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REVIEW ARTICLE

# Utilisation of Antibiotics and Metal Ions in Antibacterial Agent-Releasing Scaffolds for Bone Tissue Engineering

**Gerimis Arofah[1], Siti Fauziyah Rahman[1,2], Puspita Anggraini Katili[1,2]**

[1] Division of Biomedical Engineering, Department of Electrical Engineering, Faculty of Engineering, Universitas Indonesia, Depok 16424, West Java, Indonesia
[2] Research Center for Biomedical Engineering, Faculty of Engineering, Universitas Indonesia, Depok 16424, West Java, Indonesia

## ABSTRACT

Bone infection can impede bone regeneration. Hydroxyapatite scaffolds with antibacterial properties are essential as they can sustain high drug concentrations at the infection site for a prolonged duration. This review examines the mechanism of bacterial infection in bones and provides an overview of the fabrication and application of antibacterials in hydroxyapatite scaffolds. The mentioned antibacterial involves incorporating antibiotics into biomaterials, including doxycycline, gentamicin, vancomycin, ciprofloxacin, and metal ions such as silver (Ag), zinc (Zn), and titanium (Ti). High levels of antibiotics and the significant release of antibiotics can effectively suppress bacteria. Nevertheless, it has adverse effects, including substantial toxicity that hinders bone regeneration. This review summarised the current status of antibiotics and metal ions used to develop antibacterial activity-based hydroxyapatite scaffolds, providing insights for future research.

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**Corresponding Author:**
Puspita Anggraini Katili, MD, PhD
Email:puspita_katili@ui.ac.id
Tel : +6221-7270078

## INTRODUCTION

Bones are vital organs that shape and protect various body organs. Defects from accidents, tumours, and diseases can impact health and activities, often requiring surgery. Every year, bone defects affect millions of people around the world and can even result in severe disability (1). In treating infectious bone defects, systemic antibiotics are administered for six weeks; for superficial wounds, the treatment duration is 10 to 14 days (2). Utilising antibacterial scaffolds is a method for bone healing (3). Creating biomedical materials with effective antibiotic and osteogenic properties is crucial for repairing bones with a high infection risk (4). However, systemic antibiotic administration at infection sites may lead to resistance, cell toxicity, and adverse effects on bone regeneration (5). To address this, local strategies like antibiotic release systems on scaffolds can help eliminate or reduce bacterial attachment (6). This literature review will focus on antibacterial agents in hydroxyapatite scaffolds for bone regeneration. We aim to understand how these antibacterial scaffolds work to inhibit bacterial growth and to analyse the outcomes of antibacterial tests on these scaffolds. Our goal is to summarise and discuss the implications of these findings for bone tissue engineering and regenerative medicine. We will examine different antibacterial frameworks, evaluate their effectiveness in preventing bacterial colonisation and promoting bone healing, and discuss the challenges and future directions in bone tissue engineering.

## IMPACT OF BACTERIAL INFECTION ON BONE REGENERATION

Pathogenic bacteria such as *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Escherichia coli* are particularly problematic in causing infections associated with these devices due to their high virulence and increasing antibiotic resistance (7,8). Bacterial secretions and metabolites have been observed to stimulate osteoclast differentiation while inhibiting osteoblast activity. Bacteria can thrive on smaller bone surfaces or lie dormant within osteoblasts, evading host defences and antibiotics, which complicates eradication efforts (9). One potential mechanism involves the direct or indirect activation of osteoclastic bone resorption by bacterial components. This activation can occur through direct interaction with osteoblasts or osteoclasts via expressed bacterial components, or these components can induce the production of osteolytic cytokines as leukocytes infiltrate the bones (7). The schematic diagram of bacterial infection of the bone can be seen in Fig. 1.

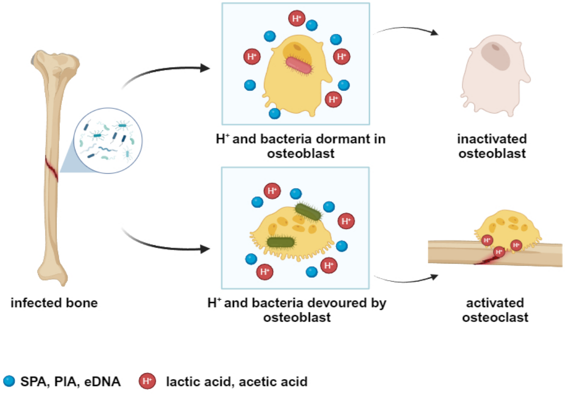

**Figure 1: Schematic diagram of bacterial infection of bones. Created with BioRender.com.**
**Abbreviations: SPA, *Staphylococcus aureus*; PIA, polysaccharide intercellular adhesin; eDNA, extracellular DNA.**

## THE ROLE OF LOCAL DRUG DELIVERY SYSTEMS AND BONE FILLERS

Treatment for bone-related conditions such as osteomyelitis (infection) and cancer includes a variety of therapies such as chemotherapy, tissue transfer, bone grafting, and the implantation of biocompatible antibiotic materials like beads, pastes, or solids. Infections present a significant challenge in medicine due to the limited accessibility of infected sites to antibiotics administered systemically. Therefore, there is a critical need to develop efficient and controlled local drug delivery systems (15,16). Managing bone defects and infections effectively requires comprehensive approaches. Alongside systemic antibiotics, which face challenges in adequately reaching infected sites, local drug delivery systems are indispensable. These systems ensure targeted therapy directly at the affected area, enhancing treatment efficacy while minimising systemic side effects. In this context, bone fillers play a crucial role by facilitating bone regeneration processes such as osteoblast and osteoclast formation and exhibiting essential antibacterial properties for combating infections (17). The utilisation of this particular bone void filler enables the complete release of antibiotics as the material undergoes absorption and remodelling (16,18).

## BONE TISSUE ENGINEERING

Bone tissue engineering relies on understanding bone structure, mechanics, and tissue formation to create new functional bone tissues. Effective bone regeneration or repair necessitates a comprehensive knowledge of bone biology and development. Bone continuously undergoes resorption and renewal, involving constant chemical exchange and structural remodelling influenced by internal mediators and external mechanical demands. Often described as the ultimate smart material, bone possesses a unique scar-less regenerative capacity. Successful bone tissue engineering requires the newly formed bone to integrate seamlessly with the surrounding host bone and perform all the essential functions of native bone (10). While bone tissue can repair itself to some extent, the complexity of its structure and the slow rate at which it regenerates often hinder the successful or timely healing of various types of bone defects (11). Recent progress in tissue engineering has led to the adoption of artificial biological substitutes to repair and regenerate bone tissue (12). Understanding the foundational requirements, types, and preparation processes of biomaterials for bone tissue engineering systems is essential for optimising their performance in damaged tissues. Scaffold materials are particularly indispensable in the reconstruction of new organs and tissues by providing a substrate for cell adhesion, proliferation, and differentiation throughout the stages of bone healing (13). These materials play a crucial role in facilitating the integration of newly formed bone with the host tissue, ensuring functional restoration and long-term success of bone repair strategies (14).

## HYDROXYAPATITE SCAFFOLD FOR BONE REGENERATION

Hydroxyapatite (HA) composite, studied for clinical viability since the mid-1980s, is renowned for its biocompatibility, bioactivity, and osteoconductivity, making it widely used as a bone substitute and scaffold for tissue engineering (19). Derived from calcium-rich materials, bioceramic hydroxyapatite scaffolds support cell mobility, metabolic processes, and oxygen and nutrient delivery due to their porous structure. The pore architecture, which influences cell seeding, viability, migration, morphology, proliferation, differentiation, angiogenesis, mechanical strength, and bone formation, must be precisely controlled to ensure effective bone regeneration (20,21). Vascularisation of the scaffold is essential for osteogenesis, requiring optimised porosity, pore size, and continuity for vascular invasion. Studies show that pore sizes less than 15–50 μm aid fibrovascular ingrowth, 50–150 μm promote osteoid formation, and over 150 μm encourage mineralised bone ingrowth (22).

## ANTIBACTERIAL AGENTS IN BONE TISSUE ENGINEERING

The release mechanisms and antibacterial actions vary depending on the antibiotic type and scaffold properties. Doxycycline although its effects on *in vivo* bone healing have not been extensively studied, research suggests it may work by directly inhibiting collagenase activity and affecting osteoclast structure and function

(23,24). Gentamicin, an aminoglycoside, is taken up by *Pseudomonas aeruginosa* through a multifactorial process involving initial ionic interactions with the cell exterior, followed by two energy-dependent phases requiring an energised cytoplasmic membrane; once inside, it inhibits bacterial protein synthesis at the ribosomal level, which is crucial for its lethal effect (25). Vancomycin operates by targeting the D-Ala-D-Ala terminus of peptidoglycan, thereby inhibiting cell wall biosynthesis (26). Ciprofloxacin inhibits cytoplasmic DNA gyrase or topoisomerase IV, both necessary for bacterial DNA replication, and bacterial resistance primarily arises through amino acid substitutions within these target enzymes (27)

The mechanisms of action and release for metal ions like silver (Ag), zinc (Zn), and titanium (Ti) from scaffolds vary based on their chemical properties and interactions with the biological environment. Pure silver and silver nanoparticles (AgNPs) are typically released through dissolution, where silver ions ($Ag^+$) gradually enter the surrounding environment. Ag nanoparticles in scaffolds release $Ag^+$ ions, which bind to negatively charged bacterial membranes, disrupt membrane permeability and integrity, destroy DNA by disrupting hydrogen bonds, inhibit transcription and mRNA synthesis, and lead to protein inactivation; dead bacteria release Ag nanoparticles and Ag+ for subsequent destruction (28,29). The silver antibacterial mechanism of action scheme on the scaffold can be seen in Fig. 2. Zinc causes bacterial death through mechanisms such as reactive oxygen species and direct reactions with bacterial proteins like phospholipids, promoting hydroxyapatite particle's antibacterial potency and bioactivity (30,31). Titanium ions penetrate the cell membrane via interaction with the –SH (thiol) group and other ligands of cell proteins, disrupting cell metabolism by reacting with ATP and releasing protons during cellular respiration (32,33).

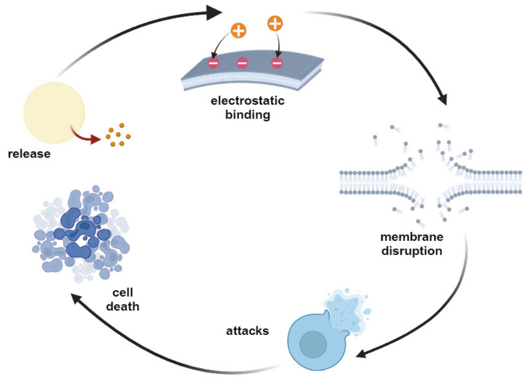

**Figure 2: Scheme of silver antibacterial mechanisms in scaffolds. Created with BioRender.com**

## 1. Antibiotics

### *Doxycycline*

Doxycycline, classified as a tetracycline antibiotic drug, exhibits multifaceted properties beneficial for bone repair processes, including anti-inflammatory effects, inhibition of osteoclast activity, stimulation of fibroblasts, anti-collagenolytic activity, and antimicrobial action (34,35). Studies have demonstrated that incorporating doxycycline into hydroxyapatite scaffolds enhances new bone formation compared to control groups without the antibiotic. This indicates the potential significance of doxycycline-loaded scaffolds in various surgical bone procedures and the treatment of local bone diseases, particularly in cases where inadequate bone vascularisation hampers effective drug delivery via systemic routes (36). Moreover, it's suggested that doxycycline may initiate demineralisation on the bone surface layer, which could lead to the release of osteogenic factors such as transforming growth factor-β (TGF-β), insulin-like growth factor (IGF), or bone morphogenetic proteins (BMPs), into the surrounding tissues, thereby triggering bone induction effects (24). In terms of drug release kinetics, an initial release of approximately 20% of the drug occurs within the first 24 hours, followed by a sustained release over nine days, with around 60% of the doxycycline remaining on the hydroxyapatite microspheres after seven days (36). Similar trends were observed in another study on the Coll/nHA/Doxy scaffold. The total release of doxycycline during the first 24 hours is 29.42%, and over 14 days, on Coll/nHA/Doxy scaffold is 66.3% (23). The combined treatment with nHA-doxycycline demonstrated that cytotoxicity is directly dependent on concentration, with a low concentration of doxycycline (5 μg/ml) exhibiting a less significant inhibitory effect on cancer cells compared to 30 μg/ml (37).

### *Gentamicin*

Gentamicin, an aminoglycoside antibiotic effective against *Pseudomonas* (38). Gentamicin can be used in a 20% hydroxyapatite implant that releases gentamicin sulfate over four weeks without burst effects, making it suitable for managing chronic osteomyelitis locally (39). Moreover, the incorporation of gentamicin with hydroxyapatite exhibited no cytotoxicity towards MG-63 cells, indicating the potential of gentamicin as a safe alternative for bioresorbable bone defect, effectively reducing implant-associated infections (40). The release of gentamicin sulfate from all implants is continuous and sustained, with the rate of release being influenced by the hydroxyapatite content of the implant. It surpasses 50% after seven days and 60% after 20 days (39).

### *Vancomycin*

Vancomycin, the primary drug against methicillin-resistant *Staphylococcus aureus* (MRSA), has its antibacterial effect influenced by the released amount (41,42). High concentrations consistently inhibit S. aureus and MRSA, while lower concentrations may not. Adjusting antibiotic release rates through different polymers and concentrations ensures bacterial growth inhibition without cytotoxicity in bone cells (42,43). Vancomycin scaffold demonstrates sustained drug release, inhibiting osteoclast activity and showing immunoregulatory effects (9). The scaffold's absence of macrometer-size pores is crucial for studying drug or scaffold interactions and determining optimal loading parameters (43,44). Additionally, the vancomycin scaffold effectively reduces inflammatory reactions and enhances bone trabeculae formation (45). A comprehensive study highlights the effectiveness of hydroxyapatite cement as a biocompatible carrier material that solidifies in vivo, enabling extended antibiotic release. The recovery rate of vancomycin at the end of the observation period varied between 54.2% for 240 mg/ml concentration and 73.9% for 80 mg/ml concentration (46).

*Ciprofloxacin*

Ciprofloxacin (CIP), a fluoroquinolone (FQs) drug, has good antibacterial activity and a 50% inhibitory concentration of 40 μg/ml at 48 and 72 hours (5,47). When combined with hydroxyapatite, a biocompatible, bioactive, and osteoconductive material, it becomes suitable for developing bone grafts (48). In vitro release of ciprofloxacin from various bone implants is sustained for weeks, showing a consistent pattern (49). The scaffolds loaded with ciprofloxacin exhibit persistent antibacterial capabilities, boosted further by the incorporation of nano-hydroxyapatite (n-HA), which promotes the differentiation of bone marrow-derived mesenchymal stem cells (BMSCs) towards osteogenic pathways (50). This dual functionality ensures a heightened concentration of antibiotics locally, crucial for combating bacterial infections at the implantation site while minimising systemic exposure to mitigate potential toxic effects (50). During the initial phase of the other study, approximately 46% of the ciprofloxacin was released from the HA-CIP composite, highlighting its controlled release profile and efficacy in therapeutic applications (48).

### 2. Metal Ions

In addition to antibiotics, metal ions such as silver, zinc, and titanium are widely recognised for their effective antibacterial properties when incorporated into hydroxyapatite. These ions inhibit bacterial growth and enhance the material's biocompatibility, making them promising candidates for various biomedical applications.

*Silver (Ag)*

#### i. Pure Ag

Silver compounds are commonly used as antibacterial agents, and studies have shown that silver ions can be incorporated into biocompatible and osteoconductive hydroxyapatite structures (51). Pure silver (Ag) releases silver ions ($Ag^+$), providing antibacterial activity (52). The release rate of silver ions from Ag-hydroxyapatite scaffolds is 0.001 ± 0.0005 wt%/h (51). Incorporating silver into Ag alloys enhances the material's mechanical, antimicrobial, and osteogenic properties (52).

#### ii. Ag nanoparticles

Nanotechnology has enhanced the physical, chemical, and biological properties of silver by transforming it into silver nanoparticles (Ag NPs). Several researchers have investigated the antibacterial mechanisms of Ag-NPs and their effects on osteogenic-related cells, suggesting that Ag-NPs at concentrations ≤10 μg/mL are safe for these cells (53,54). The antibacterial properties of silver, whether in insoluble or ionic form, show effective bacterial inhibition (29,55). Silver ions diffuse and destroy bacteria, preventing their growth by causing cell lysis, inhibiting cell replication, and reacting with peptidoglycan cell walls, plasma membranes, DNA, and proteins (56,57). Notably, the respiratory chain in bacteria occurs in the cell membrane, while in human cells, it takes place in the mitochondria. This difference affects the local concentration of Ag at the "killing site." Therefore, by optimising the concentration of Ag-NPs in the scaffold, it is possible to achieve a nanofunctionalized scaffold that balances antimicrobial and osteoregenerative properties (54).

*Zinc (Zn)*

Zinc is essential for cellular function, participating in various biochemical pathways, and its Zn2+ ions promote bone remodelling by enhancing bone formation and mineralisation while inhibiting bone resorption (58,59). $Zn^{2+}$ ions in the scaffold prevent bacterial colonisation by causing cell wall damage and cell death by binding to microbial membrane proteins to destabilise and increase permeability and interacting with bacterial enzymes to deactivate them (30,60,61). Hydroxyapatite modified with zinc ions exhibits antimicrobial activity, reducing infections in bone implants (62). Zinc-cHA microspheres adsorb zinc from biological fluids, with zinc and calcium showing similar release profiles, indicating stoichiometric dissolution. However, high accumulation of calcium and zinc can impair bone repair by inhibiting osteoconduction (63). Despite this, zinc bone grafts show promise as bone regenerative materials (64).

*Titanium (Ti)*

Alloying pure titanium with various elements to improve mechanical properties and tissue adaptation times in surgical implants is progressing rapidly. However, releasing toxic alloy elements into body fluids poses serious risks to patients, making selecting non-toxic substances like hydroxyapatite for alloying crucial. The optimal amount of hydroxyapatite added to titanium implants shows microstructural changes and improves biocompatibility, inducing bone cell growth (65). Bi-modal pore structures (macro or microporosity) in Ti-HA composites may aid bone tissue orientation (66,67). Due to interdiffusion, an intermediate layer forms between hydroxyapatite particles and the titanium matrix, maintaining interface stability even with 50% hydroxyapatite content, which is higher than typically required for bone applications (68). The Ti-HA composite demonstrates significant potential for biomedical applications and exhibits excellent cytocompatibility, as cells infiltrate the pores of the Ti-20HA composite. Observations of NIH3T3 fibroblast cell adhesion on the Ti-20HA composite revealed that the cells successfully attached and proliferated, covering the entire surface by the fourth day of culture (69).

## STATE OF THE ART OF ANTIBACTERIAL AGENT-RELEASING SCAFFOLDS FOR BONE TISSUE ENGINEERING

Incorporating antibiotics or metal ions into the bone scaffold can modify its antibacterial efficacy by leveraging its structural attributes such as scaffolds, scaffold fabrication, antibacterial types, bacteria used for testing, antibacterial loaded method, bacterial inhibition rate, zone of inhibition, pore size, and porosity. Detailed summaries of these aspects for each study reviewed are provided in Table I.

## THE USE OF ANTIBACTERIAL AGENT-RELEASING SCAFFOLDS IN BONE TISSUE ENGINEERING

### 1. Osteomyelitis

Osteomyelitis, an infection of the bone tissue, typically requires four to six weeks of treatment (70). The most commonly identified microbes responsible for chronic osteomyelitis include Staphylococcus aureus, Group A beta-hemolytic *Streptococcus,* and gram-negative bacteria such as *Salmonella*, *Mycobacterium tuberculosis*, and *Pseudomonas aeruginosa* (71,72). Conventional antibiotics can lead to side effects like antibiotic resistance and systemic toxicity, necessitating hospital monitoring (73). Therefore, scaffolds with antibacterial properties are crucial to prevent infection while promoting bone tissue formation. Effective treatment should address bacterial infections and support bone regeneration post-debridement (74). The development of scaffolds with local antibacterial properties offers an antimicrobial approach to

**Table I. The state-of-the art for antibacterial activity in scaffolds for bone tissue engineering.**

| Scaffold Type | Fabrication | Antibacterial | Antibacterial Loaded Method | Bacteria | Inhibition Rate | Zone of Inhibition | Pore Size | Porosity | Ref. |
|---|---|---|---|---|---|---|---|---|---|
| HADOX 0.15 | Freeze-drying | Doxycycline | Adsorption | *E. faecalis* | >100% after 24 h | - | 5.3 ± 0.3 | 52.30 ± 2.52% | (29) |
| Coll/nHA/Doxy | Freeze-casting | Doxycycline | Mixing | *S. aureus*<br>*P. aeruginosa.* | 1 ± 0.8 after 24 h<br>1 ± 0.6 after 24 h | - | 596 ± 69 nm | 93.00 ± 1.50 | (15) |
| GNT-HAp/Col | Freeze-drying | Gentamicin | Mixing | *E. coli* | - | 4.41 ± 0.16 after 24 h | 14.4 ± 1.0 nm | - | (32) |
| PL/vancomycin/nano-hydroxyapatite | Freeze-drying | Vancomycin | Mixing | *S. aureus* | 22.825% after 5 weeks | - | - | - | (62) |
| VCM/nHAC/PLA | Freeze-drying | Vancomycin | Mixing | *S. aureus* | 99.9% after 24 h | - | - | 80.77 ± 6.7% | (36) |
| V50 | Precipitation | Vancomycin | Adsorption | *S. aureus* | 57.14% after 6 h | - | 100-200 nm | 25% | (35) |
| HAp-ciprofloxacin | Precipitation | Ciprofloxacin | Impregnation | - | | | - | - | (43) |
| HA-cip-3 | Precipitation | Ciprofloxacin | Precipitation | *E. coli*<br>*S. aureus* | - | 3.9 ± 0.2 cm<br>38 ± 0.2 cm | - | - | (63) |
| Ag-HAp | Wet Chemical method | Ag pure | In situ doping | - | - | - | - | 49.8 ± 4.8% | (44) |
| Ag-Mg-HA | Freeze drying | Ag nanoparticles | Wet chemical method | *E. coli*<br>*S. aureus* | 99% after 24 h<br>100% after 24 h | **-** | **-** | **-** | (7) |
| mat_HA/Zn-1 | Freeze-drying | Zinc | Mixing | *E. coli*<br>*S. aureus*<br>*P. aeruginosa.* | >99,94% after 24 h<br>>99.91% after 24 h<br>>99.95% after 24 h | - | - | - | (52) |
| Ti-HA | Powder metallurgy | Titanium | Mixing | - | - | - | 0.03-10.29 µm | - | (64) |

continue

**Table I. The state-of-the art for antibacterial activity in scaffolds for bone tissue engineering.(cont.)**

| Scaffold Type | Fabrication | Antibacterial | Antibacterial Loaded Method | Bacteria | Inhibition Rate | Zone of Inhibition | Pore Size | Porosity | Ref. |
|---|---|---|---|---|---|---|---|---|---|
| Ti5-HA | Hydrothermal synthesis | Titanium | Mixing | *E. coli*<br>*S. aureus* | - | 10 mm after 24 h<br>8 mm after 24 h | 60-200 nm | - | (25) |

Abbreviations: HADOX.015, hydroxyapatite-doxycycline 1.5 mg/ml; Coll/nHA/Doxy, collagen/nano-hydroxyapatite/doxycycline; GNT-HAp/Col, gentamicin-hydroxyapatite/collagen; PL/vancomycin/nano-hydroxyapatite, platelet lysate/vancomycin/nano-hydroxyapatite; VCM/nHAC/PLA, vancomycin/nano-hydroxyapatite/poly (lactic acid); V50, vancomycin 50 mg/ml; HAp-ciprofloxacin, hydroxyapatite-ciprofloxacin; HA-cip-3, hydroxyapatite-ciprofloxacin-3; Ag-HAp, argentum-hydroxyapatite; Ag-Mg-HA, argentum-magnesium-hydroxyapatite; mat_HA/Zn; matrix hydroxyapatite/zinc; Ti-HA, titanium-hydroxyapatite; Ti5-HA, titanium-hydroxyapatite 5 wt%; h, hours; µm, micrometer; nm, nanometer; cm, centimeter; *E. faecalis, Enterococcus faecalis; E. coli, Escherichia coli; S. aureus, Staphylococcus aureus*.

osteomyelitis treatment, along with osteoconductivity (43,49,75,76). No histological evidence of infection was found on day 42 in animals receiving HA/vancomycin treatment. In contrast, the control group showed different stages of chronic osteomyelitis with higher histomorphological scores, signalling ongoing infection (77). For gentamicin, the release rates and levels into normal bone in rats were stable. Its bactericidal activity remained effective when embedded in calcium hydroxyapatite ceramic. Additionally, histological assessments confirmed that the ceramic blocks were fully biocompatible (78). However, incorporating antibiotics into hydroxyapatite scaffolds may result in limited control over the release kinetics, potentially leading to inadequate antibiotic concentration at the infection site and possible treatment failure (77,78).

### 2. Bone Tumour

Common treatments for bone tumours include chemotherapy, surgery, and radiotherapy, with surgery being the primary approach (79). Despite surgery's effectiveness, bone healing can still be impacted by residual tumour recurrence and metastasis. Scaffold properties must favour cell attachment and support antibacterial release in the tumour microenvironment to eliminate remaining tumour cells (80). Combining chemotherapy with scaffold biomaterials presents a potential therapeutic approach for regenerating bone tumour defects after surgery (81).

## CONCLUSION

The selection of antibacterial is crucial for ensuring effective and sustainable clinical treatment. In addition to the presented antibacterial test, a comprehensive understanding of chemical, biological, and mechanical characteristics is necessary to create an efficient scaffold with good osteoconductivity. Developing biomaterials with antibacterial properties is essential to address bone infections and gradually enhance bone repair. The current use of effective antibacterials lays the groundwork for future applications in bone tissue engineering.

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