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TARGETING BONE REGENERATION WITH MARINE BIOACTIVES: A SYSTEMATIC REVIEW OF CELLULAR AND MOLECULAR INSIGHTS

Nasywa Zahra Sajida Tsuroyya*, Herin Setianingsih, Indri Ngesti Rahayu, Riami Riami
Faculty of Medicine, Hang Tuah University, Surabaya, Indonesia

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Corresponding Author:
E-mail: nasywazzst@gmail.com

ABSTRACT

Background: Bone disorders, such as osteoporosis and inflammatory osteolysis, require regenerative therapies with improved safety and multimodal mechanisms. Marine natural products (MNPs) provide diverse chemical scaffolds with potential anabolic and antiresorptive actions; however, the synthesis of preclinical evidence and translational appraisal remains limited. **Objective:** To systematically synthesize preclinical evidence on the effects and molecular mechanisms of MNPs on bone, with emphasis on exemplar compounds (phorbaketal A and largazole) and translational considerations. **Methods:** The review process followed a PRISMA-based systematic literature review approach, including screening, data extraction, study quality evaluation, and thematic synthesis based on the identified molecular pathways. **Results:** Convergent pathways included inhibition of RANKL-RANK, NFATc1, and NF-κB signaling, modulation of MAPKs (ERK/JNK), and activation of Wnt/β-catenin and Runx2-dependent osteogenic programs. Some compounds, such as phorbaketal A and largazole, showed dual-action potential in osteoblasts and osteoclasts. These effects were demonstrated in both bone cell cultures and animal models, yielding statistically significant results in both. **Conclusion:** Marine products are potential sources of bone therapeutic agents with multi-target mechanisms. This synthesis provides a conceptual foundation for the development of novel therapeutics based on marine biodiversity, promoting translational research toward clinical applications, and regulatory foresight will accelerate responsible translation of promising candidates like phorbaketal A and largazole,

INTRODUCTION

Bone disorders, such as osteoporosis, inflammatory osteolysis, delayed or nonunion fractures, and tumor-associated bone loss, represent major global health burdens characterized by impaired bone remodelling and increased fracture risk[1]. These conditions arise from the dysregulation of tightly coupled cellular programs, principally osteoclast-mediated resorption and osteoblast-mediated formation, which are orchestrated by signalling networks, including RANKL-RANK, NF-κB/NFATc1 (osteoclastogenesis), Wnt/β Wnt/β-cateninRunx2 (osteoblast differentiation), MAPKs (ERK/JNK/p38), and epigenetic regulators such as histone deacetylases (HDACs)[2]. Current therapeutics (bisphosphonates, denosumab, parathyroid hormone analogs, and sclerostin antibodies) reduce fracture incidence but have limitations: they may not fully restore bone architecture, can cause adverse skeletal or extraskeletal effects, and often do not combine robust anti-resorptive and pro-anabolic actions. Consequently, there is an unmet need for new agents that modulate multiple pathways relevant to bone formation and resorption[3].

Marine natural products (MNPs) are a chemically diverse reservoir of bioactive scaffolds with demonstrated anti-inflammatory, signaling-modulatory, and epigenetic activities that are potentially relevant to bone biology[4].

Selected marine-derived compounds illustrate the breadth of mechanisms that can be harnessed for bone regeneration. For example, phorbaketal A, a

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tricyclic sesterterpenoid isolated from the sponge Phorbas sp., suppresses NF-κB signalling and induces cytoprotective heme oxygenase-1 in macrophage models, suggesting its potential to limit inflammatory osteoclastogenesis[5]. Largazole, a marine-derived prodrug that yields a potent class I HDAC-inhibitory motif, can derepress osteogenic transcriptional programs and enhance markers of osteoblast differentiation. Together, these mechanisms indicate that MNPs may simultaneously attenuate osteoclast activity and promote osteogenesis through complementary molecular pathways[6].

Despite the promising biological rationale, preclinical evidence for MNP-mediated effects on bone remains fragmented, with studies differing in cell models, in vitro endpoints, animal models, dosing regimens, and depth of mechanistic validation. Key translational gaps include limited pharmacokinetic/toxicology data, sparse target engagement experiments (genetic/pharmacologic validation), and challenges in the supply or synthetic accessibility of low-abundance marine metabolites.

The objective of this review is to systematically synthesize preclinical evidence on the effects and molecular mechanisms of marine natural products in bone biology, with an emphasis on exemplar compounds (phorbaketal A and largazole).

Although current pharmacological interventions, such as bisphosphonates, denosumab, and selective anabolic agents, play a crucial role in certain clinical conditions, their use is limited by long-term side effects (e.g., osteonecrosis of the jaw and atypical femur fractures) and their tendency to act separately on bone formation and resorption[7].

Marine natural products (MNPs) offer a range of osteomodulatory mechanisms that can potentially overcome these limitations by elucidating the modulatory mechanisms of the phorbaketal A and largazole pathways. This review provides a systematic synthesis linking the molecular mechanisms of MNPs[8].

This systematic review aims to critically assess the existing evidence on the effects of Marine Natural Products on bone biology, with a particular focus on phorbaketal A and largazole, elucidating their molecular mechanisms of action. This review provides a framework for future research and development in bone-targeted pharmacology.

Given Indonesia's status as one of the world's largest centers of marine biodiversity, with more than 8,500 aquatic species recorded by the Ministry of Marine Affairs and Fisheries in 2020, this study is highly relevant for developing sustainable bioprospection and the biomedical utilization of indigenous marine resources[9]. The findings of this review are expected to contribute to theoretical advances and practical applications in osteopharmacology and marine drug development.

METHODS

This systematic review followed the PRISMA 2020 guidelines. We searched Scopus, PubMed/MEDLINE, Embase, Web of Science, and Google Scholar from 2000 to 2025 for experimental studies reporting the effects of marine natural products on bone-related outcomes. The search combined terms for marine natural products and bone (example search string for PubMed: (“marine natural product” OR “marine-derived compound” OR “marine bioactive”) AND (bone OR osteogenesis OR “bone regeneration” OR “osteoclast” OR “osteoblast”) AND (mechanism OR pathway)).

The inclusion criteria were as follows: (1) in vitro or in vivo experimental studies evaluating marine-derived compounds with reported outcomes relevant to osteogenesis, osteoclastogenesis, bone mass/structure, or underlying molecular mechanisms; and (2) sufficient methodological details to extract outcomes. The exclusion criteria were as follows: clinical trials, purely computational studies without experimental validation, and articles lacking primary data.

The search was conducted without language restrictions; however, only articles in English were included in the final selection stage. Additional filters included journal articles and review document types, as well as open-access status, to ensure complete journal accessibility and article duplication.

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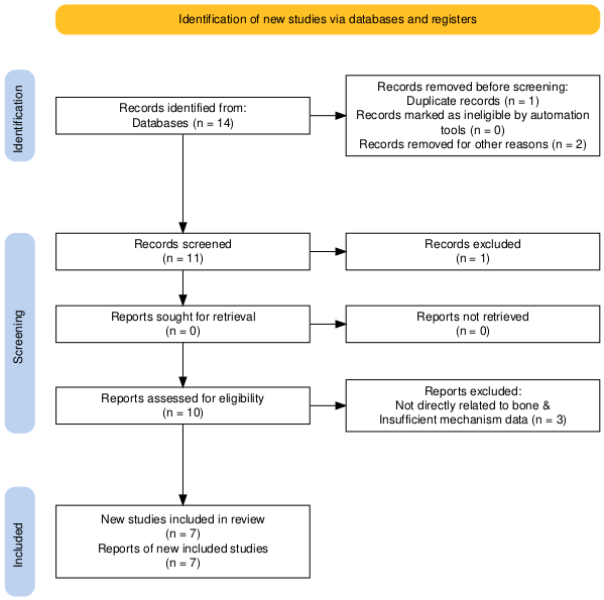

Figure 1. SLR with PRISMA Method

Study Selection

All articles (n = 14) were checked for duplicates and evaluated based on their titles and abstracts. After the initial screening process, 11 articles met the criteria for document type and data completeness. Further evaluation of the full text yielded 10 articles that explicitly evaluated the effects of marine compounds on bones and described relevant molecular mechanisms. Articles that were not directly related to bone parameters or did not mention specific biological pathways were excluded from the final synthesis, resulting in seven articles.

Study Quality Evaluation

The methodological quality of the included studies was evaluated using an internal criterion-based approach for validity and risk of bias assessment. For in vitro and in vivo experimental studies, evaluation indicators included the clarity of the experimental design, use of controls, replication, reporting of quantitative data, and statistical analysis. Review studies were discussed based on the transparency of review methods, bibliographic coverage, and depth of discussion of biological mechanisms. The risk of bias was classified as low, medium, or high, based on the consistency and rigor of the reporting.

RESULTS

Models And Dosing

In vitro, commonly used cell systems include MC3T3-E1 pre-osteoblasts, primary bone marrow macrophages (BMM), RAW264.7 osteoclast precursors, and osteoblastic lines (e.g., MG-63); reported effective concentrations range from low nanomolar to low micromolar, depending on the compound and endpoint.

In vivo: Rodent bone loss or bone repair models were used with dosing typically reported in the range of ~0.1-25 mg/kg (route and schedule variable), study durations of 1-4 weeks for most pharmacodynamic endpoints.

Biological effects; recurring patterns

Dual osteo-modulatory activity: Most MNPs with reported bone effects displayed both anti-resorptive and pro-anabolic properties, that is, inhibition of osteoclast differentiation/function together with stimulation of osteoblast differentiation, matrix mineralization, or osteogenic gene expression.

Anti-inflammatory/anti-osteoclast mechanism

Several compounds suppressed NF-κB and downstream NFATc1 induction during RANKL-driven osteoclastogenesis, consistent with the documented NF-κB inhibition by phorbaketal A in macrophage models.

Epigenetic modulation and osteogenesis: HDAC inhibition (a known mechanism of largazole and related MNPs) was associated with increased acetylation of histones, elevated Runx2 expression, and enhanced osteoblast differentiation markers (ALP and osteocalcin) in preclinical reports and mechanistic studies.

Wnt/β-catenin and MAPK crosstalk : some MNPs activated Wnt pathways or modulated MAPKs (ERK/JNK/p38), providing a mechanistic basis for enhanced osteoblastogenesis and coupling with angiogenic signals.

Translational parameters and limitations

Pharmacology and safety : Systematic pharmacokinetic, dose-response, and toxicology data are sparse or absent for most compounds, which is a major barrier to translational progression.

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Heterogeneity and mechanistic depth: The studies varied in terms of model systems, concentrations/doses, and endpoints. Although molecular pathway modulation has been reported, few studies have provided orthogonal target validation (genetic knockdown, rescue experiments, or in vivo target engagement).

Sustainable supply and synthetic accessibility: For several MNPs, low natural abundance necessitates synthetic or semi-synthetic routes (e.g., total synthesis reports for phorbaketal A), which affect the feasibility of development.

Summary of main findings

Preclinical evidence supports the concept that selected MNPs can act as multi-target osteomodulators by (1) reducing inflammatory signalling and osteoclastogenesis (NF-κB/NFATc1 suppression), (2) promoting osteoblast differentiation via Runx2/Wnt activation and epigenetic modulation (HDAC inhibition), and (3) supporting angiogenesis and matrix remodelling in some models.

Data Extraction

Data from each article were extracted using thematic variable-based matrix tables that
The following data were extracted: (1) study identity (title, author, year), (2) study type, (3) type of marine compound and biotic source, and (4) mechanism of action (biological pathway and molecular target). The extraction process was performed manually and re-verified for accuracy and consistency

Table 1. Extraction Results SLR

Title	Writer	Study Type	Marine Product (Sources & Types)	Mechanism of Action (Pathways & Targets)
Kalkitoxin Reduces Osteoclast Formation and Protects against Inflammatory Bone Loss	(10)	In Vitro and In Vivo (animal study)	Kalkitoxin (lipopeptide from the cyanobacterium Moorena producens)	Inhibition of RANKL-induced NFATcl and MAPK (ERK1/2, JNK) pathways
In Vitro Antiproliferative Evaluation of Synthetic Meroterpenes Inspired by Marine Natural Product	(11)	In Vitro	Synthetic meroterpenes (inspired by Aplidium conicum, an ascidian)	Cytotoxic effect through cell cycle arrest in the G0/G1 phase (especially compound 5)
Phorbaketal A, Isolated from the Marine Sponge Phorbas sp.,Exerts Its Anti-Inflammatory Effects via NF-κB, Inhibition and Heme Oxygenase-1 Activation in Lipopolysaccharide-Stimulated Macrophages	(12)	In Vitro and In Vivo	Phorbaketal A is a tricyclic sesterterpenoid isolated from the marine sponge Phorbas sp.)	Phorbaketal A inhibits the release of NO and the expression of iNOS and pro-inflammatory cytokines in LPS-stimulated macrophage
The Beneficial Effect of Praeruptorin C on Osteoporotic Bone in Ovariectomized Mice via Suppression of Osteoclast Formation and Bone Resorption	(13)	In Vitro	Praeruptorin C (Pra-C) from Peucedanum praeruptorum)	Pra-C Suppresses RANKL-Induced Activation of NF-kB and JNK Signaling Pathways
The Proteasome in Modern Drug Discovery: Second Life of a Highly Valuable Drug Target	(14)	Insilico	Immunoproteasome inhibitors thus far are the β1i selective IPSI-001 and the β5i selective ONX0914	The peptide aldehyde inhibitor and accumulation of ubiquitin protein conjugates and proapoptotic proteins, as well as causing caspase-mediated apoptosis
Phorbaketal A stimulates osteoblast differentiation through TAZ-mediated Runx2 activation.	(15)	In Vitro	Phorbaketal A (diterpenoid from the marine sponge Phorbas sp.)	TAZ (transcriptional coactivator with PDZ-binding motif) → Runx2 activation → osteoblastogenesis
Marine-derived angiogenesis inhibitors for cancer therapy	(16)	In Vitro	Aplidin (tunicate), Didemnin B (tunicate), Dolastin 10 (sea hare), Halichondrin B (sponge), Trabectedin (tunicate)	Inhibition of VEGF, FGF, TGF-β pathways, microtubules, and inhibition of DNA/protein synthesis

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Explanation of Extraction Result Table :

1. (10) Reported that calcitoxin, a lipopeptide compound from Moorena producens, inhibited osteoclast differentiation and resorptive activity via RANKL-induced NFATc1 and MAPK pathways, and showed protective effects against bone loss in a mouse inflammatory model. This study had a low risk of bias.
2. (11) Evaluated meroterpene-derived compounds from Aplidium conicum against MG-63 bone cancer cells and found antiproliferative activity that blocked the G0/G1 phase of the cell cycle. This mechanism is more cytotoxic than normal bone formation, indicating a moderate risk of bias.
3. (12) Phorbaketal A inhibited NF-κB transcriptional activity in LPS-activated macrophages. It reduced LPS-induced NO production and downregulated iNOS at the mRNA and protein levels. Production of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6, MCP-1) was decreased. Phorbaketal A upregulated heme oxygenase-1 (HO-1), a cytoprotective/
4. (13) Pra-C inhibits RANKL-induced activation of NF-κB and JNK signalling pathways in osteoclast precursors..
   In vitro, Pra-C reduced osteoclast formation and resorptive activity.
   In OVX mice, Pra-C treatment attenuated bone loss, consistent with suppressed osteoclastogenesis and bone resorption.
   (14) Proteasome inhibition causes the accumulation of ubiquitinated proteins, misfolded proteins, and pro-apoptotic factors, leading to caspase-mediated apoptosis in susceptible cells. Selective immunoproteasome inhibitors (β1i or β5i) modulate immune responses with potentially reduced systemic toxicity compared to broad proteasome inhibitors.
   The known effects of proteasome inhibitors (e.g., bortezomib in myeloma) include reduced osteoclast activity and increased osteoblast differentiation/osteogenesis in some preclinical and clinical contexts, suggesting bone-modulating properties.
5. (15,17) Explained that Phorbaketal A, a marine-derived diterpenoid isolated from the sponge Phorbas sp., has shown significant osteoinductive potential through its action on preosteoblast cells and in an in vitro study using the preosteoblast cell line MC3T3-E1, treatment with Phorbaketal A at concentrations ranging from 1-10 μM over a period of 48 hours resulted in increased osteogenic activity, as evidenced by increased alkaline phosphatase (ALP) activity, mineralization, and upregulation of osteoblast-specific genes, including Runx2, OCN, and ALP. The molecular mechanism underlying these effects involves the activation of TAZ (a transcriptional coactivator with a PDZ-binding motif), which upregulates Runx2, a key regulator of osteoblast differentiation and bone formation. This study had a moderate risk of bias because it employed a controlled in vitro model and utilized valid and relevant measurement parameters, with the concentration and duration of treatment clearly favoring reproducibility.
6. (16) Provides a comprehensive review of marine-derived compounds with anti-angiogenic properties, especially those with therapeutic relevance in cancer. Several bioactive compounds, sourced from tunicates (Aplidin, Didemnin B, and Trabectedin), sea hares (Dolastatin 10), and sponges (Halichondrin B), are discussed as potent inhibitors of angiogenesis. These compounds have demonstrated significant activity in preclinical models, both in vitro and in vivo, primarily through mechanisms such as the inhibition of VEGF, FGF, and TGF-β signaling pathways, disruption of microtubule dynamics, and suppression of DNA and protein synthesis. The risk of bias in this study can be classified as moderate to high because of the use of relevant preclinical models (in vitro and in vivo) and valid measurement parameters that are compatible with anti-angiogenic mechanisms.

DISCUSSION

This systematic review highlights the promising potential of Marine Natural Products (MNPs) as therapeutic agents for bone-related disorders. The reviewed studies provide converging evidence that various MNPs, including lipopeptides,terpenoids, polysaccharides, and depsipeptides, can modulate bone resorption and formation processes through various targets and molecular pathways[18].

Certain compounds, such as calcitoxin and biselyngbyaside, exhibit potent anti-resorptive

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activity by inhibiting osteoclast differentiation and function through the suppression of NFATc1-induced RANKL, NF-κB, and MAPK pathways. These findings align with the established mechanisms of osteoclastogenesis and mirror the actions of current antiresorptive drugs, such as bisphosphonates. On the anabolic side, compounds such as phorbaketal A and largazole promote osteoblast differentiation and mineralization, mediated through TAZ-Runx2 activation and HDAC inhibition (Figure 2). This demonstrates the potential of MNPs as alternatives to anabolic agents,such as teriparatide or romosozumab[19,20].

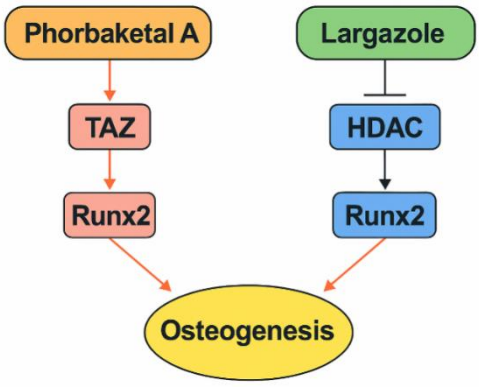

Figure 2. Process of Phorbaketal A and Largazole as alternatives for Osteogenesis

Phorbaketal A and Largazole have shown potential in osteogenesis and bone healing, albeit with differing levels of research and evidence. It can as alternatives for Osteogenesis and bone Phorbaketal A.

Although specific studies focusing on Phorbaketal A for bone healing are limited, it is believed to exert its effects through cellular signaling pathways that influence bone metabolism. This may involve promoting the differentiation of mesenchymal stem cells into osteoblasts.

The role of phorbaketal A in osteogenesis, along with the implications of transcriptional coactivators TAZ and Runx2, can be related through the cellular and molecular frameworks provided by current research. Osteogenesis is predominantly controlled by the transcription factor Runx2, which is crucial for osteoblast differentiation and bone formation (insert citation). It is regulated at multiple levels and interacts within the osteogenic differentiation pathway[21].

TAZ, a transcriptional coactivator with a PDZ-binding motif, plays a pivotal role in mesenchymal stem cell differentiation, impacting both osteoblast and adipocyte pathways. TAZ enhances osteoblast differentiation by interacting with Runx2, demonstrating how Runx2 activity can be modulated by TAZ to promote osteogenesis[22].

Additionally, TAZ nuclear translocation stimulates Runx2 activity, as evidenced by mechanical tension-induced osteogenic differentiation, demonstrating the role of the ROCK-TAZ signaling axis in this process[23].

The interaction between the transcriptional pathways involving Runx2 and TAZ has significant implications for developing treatments to enhance bone mass. The combination of polycystins with TAZ, forming a mechanosensing complex, is critical for osteoblastogenesis, as this complex can respond to physical forces in the bone microenvironment to reciprocally regulate osteoblast and adipocyte differentiation[24].

Studies have shown that polycystin-1 (PC1) regulates bone development through its interaction with the transcriptional coactivator TAZ. The C-terminal tail of PC1 stimulates TAZ, enhancing Runx2 transcriptional activity and promoting osteoblast differentiation. This relationship not only links PC1 to bone development but also emphasizes the critical role of TAZ-dependent pathways in future therapeutic strategies targeting bone disorders[25].

Given this context, the exploration of Phorbaketal A as an alternative for stimulating osteogenic pathways may involve its potential influence on the TAZ-Runx2 axis, although specific studies are still needed to confirm these interactions. Researchers could investigate whether Phorbaketal A can modulate TAZ or Runx2 activity, as seen in the identified impacts of low molecular weight, which enforces TAZ localization, inhibits PPARγ-mediated adipogenesis, and thus stimulates osteogenesis[23].

By targeting the interactions and functions of TAZ and Runx2, therapeutic interventions can be designed to stimulate bone formation and provide insights into the management of conditions such as osteoporosis and other bone density-associated diseases. Therefore, the investigation of Phorbaketal A as an osteogenic alternative should focus on its potential to influence these transcriptional regulators,

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further extending our understanding of bone biology and regulation of osteogenesis[26].

Largazole, a marine-derived histone deacetylase (HDAC) inhibitor, has shown promising potential for promoting osteogenesis and bone regeneration in MSCs. Largazole exerts its effects by modulating chromatin structure, thereby influencing gene transcription critical for bone formation. In particular, largazole significantly induced the expression of essential osteogenic markers, such as alkaline phosphatase (ALP) and osteopontin (OPN). This activity is mediated through the increased expression of runt-related transcription factor 2 (Runx2) and bone morphogenetic proteins (BMPs), both of which are crucial in promoting osteogenesis[27].

Research on largazole underscores the importance of HDAC inhibitors in maintaining bone health. By altering histone acetylation, largazole modulates the expression of genes involved in cell cycle regulation, apoptosis, and other processes that contribute to its osteogenic and anti-cancer properties. Therefore, largazole not only offers hope for enhancing bone regeneration but also extends its therapeutic potential to other areas, such as cancer and liver fibrosis, owing to its regulatory effects on the TGF-β and VEGF signaling pathways[28].

Largazole has demonstrated significant osteogenic activity both in vitro and in vivo, notably in mouse calvarial and rabbit fracture models. Its dual capability to stimulate bone formation while inhibiting bone resorption makes it a noteworthy candidate for treating bone disorders[29].

Previous research in this field. For example, marine-derived peptiroles have been shown to havean osteoprotective role, as these compounds can induce anti-resorptive effects by suppressing Receptor Activator of Nuclear factor Kappa-B Ligand (R-NKL) mediated osteoclastogenesis[30]. This study demonstrates that the interaction between the RANKL signaling pathway and these substances can help prevent bone density reduction, a significant issue in the context of osteoporosis. Marine compounds modulate bone turnover through a complex regulatory network, significantly affects osteoclast and osteoblast activity (30). Bone metabolism is determined by the delicate balance between bone resorption by osteoclasts and bone formation by osteoblasts. The imbalance caused by overactivated osteoclasts plays an important role in various diseases. Activation of the NF-κB and MAPK signaling pathways by receptor activator of nuclear factor-κB ligand (RANKL) is vital for osteoclastogenesis. Here, we for the first time explored the effects of 18β-glycyrrhetinic acid (18β-GA), a pentacyclic triterpenoid found in the Glycyrrhiza glabra L roots, on RANKL-induced osteoclastogenesis, osteoclast functions and signaling pathways in vitro and in vivo[31].

Theoretically, these findings support the conceptual expansion of bone-targeted pharmacology by integrating marine-derived agents into osteotherapeutic strategies. MNPs represent a structurally unique reservoir of molecules with the capacity to engage both genomic and non-genomic pathways in bone cells. The application of MNPs may complement existing treatments for osteoporosis, bone metastasis, and fracture healing, especially in patients intolerant to current drugs or those requiring adjunctive therapy. In addition, some MNPs, such as trabectedin and cytarabine, although not currently used for bone-specific indications, may have repositioning potential because of their influence on bone-related signaling cascades[30,32].

FINDINGS

1. This review synthesizes preclinical evidence on the effects and molecular mechanisms of marine natural products (MNPs) on bone biology, with a comparative focus on two exemplar compounds, phorbaketal A and largazole, a synthesis rarely compiled systematically in previous literature.
2. Highlights multi-target mechanisms that can combine antiresorptive and pro-anabolic effects (e.g., antagonism of RANKL-RANK ;NFATc1/NF-κB signaling together with activation of osteogenic programs such as Wnt/β-catenin, Runx2, and epigenetic modulation via histone acetylation). This study proposes a molecular framework for “dual-action” osteomodulatory agents.
3. It integrates thematic pathway convergence analysis with translational readiness assessment, emphasizing critical gaps: limited pharmacokinetic/toxicology (PK/Tox) data, scarce target engagement validation (genetic or pharmacologic), and supply/synthesis constraints, thereby assessing both biological promise and translational feasibility.

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4. Connects bioprospecting relevance (including biodiversity-rich regions such as Indonesia) to sustainable pharmacological development and ethical and regulatory considerations that are often underreported in mechanistic reviews.

SUGGESTION

Several practical recommendations can be implemented based on the findings of this study. First, researchers in the biomedical and pharmaceutical fields should prioritize the isolation of marine active compounds with osteoprotective effects, particularly those that act through the NF-κB, MAPK, and TAZ-Runx2 pathways, for formulation as new drug candidates. Second, future research should focus on the systematic exploration of the chemical structures and biological activities of Marine Natural Products that have not been thoroughly characterized, particularly compounds from Indonesian marine sources, which have high biodiversity but are less explored. Further studies should employ multi-omics and network pharmacology approaches to identify novel molecular targets and elucidate the synergistic effects of the pathways involved in osteogenesis and osteoresorption.

CONCLUSION

This review supports the premise that marine natural products are a promising source of osteomodulatory agents capable of multi-target actions that may combine antiresorptive and pro-anabolic activities, which is an advantage over single-target therapies. Phorbaketal A and largazole stand out as illustrative candidates: phorbaketal A has an anti-inflammatory/NF-κB inhibitory profile that potentially suppresses inflammation-driven osteoclastogenesis, and largazole has HDAC-inhibitory activity that may unlock osteogenic transcriptional programs.

ETHICAL APPROVAL

This study did not require ethical approval.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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