Zinc-Based Biomaterials for Antimicrobial Therapy and Tissue Regeneration: Design, Mechanisms, and Biomedical Application

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Abstract. Zinc-based biomaterials represent a revolutionary advancement in the field of biodegradable metals for biomedical applications. Their primary use currently lies in orthopedics and dentistry, featuring innovative devices such as the Mg-Ca-Zn alloy screws, presenting a superior alternative to traditional titanium implants due to their biocompatibility, and zinc-based nanoparticles, demonstrating enhanced biodegradation and antibacterial properties tailored for treating dental caries. Zinc is vital for numerous biological functions, including immune response and cellular proliferation. Its high biocompatibility underscores its suitability for clinical use, and zinc alloying has demonstrated promise in promoting bone regenerating activity and exhibiting anti-tumour effects. Nevertheless, challenges like limited mechanical strength and the need for controlled degradation rates remain obstacles to its clinical translation. Designing a zinc-based biomaterial that provides a sustained release of ion sufficient to have antimicrobial effects without reaching cytotoxic thresholds is difficult. Hence, current research efforts focus on developing zinc-based alloys through techniques such hot extrusion and compositional modifications, aiming to enhance zinc's in vivo performance and expand its biomedical utility.

Keywords: Zinc-based Biomaterial, Antimicrobial activity, Bone regeneration, Biodegradable metals.

1. Introduction

Zinc is a fundamental micronutrient in the human body, and is commonly obtained from various food sources. It participates in numerous biological pathways across all living organisms and plays critical roles in immune function [1] and bone metabolism [2]. It acts as a cofactor for more than 300 enzymes and is involved in over 3000 enzymatic processes [3]. Globally, roughly 17% of the population is at risk of insufficient zinc intake, as reported by the National Center for Biotechnology Information (NCBI) [4]. The human body contains around 2-3 grams of zinc, predominantly found in bone, muscle and prostate tissues [5]. Zinc deficiency results in impaired growth and increased susceptibility to infectious diseases [6]. Beyond its biological roles, zinc is also recognized as a promising novel biodegradable material, particularly in clinical applications.

Traditional biodegradable metals face crucial limitations that restrict their long-term safety and efficacy. A primary issue concerns degradation behaviour. Many biodegradable materials either have an overly high degradation rate or an inadequate degradation rate, both of which increase the risk of implant failure. Titanium, for example, has a corrosion rate of lower than 0.02mm/ year [7], which may often cause implant instability in the human body. In contrast, magnesium degrades much more rapidly, at approximately 0.75mm/year [8], leading to excessive ion release and undesirable cytotoxicity [9]. Furthermore, the bio-inert nature of widely used metals such as titanium alloys often results in poor integration with surrounding tissues and the formation of fibrous encapsulation around the implant [10], which ultimately compromises its long-term performance.

Compared to other permanent metals, the corrosion rate of zinc is more suitable for physiological environments. Zinc degrades at a rate between that of magnesium and iron [11], offering a balance between mechanical stability and predictable ion release. Additionally, Zn-based biomaterials exhibit outstanding biocompatibility, as zinc ions naturally exist in the body as essential metabolic ions, and are regulated through homeostasis processes. This prevents harmful accumulation and cytotoxicity, making zinc an appropriate material for supporting tissue regeneration.

To further understand this topic, this study summarizes common design strategies for Zn-based biomaterials, followed by a discussion of their effectiveness in various clinical applications, including orthopedics, dentistry, wound healing, and anti-tumour therapy. It also evaluates the challenges faced by Zn-based materials, and highlights potential solutions to these limitations.

2. Zinc Biomaterial Design and Mechanism

The study of Zn-based biomaterials has been a prominent focus within contemporary biomedicine due to their excellent biodegradability and favorable physical properties. Conventional metallic biomaterials, such as titanium alloys and stainless steel, have been widely used in clinical settings as integral components of tissue implants [9]. Although generally regarded as hypoallergenic, corrosion inevitably occurs for these metallic materials. Corrosion begins immediately upon implantation, forming an oxide layer [12]. This represents significant limitations of metallic biomaterials: metal ions, such as nickel ions, released from stainless steel during implantation or continuous degradation, can induce cytotoxic effects [9]. In contrast, Zinc^{2+} ions released during the degradation of zinc-based implants tend to exert milder biological responses [13]. Notably, part of their mechanism involves activating osteogenesis and angiogenesis, thereby enhancing the therapeutic effects of the implants [14].

In this study, the term ‘Biomaterial design’ refers to the composition and structure of the material. Zn-based materials can be broadly categorized into three major types based on their biomaterial design: zinc alloys, Zn-based nanoparticles, and zinc coatings. Each possesses unique properties in clinical application *(Table 1)*. Zn-based alloys, such as zinc-magnesium (Zn-Mg), are promising biomaterials widely used in orthopedic surgeries and tissue implantation. A recent study by Wang et al. reported that Zn-Mg can suppress microbial activity.

Table 1. A comparative overview of zinc-based biomaterial classification.

Type	Example	Advantage	Disadvantage
Zinc Alloy	Zn-Mg	High strength	Potential cytotoxicity
Zinc-based Nanoparticles	$ZnFe_2O_4$ NPs	Synergistic antioxidant effects	Complex synthesis
Zinc Coating	ZnHAp	Slow degradation	Low mechanical strength
Zinc Alloy	Zn-Mg-Ca	Controlled degradation rate stabilized by Ca	Risk of excessive ion release
Zinc-based Nanoparticles	ZnO NPs	Strong antimicrobial effects	Dose-dependent cytotoxicity

This table outlines some of the common zinc-based biomaterials under investigation for biomedical applications. For each category, the principal advantages and disadvantages that restrict their clinical applications are summarized [15-19].

Table 1 outlines some of the common zinc-based biomaterials categorized based on their biomaterial design, where the principal advantages and disadvantages that restrict their clinical applications are summarized. The synthesis of zinc nanoparticles has long been studied in nanotechnology; however, their biomedical applications have only recently emerged. Haghniza et al. provided evidence that $ZnFe_2O_4$ nanoparticles (NPs), when applied to burn wounds, can enhance cell migration toward the wound site, resulting in an over 20% scratch closure 18 hours post-treatment [16]. Zn-based coatings, which come in various forms, are typically used for protection against corrosion of metallic materials [17]. One common limitation of Zn-based coatings is the size of zinc particles. Kalendová (2003) reported that coatings composed of smaller zinc particles tend to exhibit stronger anticorrosion effects in vitro [20]. This phenomenon is attributed to the permeation of moisture and gases through the gaps between larger zinc particles, which reduces the durability of the coating.

As an essential cofactor in over 300 human enzymes [3], zinc plays a critical role in metabolism, immune function and cancer regulation [21]. Zn-based biomaterials exert their effects in vitro via two main mechanisms. The non-contact release of Zn2+ ions, along with reactive oxygen species (ROS) that damage bacterial walls, contributes to their antimicrobial activity [22]. In contrast, the physical disruption of bacterial membranes is caused by the serrated or jagged morphology of zinc-based nanoparticles, such as zinc oxide nanoparticles (ZnO NPs) [23].

3. Application of Zinc-based Biomaterial

Zinc-based biomaterials offer significant potential in modern healthcare, capable of promoting osteogenesis activities [2] and acting as an antibacterial agent against a broad spectrum of bacteria. Zinc-based biomaterials have diverse potential applications [24], ranging from serving as an alternative dental material [19, 25] to offering new therapeutic strategies for conditions like inflammatory bowel disease (IBD) and even preventing the formation of colorectal tumours [26]. This section will give an overview of the key roles of zinc-based biomaterials in clinical application. To understand the underlying mechanism, the following discussion will begin by exploring its effects on osteogenic activities.

3.1. Orthopedics

Zn-Mg alloy is one of the most widely used Zn-based alloys due to its osteogenic and angiogenic properties. A recent study by Chow & Kwun suggests that zinc ions released from Zn-Mg alloy lead to the upregulation of the osteogenesis-related gene Runx2 [2]. Runx2 is widely recognized as a master osteogenic transcription factor, playing a critical role in osteoblast marker gene expression and inducing osteoblast proliferation by stimulating alkaline phosphatase (ALP) activity [2]. A similar study by Wang et al. (2022) examined additional aspects of how Zn-Mg alloy influences osteogenic differentiation. The result showed that altering the proportions of zinc and magnesium in the alloy changes the levels of metallic ions released, which in turn continuously promotes osteoblast proliferation [15]. This effect is thought to result from the balanced release of Mg^{2+} and Zn^{2+}, as pure Zn extract has been shown to inhibit osteoblast proliferation [15]. Another study by Lee et al. conducted a few years earlier, explored ways to improve the stability of metallic screws used in maxillofacial surgeries [18]. The research focused on magnesium-calcium-zinc (Mg-Ca-Zn) alloy as a viable alternative to the conventional polymer and titanium screws [18].

3.2. Dental Therapeutics

Tooth decay in the human oral cavity is primarily caused by several key bacterial species. Nearly 90% of adults worldwide experience tooth decay annually [27]. Conventional restorative dental materials include ceramic, gold, amalgam, and various other cements [25]. Building on this concept, recent studies have explored the potential use of ZnO as an alternative dental material [19]. ZnO NPs have been reported to possess antibacterial properties. This property is enhanced when ZnO NPs are incorporated into resin-based materials, which can effectively suppress the growth of *S. mutans*, a main cause of the formation of dental plaques [24].

3.3. Anti-Inflammatory Effects in Wound Management

A central challenge in wound healing is the rapidly evolving antibiotic resistance of the bacteria. Mainstream alloy implants currently used in clinical practice do not inherently provide sufficient antimicrobial effects. Given these persistent challenges, scientists have increasingly focused on zinc-based biomaterials as a viable alternative to current alloy implants. Key studies suggest that zinc ferrite nanoparticles ($ZnFe_2O_4$ NPs) effectively inhibit the growth of both Gram-positive and Gram-negative bacteria [24]. $ZnFe_2O_4$ NPs can be synthesised via a modified co-precipitation method [16]. To analyse both the antimicrobial effect and cytotoxicity of $ZnFe_2O_4$ NPs, Haghniza et al. conducted a series of in vitro assays to evaluate their performance [16]. The results showed that $ZnFe_2O_4$ NPs exhibit dose-dependent cytotoxicity toward human dermal fibroblasts (HDFs) [16]. At concentrations ≤125 ug/mL, they effectively inhibit bacterial growth, where concentrations ≥500 ug/mL can cause severe cytotoxic effects [16].

3.4. Tumorigenesis Inhibition

Ulcerative colitis (UC) is a type of IBD that results in ulcers or sores in the lining of the digestive system. Over the long term, this condition may progress to colorectal cancer due to chronic inflammation in the colon [26]. Li et al. provided preclinical evidence that ZnO NPs could serve as an alternative therapy for IBD [26], potentially preventing colorectal tumour formation. In the study by Li et al., administration of ZnO NPs at 50 mg/kg significantly reduced immune responses induced by Dextran sulphate sodium (DSS)-induced ulcerative colitis in mice [26]. This was manifested as a significant decrease in white blood cell counts and restoration of haemoglobin levels, indicating the anti-inflammatory effects of ZnO NPs in vivo [28]. Nuclear factor-erythroid 2-related factor 2 (Nrf2) is a transcription factor that acts as a promoter during the synthesis of antioxidant and detoxifying enzymes. ZnO NPs may directly interact to suppress IBD via upregulation of the Nrf2 signalling pathway, thereby achieving an anti-proliferation effect.

4. Challenges and Improvements

4.1. Degradation Rate and Cytotoxicity Control

Despite the encouraging prospects of zinc-based biomaterials in the domain of biomedicine, numerous significant challenges impede their clinical translation. A primary concern is the regulation of the degradation rate. The degradation mechanism of zinc has been extensively studied over many years. Although zinc’s corrosion rate is relatively moderate compared to other metallic alloys, it inevitably affects the human body in both beneficial and adverse ways. Without precise control of the degradation rate, insufficient zinc ion release may fail to support osteogenesis, as suggested by Chow & Kwun (2018), whereas excessive ion release can inhibit cell proliferation and tissue regeneration [2, 29].

Interestingly, the human body exhibits innate mechanisms that partially mitigate this challenge, such as forming a protective barrier around zinc particles. Torne et al., pioneers in this field and among the first to investigate zinc degradation in human plasma, revealed that the corrosion process is influenced by the local microenvironmental factors such as pH variations and specific proteins. The degradation mechanism of zinc in whole blood is dynamic [30], with differences in local environments affecting the degradation rate. The plasma microenvironment was identified as the second most corrosive against zinc, following whole blood [30]. The initial corrosion rate in plasma was high (0.3mm/year) but gradually decreased to 0.1mm/year over 72 hours, due to the formation of an organic-inorganic hybrid film on the zinc surface, facilitated by the incorporation of plasma proteins and other biomolecules [30]. These findings provide strong evidence of the body’s natural response to counteract the effect of zinc-ion release.

4.2. Mechanical Weaknesses

Another limitation is the inherent mechanical weakness of pure zinc and several early-stage alloys. Their relatively low ultimate tensile strength (UTS) and yield strength (YS) *(Table 2)* make them inadequate for load-bearing orthopedic applications.

Table 2. UTS and YS of pure zinc, grade 304 stainless steel, and pure magnesium.

Metal	Ultimate tensile strength (MPa)	Yield Strength (MPa)
Pure Zinc	≈ 20	≈ 10
Stainless steel 304	≈ 515	≈ 205
Pure Magnesium	≈ 219	≈ 187

Data obtained from: Pure zinc [28], Stainless steel 304 [31], Pure magnesium [32]

Enhancement of zinc's mechanical properties is typically achieved through fabrication techniques such as alloying, which numerous studies have shown to effectively enhance the UTS and YS values. Major alloying elements for zinc-based alloys include magnesium, copper, manganese, and others [28]. Alloying zinc typically involves two main steps: solid solution strengthening and precipitation hardening [28]. Consequently, the UTS and YS of zinc alloy increase substantially compared to pure zinc *(Table 3).* As table 3 demonstrates, applying hot extrusion at 250 Degrees Celsius on Zn-0.8Mn-0.8Cu can further improve the mechanical properties of zinc [33]. Another research done by Bazhenoc et al. also found something similar: that when the alloy Mg-Y-Zn-Mn is being hot extruded at temperatures ranging from 400-450 Degrees Celsius, the anisotropy of the alloy or in other words, the directional strength of the alloy increases parallel to its YS and UTS values [33]. This is because the application of heat facilitates the formation of a 'bimodal grain structure' consisting of both the recrystallized grains, and the non-recrystallized grains [33]. The recrystallized grains line up in the same direction, granting the alloy directionality, whereas the non-recrystallized grains get stuck in between the lined-up crystals, enhancing the stability of the structure.

Table 3. Percentage increase in UTS and YS illustrating the effects of alloying and thermomechanical processing on the zinc's mechanical properties.

Alloyed Zinc	% Change in UTS compared to Pure Zinc	% Change in YS compared to Pure Zinc
Zn-0.8Mn	234	168
Zn-0.8Mn-0.8Cu	564.5	378
Zn-0.8Mn-0.8Cu Extruded at 250 C	1253	2192

The UTS and YS value of pure zinc used to calculate the percentage change was taken from Table 2. UTS and YS values after alloying and thermomechanical processing were obtained from Kumar et al., 2025 [33].

4.3. Scalability and Standardization for Clinical Translation

The clinical translation of metallic alloys into biodegradable implants is often traced back to 1878, when Edward C. Huse achieved hemostasis using pure magnesium wire ligatures [34]. In comparison, research on zinc-based materials is a more recent development. The clinical adoption of zinc-based materials remains highly dependent on the scalability and standardisation of their manufacturing processes.

Good scalability is key to bridging the gap between laboratory research and clinical application. Common laboratory techniques for synthesizing zinc, such as casting, wrought processing [10], and thermomechanical processing, are not always feasible for large-scale production. Fluctuations in critical manufacturing parameters, such as stirring speed, pH, and reaction temperature, can lead to variability in product outcomes [35]. This methodological heterogeneity introduces significant uncertainty in large-scale production of zinc-based biomaterials, and the lack of reproducible outcomes poses a critical challenge for regulatory bodies such as the FDA.

5. Conclusion

This study systematically reviews the current understanding of biodegradable Zn-based materials, focusing on the mechanisms underlying zinc's biocompatibility and processibility, which make it a promising candidate for use in targeted drug delivery. It highlights the extensive applications of Zn-based biomaterials in biomedicine, including the osteogenesis potential of Zn-alloys such as Zn-Mg and their notable antibacterial properties. The findings also suggest that zinc could serve as an alternative dental material to replace traditional metallic options that lack inherently antimicrobial activity. Additionally, recent research indicates the potential of Zn-based materials in cancer immunotherapy, particularly in modulating the progression of inflammatory diseases like UC.

However, the clinical adoption of biodegradable Zn-based materials is limited by significant obstacles. A primary limitation is their mechanical weakness. Pure zinc is known to have significantly lower strength compared to other biodegradable metallic materials such as stainless steel. Unfortunately, common limitations observed in other biodegradable metallic alloys, such as the cytotoxicity and uncontrollable degradation rates, also exist for zinc. Hence, for this material to become more clinically viable, these problems must be addressed. To conclude, despite the significant progress that has been made in the study of zinc as a biodegradable material, more research is still needed to improve the clinical feasibility of Zn-based biomaterials. Such efforts are essential for continued advancement of this field.

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