RANKL from binding to its receptor (RANK) and inhibit RANKL release through BCP, a selective CB2 receptor agonist. Statin-induced OPG via ER-α activation further inhibits RANKL binding. BCP also mitigates the inflammatory response from high statin levels, while statins reduce BCP's cytotoxicity.[78] Understanding the synergistic effects of BCP and statins on bone's piezoelectric properties could further improve fracture healing and bone health. Bone remodeling involves cellular responses of osteoblasts and osteoclasts to several key cytokines and an electrochemical process due to piezoelectric dipoles generated by bone tissue deformation. This dual process influences osteocyte activity, regulating bone resorption and formation through cytokine production. The piezoelectric effect plays a vital role in bone healing and repair. During a fracture, mechanical loading can stimulate the piezoelectric effect, enhancing the healing process. Compressive pressures generate negative potentials, while tensile stresses produce positive potentials, influencing the electric charges and amplitudes generated during activities such as walking. The piezoelectric potential produced by bone tissue deformation influences osteocyte activity within the bone matrix. Osteocytes sense mechanical force via their processes in the canaliculi and then produce several cytokines to regulate osteoclast-mediated bone resorption and osteoblast-mediated bone formation.[79] Further preclinical and clinical studies are needed to explore these effects and optimize dosing and administration strategies for the best therapeutic outcomes. Research on the combinatorial use of BCP and statins could lead to more effective and personalized fracture treatments, ultimately improving patient outcomes.

Strengths, Limitations, and Future Perspectives

This article comprehensively reviews the potential roles and mechanisms of action of BCP and statins in bone fracture healing, covering both preclinical and clinical evidence. It offers valuable insights into potential therapeutic strategies for enhancing bone fracture healing. However, limitations include a primary focus on mechanistic aspects with limited discussion on clinical outcomes and patient perspectives. While the manuscript discusses novel treatment approaches, such as combinatorial therapy using BCP and statins, and in particular lovastatin, further exploration of clinical trial data and translational implications would enhance its relevance to clinical practice. Further preclinical investigations to assess the synergistic effects of combining BCP and statins on bone fracture healing could delve into optimal dosing regimens, formulations, and delivery methods to maximize therapeutic efficacy while minimizing potential adverse effects. Mechanistic studies elucidating the underlying pathways involved in the synergistic action of BCP and statins on bone regeneration could provide valuable insights for future drug development and personalized treatment approaches in bone fracture care.

Clinical Implications and Translational Opportunities

The possible combinatorial use of BCP and statins holds significant clinical implications and translational opportunities. When proven effective and safe in clinical trials, this approach can transform fracture treatment approaches, particularly in complex cases or for patients at high risk, such as the elderly, individuals with comorbidities, and smokers. This strategy may offer substantial benefits for managing osteoporosis and other bone defects, potentially improving outcomes for patients with compromised bone health. Potential applications include developing localized delivery systems, such as implants, scaffolds, or injectable formulations, for controlled and sustained release at the fracture site, thereby reducing the risk of systemic side effects associated with oral administration of statins. Furthermore, the anti-inflammatory properties and potential modulation of the immune response could have implications beyond fracture healing, finding applications in other musculoskeletal conditions involving inflammation and tissue repair. The development of controlled-release formulations for localized and sustained delivery to the fracture site represents a critical area for future investigation.

Conclusion

The combination of BCP and statins holds promise for enhancing bone fracture healing. BCP, with its anti-inflammatory and bone-promoting properties, stimulates osteoblast activity and inhibits osteoclast formation, while statins promote osteoblast differentiation, inhibit osteoclasts, and improve angiogenesis. Together, they target complementary pathways,

potentially accelerating healing and improving bone density. Although preclinical results are promising, further research is needed to optimize dosing, delivery methods, and long-term safety. Successful validation in clinical trials could lead to more effective, patient-friendly fracture treatments, especially for high-risk populations, with potential applications in other musculoskeletal conditions.

Abbreviations

Akt/PI3K, Akt/phosphatidylinositol 3-kinase; BCP, β-caryophyllene; BMP-2, Bone morphogenetic protein-2; CB2, Cannabinoid receptor type 2; CYP3A4, Cytochrome P450 3A4; ER-α, Estrogen receptor-alpha; FPP, Farnesyl pyrophosphate; GGPP, Geranylgeranyl pyrophosphate; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; IL-1β, Interleukin-1 beta; IL-6, Interleukin-6; IL-13, Interleukin-13; LIPUS, Low-intensity pulsed ultrasound; MeSH, Medical subject heading; OPG, Osteoprotegerin; RANKL, Receptor activator of nuclear factor-kappa beta ligand; TGF-β, Transforming growth factor-beta; VEGF, Vascular endothelial growth factor.

Acknowledgments

Manuscript writing assistance, editorial, and publication support were provided by Dr. Harsha SK and Dr. Priyanka Biswas Karmakar from Turacoz Group (www.turacoz.com).

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This research was fully funded by OrthoTreat Ltd., which provided the financial resources necessary to execute the review.

Disclosure

All authors are employees, managers, and advisors of OrthoTreat Ltd., who analyzed and submitted the article. Dr Nathan Skelley reports personal fees for consultancy from Conmed corporation, outside the submitted work. Dr Tami Ehrmann Barr has a patent WO2023/021514A1 pending to OrthoTreat Ltd. The authors declare that they have no other competing interests in this work.

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