Rare earth smart nanomaterials for bone tissue engineering and implantology: Advances, challenges, and prospects

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Abstract
Bone grafts or prosthetic implant designing for clinical application is challenging due to the complexity of integrated physiological processes. The revolutionary advances of nanotechnology in the biomaterial field expedite and endorse the current unresolved complexity in functional bone graft and implant design. Rare earth (RE) materials are emerging biomaterials in tissue engineering due to their unique biocompatibility, fluorescence upconversion, antimicrobial, antioxidants, and anti-inflammatory properties. Researchers have developed various RE smart nano-biomaterials for bone tissue engineering and implantology applications in the past two decades. Furthermore, researchers have explored the molecular mechanisms of RE material-mediated tissue regeneration. Recent advances in biomedical applications of micro or nano-scale RE materials have provided a foundation for developing novel, cost-effective bone tissue engineering strategies. This review attempted to provide an overview of RE nanomaterials’ technological innovations in bone tissue engineering and implantology and summarized the osteogenic, angiogenic, immunomodulatory, antioxidant, in vivo bone tissue imaging, and antimicrobial properties of various RE nanomaterials, as well as the molecular mechanisms involved in these biological events. Further, we extend to discuss the challenges and prospects of RE smart nano-biomaterials in the field of bone tissue engineering and implantology.

KEYWORDS
bone grafts, bone tissue engineering, implantology, nanomaterials, RE materials

1 | INTRODUCTION

Rare earth (RE) materials are found naturally in a thin layer of earth surfaces.1–3 RE metals are found in the ores like basalts, granites, gneisses, shales, clays, and silicate rocks. Yttrium and lanthanides are the commonly known RE metals. The Finnish chemist Johan Gadolin isolated the first RE element yttrium in 1794 from gadolinite near Ytterby (Sweden). Seventeen lanthanides have been identified so far.4 Among lanthanides, cerium is the most abundant element (60–68 ppm), followed by neodymium and lanthanum.5,6 Praseodymium, samarium, gadolinium (Gd), and dysprosium have abundances in the range of 5–10 ppm, while other elements are less abundant, with lutetium being the least abundant (<0.5 ppm).7 The electronic configuration of RE elements is ([Xe]4fⁿ5s²5pⁿ [n = 0–14]) and usually exists as trivalent cations. The outer 5s substantially shield the 4f electrons and 5p electrons, and hence the electronic transitions from 4f to 4f or from 4f to 5d are barely affected by the surrounding environment. Therefore, the RE materials have sufficient energy levels and several unique spectroscopic characters such as extended lifetime emission and narrow bandwidth with sharp fluorescent emissions via photoluminescence.8,9
Generally, photoluminescence obeys Stokes law that means the wavelength of the emitted fluorescence light is more extended than incident light, termed the “downconversion” luminescence. Downconversion luminescence converts higher-energy photons into lower-energy photons. For instance, ultraviolet (UV) radiation excites Eu³⁺, Tb⁴⁺, and Dy³⁺ and emits in the visible region. UV excitation of Nd³⁺ emits in the near-infrared (NIR) region. Excitation by long-wavelength radiation (i.e., anti-Stokes luminescence) of Er³⁺ or Tm³⁺ emits shorter-wavelength light. The emitted fluorescence light is in a shorter wavelength and higher energy than the incident light; thereby, it is called anti-Stokes luminescence or “upconversion” luminescence. Therefore, RE materials are gaining their significance in biomedical imaging owing to the reduction of autofluorescence and penetrating properties in the tissues of biological systems.⁺⁻¹²

Various electronic configurations and variable valence states are crucial in enhancing the stability, broadening the absorption range endowed RE ions with flexible redox properties and unique luminous and electromagnetic characteristics.¹³⁻¹⁵ These properties of RE elements attribute to the design of nanostructured materials either as major components or as dopants paving the way for new tissue engineering applications. The particle size ranging from 1 to 100 nm of nanoparticles and geometry has been reported to play an essential role in cell–material interactions, affecting cellular uptake, and cell functioning.¹⁶ Most cell–nanoparticle interactions have been facilitated at nano-biointerface by several factors such as nanoparticle’s shape and surface morphology.¹⁶ The shape/geometry of the nanoparticles directly influences their cellular uptake. It has been observed that rod-shaped particles have the highest uptake, followed by spheres, cylinders, and cubes.¹⁷ Similarly, the neodymium nanoparticle’s shape influences the cellular activity in terms of altered mitochondrial membrane potential, reactive oxygen species (ROS), and eventually angiogenesis in endothelial cells.¹⁸ The cellular uptake of nanomaterials such as liposomes,¹⁹ iron oxide,²⁰ polymeric²¹ gold,²²⁻²⁴ and silica nanoparticles²⁵ is size dependent. The particle size of the polystyrene spheres increased the binding and affected the immune response in human dendritic cells.²⁶ Similarly, the RE materials like ceria have the highest cellular uptake and reactive oxygen species production in human monocyte cell line U937,²⁷ size dependence cell viability in Hela and HEK cells,²⁸ and size dependence biodistribution of ceria was also observed in rat animal model.²⁹ Further, rare-earth fluorides such as erbium showed good cell imaging features depends on their size.²⁹ Besides that, many factors, such as surface chemistry and oxidation states of RE metals like ceria, affected the physiological conditions.³⁰ Few studies reported that RE materials doped mesoporous silica nanoparticle and polymeric nanoparticles possess positively charged that could be facilitated the cell nanomaterial interactions.²¹

Moreover, in vivo assay usually demands controlled particle size to use the enhanced permeation and retention effect, high colloidal stability, and low toxicity.³¹ RE metal-based nanoparticles are used in different imaging approaches other than luminescent imaging like magnetic resonance imaging (MRI) and computed tomography (CT).³² RE materials hold a robust therapeutic potential owing to biocompatibility, optical, and physicochemical properties. Lanthanides are widely used in the electronic and painting industry due to their magnetic and adsorption properties.³³,³⁴ The magnetic properties of some lanthanide cations such as Gd³⁺, Ho³⁺, and Dy³⁺ make RE-based nanoparticles of these cations very useful in MRI because these cations can induce additional contrast between normal and abnormal regions.³⁵,³⁶ In the biological field, various functions of RE elements have been reported. Recently, researchers have been trying to use the intrinsic optical properties of RE nanomaterials for in vivo imaging to monitor the physiologic processes.³⁷⁻³⁹ Besides that, in compliance with unique features, these materials are used for in situ bio-labeling of cellular organelles, photodynamic therapy in tumor targeting, site-specific delivery of therapeutic molecules with a combination of fluorescence and the therapeutic effect as a theranostic tool.⁴⁰⁻⁴⁴ Due to the high adsorbing affinity, RE has been widely used as a doping material with metal to produce alloy materials for bone and dental prostheses production.⁴⁵,⁴⁶ RE nanoparticles can be incorporated into the connectivity centers or inside the metal–organic frameworks.⁴⁷ Highly porous and oriented structures allow RE nanoparticles to accommodate many different functional carrier cargoes like drugs, growth factors, and make them attractive materials for biomedical applications.³³ The development of RE-based smart nano-biomaterials with osteogenic, angiogenic, and immunomodulatory potential and in vivo imaging has a massive scope in the field of bone tissue engineering and implantology. Significant advancements have been made with RE in bone grafts and prostheses design in the past two decades. Here, we have listed the advances and potential applications of these RE smart nano-biomaterials in bone tissue engineering and implantology.

## 2 | BONE CELL BIOLOGY

Bone is a metabolically growing vital organ that gives the body structural (mechanical stability) and functional properties. The bone progenitor cells carry out different functions such as bone formation, resorption, repair, and mineral homeostasis. The bone progenitor cells originate from two cell lineages, mesenchymal and hematopoietic.⁴⁸ Osteoblasts and osteocytes are differentiated from the mesenchymal stem cells (MSCs). Bone narrow mononuclear hematopoietic cells differentiate into osteoclasts.⁴⁹⁻⁵¹ Osteoclasts resorb old and defected bone matrix, and osteoblasts deposit new bone matrix in that place. This phenomenon is called bone remodeling.⁵²⁻⁵⁹ Balanced osteoblast and osteoclast activity maintain healthy bone.⁶⁰ Certain pathological conditions disrupt the osteoblast and osteoclast function, causing bone loss or excessive bone mass.⁶¹ Osteocytes are embedded in the bone matrix, comprise 95% of cells in bone, and have the most extended half-life (25 years) among the bone cells.⁶² A bone matrix consists of organic and inorganic components. The inorganic matrix, calcium, phosphorus, sodium, and magnesium are associated with bone mineral crystals. Bone mineral crystals have shown in the form of apatite, hydroxyapatite (HAp), (Ca₅[PO₄]₃[OH]), and acid phosphate groups (HPO₄)₂ containing brushite (CaHPO₄·2H₂O). These minerals serve as an ion reservoir, which helps maintain their extracellular fluid
concentrations for critical physiological functions and gives stiffness and strength to the bone.62

Osteocytes sense biological and mechanical stimuli and produce a range of signaling molecules to control osteoblast64–67 and osteoclast functions.68–70 The balanced function of osteoblasts, osteoclasts, and osteocytes is vital for effective bone regeneration and implant success.71,72 Researchers are currently developing bone-biomaterials and implants that can modulate osteoblast, osteoclast, or osteocyte function.73–75 RE materials have shown the potential to modulate osteoblast, osteoclast, or osteocyte function.76–79 Therefore, RE-based bone-biomaterials and implants could be the next generation bone graft, implant, and prosthetics for effective bone tissue engineering.

Besides these, endothelial cells, immune cells, and neuronal cells regulate bone regeneration and homeostasis. These cells produce various signaling molecules affecting bone cells' functions in an autocrine or paracrine manner. Endothelial cells influence bone formation through neovessel formation and release of various growth factors needed for osteogenic differentiation of precursor cells. The endothelial cells lie nearby the bone cells and secrete growth factors like platelet-derived growth factor (PDGF)-BB and vascular endothelial growth factor (VEGF) to promote osteogenic differentiation of precursor cells.80,81 Moreover, neovascularization is crucial to supply oxygen and growth factors for the precursor cells migrated to the defect sites. Osteogenic cell-secreted osteopontin induces early angiogenesis in developing bone.82,83 The immune cells, including monocytes, neutrophils, dendritic cells, and B and T lymphocytes, play a vital role in osteoimmunomodulation. Biomaterial-mediated M1 and M2 polarization of macrophages regulate different stages of bone defect healing.84,85 The key molecules responsible for the signaling between osteoclasts and osteoblasts are regulated by immune cells.86–88 The immune cell-secreted tumor necrosis factor-α (TNF-α), interleukin (IL)-6, and IL-1β enhance osteoclast differentiation and bone resorption via receptor activator for nuclear factor-κB ligand (RANKL) secretion.89 These pro-inflammatory cytokines inhibit osteoblast differentiation.90 Whereas anti-inflammatory cytokines, including IL-4 and IL-10, increase bone formation by inducing osteoblast function and inhibiting osteoclastogenesis.90 Chen et al. have summarized the biomaterial–immune cell interaction and its effect on bone defect healing and osseointegration.84,85 Their review suggested the development of novel biomaterials with osteoimmunomodulatory properties for orthopedic and dental applications. Reports from literature had shown the immunomodulatory potential of RE materials,91,92 which is thoroughly discussed in Section 5.1.2 of this review.

Neuronal cells also significantly contribute to maintaining skeletal homeostasis. The bone marrow consists of the sympathetic nervous system (SNS) and parasympathetic nervous system (PNS). SNS closely associates with the blood vessels through the nutrient foramen and innervating different regions; some nerves reach bone marrow and connect with transcortical vessels in the bone.93 Further, neuron regulates various hematopoietic cell functions via neurotransmitters' binding to beta-adrenergic receptors.94 The PNS may innervate the distal femoral metaphysis and uses acetylcholine as the primary neurotransmitter, which binds to muscarinic or nicotinic receptors.95 Apart from the direct regulation of hematopoietic cells, PNS regulates bone remodeling.96–99 Implant-derived magnesium has been reported to promote bone healing via local neuronal production of calcitonin gene-related polypeptide-α (CGRP),100 RE element Gd-doped magnesium scaffold has been reported to enhance bone defect healing via neuronal CGRP-mediated effect on osteogenesis and angiogenesis.101 These findings further strengthen the scope of RE-based biomaterials in orthopedics and implantology.

3 | NANOMATERIALS AND CELLS INVOLVED IN BONE REGENERATION

The unprecedented pathological or congenital malfunctions affect bone metabolism by aberrant or restricted actions of the aforementioned bone cells. Thereby understanding the pathophysiology of these cells cues the novel therapeutic targets for bone-related diseases. Many therapeutic strategies have been developed like small molecules, recombinant proteins, peptides, and plant-based phytochemicals to eliminate bone therapy-related complications. Recently, the role of nanoparticles has significantly compromised the need for bone therapeutics. The organic and inorganic components of the bone matrix directly facilitate bone regeneration and maintain bone homeostasis. RE nanomaterials can be designed in combination with organic and inorganic components of the bone matrix to improve bone regeneration. Various metal ions, including RE, had been reported to modulate the osteocyte, osteoblast, and osteoclast activity. Gold nanoparticles incorporated gelatin hydrogels promote proliferation and differentiation of human adipose-derived stem cells toward osteoblast cells in a dose-dependent manner.102 Another study indicated that the gold nanoparticles suppress osteoclast formation in a dose-dependent manner and increase bone density that can be useful in preventing and treating osteoporosis.103 The gold nanoparticle-labeled MSCs improve contrast for imaging, and gold nanoparticles preserve the migratory capacity of MSCs.104 The gold nanoparticle-functionalized mesoporous silica nanoparticles synergistically increase the immunomodulatory effects and direct osteogenic stimulation by increasing the osteogenic differentiation capability of MC3T3-E1 cells and accelerate new bone formation in a critical-sized cranial defect site in rats.105 The therapeutic potential of Ag–Au–HA compositions would be excellent for bone regeneration and fracture healing.106 Surface modification of bone grafts with silver nanoparticles, samarium, and TiO2 prevents the risk of contamination and infection in alveolar bone and dental implant surgery.107,108 The iron oxide nanoparticles coated with dextrin and chitosan increase osteoblast proliferation and differentiation.109,110 The inorganic nanoparticles like calcium phosphate nanoparticles increase the osteogenic differentiation of rat bone marrow stromal cells,111–113 and magnesium-containing biocomposites facilitate femur fracture repair.100,114–121 In this pipeline, the RE nanoparticles have tremendous potential for bone graft development since it has versatile bio applications, including an antioxidant to antimicrobial effect.122–124
Furthermore, RE metals can be doped in the abovementioned nanoparticles to redevelop the smart nano-biomaterials with improved antimicrobial, immunomodulatory potential of ceria,125,126 the osteo-angiogenic effect of europium,127–129 contrast imaging potential of Gd130,131 and laser irradiation property of neodymium.132,133 This review exemplifies the role of various RE nanomaterials for the therapeutic modulation of these important bone cells.

4 | BONE DEFECT HEALING

Critical size or large bone defects need medical interventions to restore.134–136 A typical bone defect repair consists of four overlapping stages: the initial inflammatory response, soft callus formation, hard callus formation, and bone remodeling.137,138 Bone defect healing starts with an initial anabolic phase, where local tissue volume increases through inflammation, and hematoma is formed at the defect site immediately.139,140 It has been reported that mesoporous silica nanoparticles, silver and gold nanoparticles can induce inflammation, activating the inflammatory cascades to recruit endothelial cells and neutrophils. Ceria nanoparticles and europium-doped mesoporous silica nanospheres (Eu-MSNs) stimulated the pro-inflammatory response in macrophages, osteogenic differentiation of BMSCs, and angiogenic activity of HUVECs. Bone precursor cells and endothelial cells contribute to form cartilaginous bony callus (soft callus), which bridge the gap between the bone fragments.141,142 Chronic inflammation is deleterious to proceed to heal the wound trajectory. Therefore, immunomodulatory nanobiomaterials have been developed using RE nanoparticles such as ceria, which facilitate immunomodulatory action by switching M1 macrophage to M2. M2 macrophages recruit and activate precursor cells to form a cartilaginous soft callus. Soft callus, along with endothelial cells and osteoblasts, then progresses to hard callus formation, also known as primary bone formation; this stage represents the most active period of osteogenesis.143 Following these processes, the bone remodeling phase begins with coordinated osteoblast and osteoclast activities. Reabsorption of callus tissues by osteoclast is followed by lamellar bone formation. The ROS-producing ability of RE nanoparticles such as ceria activates the RANKL pathway to induce osteoclastogenesis.78,79 Moreover, angiogenesis is a critical factor for bone remodeling because it provides the appropriate conditions for osteoblast and osteoclast activities.143–145 The RE materials such as europium has the potent role of angiogenic activity via ROS production.127,128

5 | APPLICATION OF RE SMART NANOBIOMATERIALS IN BONE TISSUE ENGINEERING

Bio-implants are orchestrated specialized materials that render the ability to replace or restore the specific functions of the damaged organs or tissues.146,147 One of the recently identified such materials belongs to RE metal groups. The different RE nanomaterial synthesis methods and their physicochemical properties are listed in Table 1. In addition, RE nanomaterials have a lot of biological applications. Reports from literature had report antioxidants potential of ceria,125,126 osteo-angiogenic effects of europium,127–129 laser irradiation property of neodymium,132,133 and contrast imaging potential of Gd.130,131 Various biological applications, especially concerning bone tissue engineering application of RE materials, are summarized in Table 2. The outcomes of bone fracture healing strategies are still not satisfactory due to the lack of osteoinduction, osteoconductivity, immunomodulation, and osteointegration ability of biomaterials. The use of emerging RE nanomaterials has the potential to address these challenges. In the past two decades, significant advancements have been made using RE materials in bone implants and prostheses design. This review attempts to comprehensively exemplify the potential usage of RE elements in bone graft and implant development. We profoundly discuss the challenges in using RE nanomaterials in bone regenerative medicine, particularly in the osteogenic process.

5.1 | Cerium

Cerium is the most abundant RE element, approximately 50–60 ppm found on the earth’s surface. Cerium exhibits unique redox behavior due to its electron configuration, filling the 4f orbital in the ground state and standard oxidation numbers of -3 or +4. Oxide forms of cerium include cerium (VI) oxide or ceria (CeO2), and dicerium trioxide or sesquioxide (Ce2O3) has been broadly utilized for various applications, such as electrolytes in fuel and solar cells, detection systems, surface polishing, and catalysis. The redox equilibrium between two oxidation states results in the ROS and reactive nitrogen species (RNS) regulation. At the nanoscale level, the reactivity of CeO2 is more effective as the high surface-to-volume ratio results in elevated surface oxygen vacancies, which is responsible for the enhanced biological activities such as antimicrobial, antioxidants, and angiogenic responses.91 The applications of CeO2, especially in bone formation, are discussed in the following sections.

5.1.1 | Redox modulator

Redox signaling is essential for physiological and pathological conditions. Under physiological conditions, there will be a balance between oxidants and antioxidants, which maintains the redox state at the threshold level. The redox states altered beyond the tolerable threshold level lead to apoptosis. Oxidative stress caused by generating abundant ROS in the living system is obnoxious. The body itself has a defense mechanism to modulate such redox states, whereas, in some pathological conditions like bone fracture microenvironment, the levels of ROS are abundantly high and affect bone reconstruction. Excessive ROS production can induce osteoclastogenesis and suppresses the osteoblastic differentiation process. Therefore, it is essential to balance the equilibrium by using antioxidants to modulate the redox states. Nanoceria acts as an antioxidant therapeutic. The different sizes (5, 15, 30, or 55 nm) of ceria particles biodistribution had
| S.no | Method | Nanoparticles | Reductant/modification | Properties | References |
|------|--------|---------------|------------------------|------------|------------|
| 1.   | Hydrothermal | Cerium oxide (CeO₂) | Sodium dodecyl sulfate | Weak agglomeration | 148        |
| 2.   | Hydrothermal | Pr-, Gd-, and Sm-doped ceria nanoparticles | 20% Pr and Sm 10% Gd | Weak agglomeration (13-25 nm) | 149        |
| 3.   | Solution casting | Ce₂O₃ | PLGA | Sustained release of the ceria nanoparticles | 150        |
| 4.   | Flame spray pyrolysis | Nanoceria | Heparin and 3-amino propyl triethoxy silane | 12 nm | 151        |
| 5.   | Sol–gel | Ce₂O₃, Ga₂O₃ doped ZnO | 0.2% Ce₂O₃ and 1.0% Ga₂O₃ | Mesoporous | 152        |
| 6.   | Plasma spraying | CeO₂ | Calcium silicate | Antioxidant | 153        |
| 7.   | Plasma spraying | CeO₂ | Titanium | Antioxidant | 154        |
| 8.   | Sol–Gel | CeO₂ nanoparticles | Oligochitosan alginate and gelatin | Injectable hydrogel | 155        |
| 9.   | Microemulsion | Ceria nanoparticles | Alendronate-PEG 600 | Endochondral ossification | 125        |
| 10.  | Melt quench and Polymer foam replication | Ce₂O₃ and Ga₂O₃ | Borate (13-93b3) | Bioactive glass powders | 156        |
| 11.  | Plasma sprayed | CeO₂ | Calcium silicate | Antimicrobial activity | 157        |
| 12.  | Ultrasonication | EuF₃– and TbF₃-coated multiwalled carbon nanotubes | Sodium dodecyl sulfate | 10 nm thickness of coating | 158        |
| 13.  | Solution synthesis | Eu³⁺-doped Y₂O₃ | Alumina nanoparticles | Ultragelin films | 159        |
| 14.  | Microemulsion | Eu(DBM)₃ dibenzoylemethanate phenanthroline nanoparticles | Triton X-100, Octanol, and cyclohexane | 40 nm in size, spherical shape, and good dispersibility | 160        |
| 15.  | Chemical etching | Re₂Pb₀₂F₆₅ Re-Er²⁺, Yb³⁺, Eu²⁺, Dy³⁺, Ho³⁺, Tm³⁺ | Oxyfluoride nano-glass-ceramics | 8 nm diameter | 10         |
| 16.  | Solution Combustion-fluoridation | RE-doped Lu₂O₃ and Y₂O₃ powders | Eu³⁺-doped and codoped with Yb³⁺/Ho³⁺ | 200–300 nm size | 161        |
| 17.  | Co-precipitation-solvothermal | Eu-doped Y₂O₃ | Aqueous and ethylene glycol | Y2O3:Eu wires and spherical, photoluminescence | 162        |
| 18.  | Conjugation | Eu³⁺-doped Gd³⁺ | Fe₃O₄ nanoparticles via PEG-NH₂ linker | Water-soluble cell fluorescence imaging | 40         |
| 19.  | Microwave | Tb³⁺-doped Eu³⁺ | Polyethyleneimine | 12 nm multicolor luminescent LaF₃ | 163        |
| 20.  | Sol–gel | Eu³⁺, Sm³⁺, and Tb³⁺-doped TiO₂ | Titanium (IV)-isopropoxide, water, ethanol, and nitric acid in the molar ratio of 1:3:20:0.08 | Red emission in Eu³⁺, Sm³⁺-doped TiO₂ | 164        |
| 21.  | Sol–gel | Eu(III) | Europium(III)-doped yttrium, lanthanum, and gadolinium oxides | Sub-10 nm, luminescent properties | 165        |
| 22.  | Emulsifier-free emulsion polymerization | Eu nanoparticles | Oleic acid and sodium undecylenate modified Fe₂O₄ | 120 nm exhibit superparamagnetism | 166        |
| 23.  | Conjugation | Gd-FITC mesoporous silica nanoparticles | Diethylene triamine pentaaetatic acid, phenyl thiourea, tetraethyl orthosilicate, and cetyltrimethylammonium bromide | Red fluorescence and paramagnetism | 167        |
| 24.  | Thermolysis (>250°C) | Er³⁺/Yb³⁺ co-doped NaGdF₄ | Oleic acid, 1-octadecene, sodium trifluoroacetate, polyacrylic acid, and chloroform RGD | 32 ± 9 nm in size, optical, and magnetic properties | 168        |
been analyzed by intravenous injection in rats.\textsuperscript{28} The nanoceria was detected in blood, brain, liver, and spleen. The liver and spleen contain a large percentage of the injected dose, with no significant clearance over 720 h and very little nanoceria entered brain parenchyma. Superoxide dismutase mimetic activity retains in PLGA encapsulated ceria nanoparticles for 90 days under different pH.\textsuperscript{150} Plasma-sprayed CeO\textsubscript{2} coating enhances superoxide dismutase activity and reduces ROS in hydrogen peroxide (H\textsubscript{2}O\textsubscript{2})-treated osteoblasts.\textsuperscript{153} The heparin-functionalized nanoceria enhances cellular uptake and ROS scavenging.\textsuperscript{151}

### Table 1 (Continued)

| S.no | Method | Nanoparticles | Reductant/modification | Properties | References |
|------|--------|---------------|------------------------|------------|------------|
| 25   | Green chemistry | Gd nanoparticles | Dextran, ammonium hydroxide | Ultrafine sub-10 nm | 169 |
| 26   | Molecular dynamics simulations | Metallofullerenol Gd@C\textsubscript{82}(OH)\textsubscript{22} | Fullerene C82 | Inhibition of MMP-2 and MMP-9 | 170 |
| 27   | Solvothermal | GdPO\textsubscript{4}•H\textsubscript{2}O nanobundles | NH\textsubscript{4}H\textsubscript{2}PO\textsubscript{4}, HA, and PLGA | \(~1\ \mu\text{m in length, \sim 30 nm in width, paramagnetism} | 171 |
| 28   | Polyol | Gadolinium (III) oxide | 3-glycidoxypropyl trimethoxysilane, Bisphosphonate | 70 nm, and long-term follow-up imaging studies | 131 |
| 29   | Lyophilization method | GdPO\textsubscript{4}\textsubscript{2}/CTS | | | 172 |
| 30   | Lyophilization method | Gd-doped MCS/CTS (Gd-MCS/CTS) scaffolds | CTAB, NH\textsubscript{3}H\textsubscript{2}O, TEOS | Hierarchically porous structures | 173 |
| 31   | Thermolysis (>250°C) | Er\textsuperscript{3+}/Yb\textsuperscript{3+} co-doped NaGdF\textsubscript{4} | Oleic acid, 1-octadecene, sodium trifluoroacetate, polyacrylic acid, chloroform RGD | 32 ± 9 nm in size, optical, and magnetic properties | 168 |
| 32   | Green chemistry | Gd nanoparticles | Dextran, ammonium hydroxide | Ultrafine sub-10 nm | 169 |
| 33   | Hydrothermal | Neodymium oxide | Acetic acid | Fibrous/rod-like particle | 174 |
| 34   | Solvothermal | Neodymium oxide | Nitric acid/acetic acid | Fibrous/needle-like particle | 175 |
| 35   | Chemical | Nd(OH)\textsubscript{3} | Borohydride | 30–100 nm | 176 |
| 36   | Microemulsion | Nd(OH)\textsubscript{3} | n-butanol, n-octane, CTAB | Cube, sphere, and oval like | 177 |
| 37   | Radiofrequency sputtering | N\textsubscript{d}-doped TiO\textsubscript{2} | TiO\textsubscript{2} and metallic Nd (RF:13.56 MHz) | Red luminescence | 178 |
| 38   | Wet co-precipitation | NdPO\textsubscript{4} | NH\textsubscript{4}H\textsubscript{2}PO\textsubscript{4} | 92 nm, monoclinic, spherical | 179 |
| 39   | Inverse microemulsion and sol gel | Neodymium oxalate | Organically modified silane (Oromsil) | 10–40 nm, violet emission | 180 |
| 40   | Polyl | Neodymium oxide | Diethylene glycol, NaOH | 2–5 nm in size spherical shape | 181 |
| 41   | Sol–gel | CeO\textsubscript{2}, Pr\textsubscript{2}O\textsubscript{5}, and Nd\textsubscript{2}O\textsubscript{3} | Citric acid | 10–30 nm, spherical shape | 182 |
| 42   | Chemical reduction | Nd | Sodium borohydride, hydradine hydride, ammonia | Spherical, cube, and rod | 18 |
| 43   | Electrospinning | Nanofiber | Polyvinyl acetate | Crystalline 20 nm diameter | 183 |
| 44   | Sol–gel | Pr\textsuperscript{3+} | Citric acid, ammonia solution | Spinel cubic crystal and larger ionic radii | 184 |
| 45   | Polyl | Pr\textsubscript{3}O\textsubscript{11} | Diethylene glycol and sodium hydroxide | 10 nm | 185 |
| 46   | Hydrothermal | Ce/Pr-CQDS | EDTA, Glycine | Hydroxyl radical scavenging | 186 |
| 47   | Ball milling | SmCo\textsubscript{5} and PrCo\textsubscript{5} | Dry HEBM under argon, Wet HEBM–heptane, and oleic acid | 10 nm | 187 |
| 48   | Surface functionalization | Sm-doped YV\textsubscript{2}O\textsubscript{4} | Citrate and polyvinyl pyrrrolidone | 20–50 nm | 188 |
| 49   | Emulsion | Sm153 | EDTMP | 200–500 nm | 189 |
| 50   | Thermal decomposition | Y\textsubscript{2}O\textsubscript{3} nanoparticles | Oleic acid | 30 nm, green fluorescence at room temperature | 190 |
| 51   | Microwave irradiation method | Terbium hydroxide nanorods | NH\textsubscript{4}OH | 340 nm length, 65 nm width | 191 |
| 52   | Solvothermal | YbFeO\textsubscript{3}(0–YbFeO\textsubscript{3}) | Ytterbium acetate, Yb chlorides, and iron acetylacetonate | Hexagonal orthorhombic perovskite structure | 192 |
### TABLE 2 Applications of RE smart nano-bio materials in bone tissue engineering

| S.No | RE materials                  | Biological property       | Model                          | Mechanism/pathway                      | References |
|------|--------------------------------|---------------------------|--------------------------------|----------------------------------------|------------|
| 1    | Nanoceria                      | Antioxidants              | Homozygous tubby (tub/tub) mice | Neuroprotection genes                  | 193        |
| 2    | CeO$_2$ nanoparticles          | Antioxidant               | Osteoblastic cell line (MC3T3-E1) | ROS production                         | 153        |
| 3    | CeO$_2$ nanoparticles          | Antioxidant               | MC3T3-E1                       | Wnt/β-catenin                          | 194        |
| 4    | CeO$_2$ nanoparticles          | Antioxidant               | MC3T3-E1                       | Osteoradionecrosis                     | 195        |
| 5    | Cerium (III)                   | Osteoclastogenesis        | RAW264.7                        | NADPH oxidase 1                         | 79         |
| 6    | CeO$_2$ nanoparticles          | Pro-angiogenic property   | MSCs                            | Increased Ca$^{2+}$ level, HIF-1α, VEGF signaling | 196        |
| 7    | SmCeO$_2$                      | Pro-angiogenic property   | Endothelial cells               | p38MAPK/HIF-1α                          | 197        |
| 8    | CeO$_2$ nanoparticles          | Osteoinductive and anti-inflammatory | BMSCs, RAW264.7 | BMP2 and TGF-β1, CD206, IL-1ra, and IL-10 | 194        |
| 9    | Ce$^{3+}$                      | Osteoinductive and anti-inflammatory | BMSCs                        | Smad/BMP                               | 198,199    |
| 10   | Ceria nanoparticles            | Endochondral ossification | Mice critical-sized bone defects | DEAH (Asp-Glu-Ala-His) box helicase 15 and p38 MAPK | 125        |
| 11   | Nanoceria                      | Anti-angiogenic and pro-inflammatory | Vldlr null mice | ERK 1/2, JNK, p38 MAP kinase, and Akt | 200        |
| 12   | Oligochitosan coated CeO$_2$ nanoparticles | Anti-angiogenic and pro-inflammatory | Human retinal pigment epithelium-19 and umbilical endothelium cell lines | Inhibition of VEGF and inflammatory-related protein expression | 155        |
| 13   | Ce (III)-based alginate/ hyaluronate hydrogel | Osteoconductivity and antimicrobial ability | MG63 cells, Staphylococcus epidermidis, Pseudomonas aeruginosa, and Candida albicans | MG63 cell viability | 201        |
| 14   | Ceria inclusion in the graphene hydroxyapatite (GR-HA) matrix | Osteoconductivity and antimicrobial ability | MG63 cells, Staphylococcus aureus, Staphylococcus epidermidis, Pseudomonas aeruginosa | Expression of the osteoblastic genes Runx2, Col I, ALP, BMP-2, OC and OPG | 202        |
| 15   | Ceria and silver-reinforced HA composite | Antioxidant and antibacterial | E. coli and S. aureus | Mechanical integrity and cytocompatible | 126        |
| 16   | CeO$_2$ incorporated calcium silicate | Dental implants and antimicrobial activity | E. faecalis | ALP, OCN, and BSP | 157        |
| 17   | Ceria nanoparticles on the poly-L-lactide scaffold | Cell-material interactions | Human MSCs and osteoblast-like cells (MG63) | Ce$^{4+}$ enhances proliferation, migration, and adhesion behavior | 14         |
| 18   | Cerium                          | Osteogenic differentiation and mineralization | MC3T3-E1                        | Runx2, BMP2, ALP, BSP, Col I, and OCN | 77         |
| 19   | Nanoceria                      | Osteogenic differentiation | BMSCs                           | Dose-dependent manner, 24–72 h         | 203        |
| 20   | Ceria                          | Osteogenic differentiation | MSCs                            | TGF-β1/BMP                             | 204        |
| 21   | Ceria                          | Osteogenic differentiation | BMSCs                           | Smad/BMP                               | 205        |
| 22   | Ceria-stabilized zirconia/ alumina | Mandibular implant       | Clinical report                  | Elasticity equivalent to that of a cobalt-chromium | 206        |
| 23   | Cerium-based zirconia/ alumina composite | Osteogenic response | MC3T3-E1 and male Sprague–Dawley rats | Osteogenic response in vitro and the osseointegration capability in vivo | 207        |
| 24   | Nano CeO$_2$                   | Bone regeneration         | BMSCs and male Sprague–Dawley rats | Enhancing bone regeneration in a critical-size defect rat model | 208        |
| 25   | CeO$_2$ nanoparticles-modified bioglass scaffolds | Osteogenic differentiation | Human BMSCs and in vivo rat, cranial defect models | ERK pathway, collagen deposition, osteoclast formation, and bone regeneration | 76         |

(Continues)
| S.No | RE materials                        | Biological property              | Model                          | Mechanism/pathway                                  | References |
|------|------------------------------------|----------------------------------|-------------------------------|---------------------------------------------------|------------|
| 26   | Nanocrystalline CeO₂                | Dentinogenesis                   | Chinchilla breed rabbits      | Dentin and bone regeneration effectively          | 209        |
| 27   | CeO₂ nanoparticles                 | Chemotherapeutic action          | Osteosarcoma cell line SAOS-2 | pH-sensitive manner                                | 210        |
| 28   | CeO₂ nanoparticles                 | Osteoclastogenesis               | Bone marrow-derived macrophages | ROS-mediated RANKL pathway                        | 78         |
| 29   | Eu(III) complex                    | Contrast agent                   | Bovine tibia specimens        | Bone structure analysis                            | 211        |
| 30   | Gold nanoparticles conjugated with the europium | Luminescent probe               | Human platelets                | Targeted the platelets in low pH 6.5              | 212        |
| 31   | Europium hydroxide nanoparticles  | Angiogenesis                     | Endothelial cells             | PI3K/Akt                                          | 213        |
| 32   | Europium (III) hydroxide nanoparticles | Pro-angiogenic properties       | Endothelial cells             | MAPK pathway                                      | 129        |
| 33   | Gd₂O₃:Eu³⁺ nanotubes               | Bone mineral density             | MC3T3-E1                      | High ALP activity, mineralization, BMP signaling pathway | 214        |
| 34   | Bioactive glass incorporated europium scaffolds | Luminescent property and new bone formation | Osteoporotic bone defects in OVX rats | Bone formation                                    | 128        |
| 35   | Europium-doped mesoporous silica nanoparticles | Pro-inflammatory and osteogenic differentiation | Macrophage and HUVECs | New bone formation at a critical-sized cranial defect site | 215        |
| 36   | Europium-doped bioactive glass nanoparticles | Osteogenic differentiation | Human MSCs                      | ALP activity, COL I secretion, ALP, COL I, OPN, Runx2 | 127        |
| 37   | Eu³⁺-doped nanohydroxyapatite      | Luminescent property and osteogenic differentiation | hASCs                         | GSK3β /β-catenin                                  | 216        |
| 38   | Gd doped FITC silica nanoparticles  | Differentiation into adipocytes, osteocytes, and chondrocytes | Human MSCs | Green fluorescence and paramagnetism              | 167        |
| 39   | RGD functionalized Er³⁺/Yb³⁺-co-doped NaGdF₄ | Tumor angiogenesis               | U87MG tumor cells              | Target the αvβ₃ integrin-expressing tumor cells    | 168        |
| 40   | Gd@C₈₂(OH)₂₂                       | High antitumoral efficacy       | Molecular dynamics simulations | Inhibit MMP-2 activity                             | 170        |
| 41   | Gd-based nanoparticles              | Tumor angiogenesis               | Balb/c tumor-bearing mice      | Determination of tumor boundary by MR imaging    | 169        |
| 42   | GdPO₄H₂O nanobundles               | MRI and X-ray tracing and osteogenesis | MC3T3-E1 and in vivo rabbit radius defects | OCN and mineralization                           | 171        |
| 43   | GdPO₄/CTS scaffolds                | Osteoconductivity                | Rabbit BMSCs                   | ALP, Runx-2, OCN, Col-I, and Smad/Runx2           | 172        |
| 44   | Gd-doped MCS/CTS scaffolds         | Osteogenic differentiation       | Rabbit BMSCs                   | Wnt/β-catenin                                     | 173        |
| 45   | Gd-BG scaffolds                    | Osteogenic differentiation       | Human BMSCs                    | Akt/GSK3β                                         | 217        |
| 46   | Ca−P–coated Mg−Zn−Gd scaffolds     | Orthotopic reconstruction of large-sized orbital bone defect healing | Canines                        | CGRP-mediated angiogenesis and osteogenesis       | 101        |
| 47   | Gadolinium MRI enhancer            | Assessment of perfusion in carpal bones | Kienbock’s disease          | Diagnose altered perfusion in patients with Kienbock’s disease | 218        |
| 48   | Gadolinium (III) oxide nanoparticles | Monitor in vivo implantation     | Condyle defect rat model       | Long-term follow-up imaging studies               | 131        |
| 49   | Gadolinium (III) nanocages         | MRI imaging                      | KPC transgenic mouse models    | Detect neuropilin-1-positive in pancreatic cancer | 219        |
| 50   | Gadolinium                        | Whole-body magnetic resonance imaging | Breast cancer, prostate cancer, and lung cancer patients | Detection of bone metastasis                      | 130        |
Radiation causes bone damage, including a decrease in osteocyte number and osteoblastic activity. CeO₂ nanoparticles exhibit protective effects on irradiation-induced osteoradionecrosis in MC3T3-E1 cells by reducing oxidative stress. Further, increasing the content of CeO₂ in HA coatings diminishes the H₂O₂-induced inhibition of osteogenic differentiation and increases alkaline phosphatase (ALP) activity, calcium deposition activity, and mRNA expression levels of osteogenesis markers runt-related transcription factor-2 (RUNX2).

### TABLE 2 (Continued)

| S.No | RE materials | Biological property | Model | Mechanism/pathway | References |
|------|--------------|---------------------|-------|-------------------|------------|
| 51.  | Yb³⁺/Ho³⁺ Co-doped apatite nanoparticles | Bone regeneration | MG63 cells and New Zealand white rabbits | Distinguish implanted material from bone tissue | 220 |
| 52.  | Magnetic lanthanum-doped HA/CS scaffolds | Macrophage polarization and bone regeneration | Rat bone marrow mesenchymal stem cells | Upregulation of Smad 1/5/9 pathway | 92 |
| 53.  | Lanthanum phosphate chitosan scaffolds | Osteogenic differentiation | BMSCs and rat critical-sized calvarial defect sites | Wnt/β-catenin signaling pathway | 221 |
| 54.  | La³⁺ ions calcium silicate chitosan bone scaffolds | Osteogenic differentiation | Rabbit BMSCs | TGF signal pathway | 222 |
| 55.  | Nd: YVO₄ | Laser oscillator for drill the cortical bone | Femoral bone of a pig | 160 mW for 0.75-mm thick drilling | 223 |
| 56.  | Nd: YAG silicon carbide on Ti6Al4V | Laser irradiation on bone healing | Osteoblast | Bone healing | 224 |
| 57.  | High-power, low-level Nd: YAG laser | Laser irradiation on bone healing | MC3T3-E1 osteoblasts | BMP-2-related signaling pathway | 132 |
| 58.  | Nd: YAG laser with EMP | Healing intrabony defects | Periodontal disease | Probing depth decrease and increased clinical attachment level (CAL) | 225 |
| 59.  | Nd: YAG laser with SRP | Periodontal inflammatory response | Periodontal inflammation | Plaque index (PI), gingival index (GI), probing pocket depth (PPD), and marginal bone loss | 226 |
| 60.  | Nd₂O₃ | Inflammatory response | Human bronchial epithelial cells | STAT3 | 227 |
| 61.  | Nd nanoparticles | Redox-mediated angiogenic response | EA.hy926 endothelial cells | PKM2-NOX4 signaling pathways | 18 |
| 62.  | Nd:YAG | Laser irradiation | Male Wistar rat | Accelerate bone metabolism during tooth movement | 228 |
| 63.  | Nd:YAG Q-switch laser | Antimicrobial | Peri-implantitis | Disinfected the contaminated implant | 229 |
| 64.  | Nd-Ca-Si silicate glasses and alginate composite hydrogels | Anticancer and wound healing bioactivity | HUVEC cells, nude mice, and BALB/c mice | Thermal therapy for cancer treatment and burn wound healing | 230 |
| 65.  | Samarium with EDTMP and Technetium-99m | Targeted delivery for bone metastasis | Male Wistar rats | 150 min accumulation and release of EDTMP at bone tissue | 189 |
| 66.  | Sm³⁺-doped P₂O₅ glass-reinforced hydroxyapatite | Osteogenesis and antimicrobial | MG63 cells, Staphylococcus aureus, Staphylococcus epidermidis, and Pseudomonas aeruginosa | F-actin cytoskeleton organization and cell proliferation in MG63 and potent antimicrobial activity | 231 |
| 67.  | Y₂O₃ nanoparticles incorporated polycaprolactone scaffolds | Cell proliferation and angiogenesis | Fibroblasts (L-929) and osteoblast-like cells (UMR-106) | VEGF and EGFR | 232 |
| 68.  | Er:YAG laser irradiation | Evaluate the moisture content, roughness, and thickness | Cortical bone | Optical coherence tomography (OCT) | 233 |

Abbreviations: ALP, alkaline phosphatase; BMSCs, bone marrow mesenchymal stem cells; BSP, bone sialoprotein; CGRP, calcitonin gene-related polypeptide-α; EDTMP, ethylenediamine tetramethylene phosphonic acid; MSCs, mesenchymal stem cells; OCN, osteocalcin; VEGF, vascular endothelial growth factor.
ALP, and osteocalcin (OCN) in bone marrow mesenchymal stem cells (BMSCs). Furthermore, CeO2 induces the gene and protein expressions of β-catenin and cyclin D1. Similarly, Varini et al. found that mesoporous glasses with 1.2% and 3.6% CeO2 prevent oxidative stress improves MC3T3-E1 cell proliferation. The schematic representation of the preparation of the alginate/glass beads with ceria is given in Figure 1I. The topical application of water-soluble CeO2 nanoparticles (nanoceria) accelerates the healing of full-thickness dermal wounds in mice by reducing oxidative damage to cellular membranes. Furthermore, nanoceria enhances the proliferation and migration of fibroblasts, keratinocytes, and vascular endothelial cells.

**FIGURE 1**

I. Schematic representation of the preparation of the alginate/glass beads with ceria to prevent oxidative stress in MC3T3-E1. Source: Reprinted with permission from ref. 234. Copyright 2019, Elsevier.

II. The effect of cerium-doped nanoparticles on osteogenesis (a–d).

Representative micro-CT (b, d) and 3D reconstruction (a, c) images of femurs 12 weeks after ceria-based scaffold implantation. The red solid line frame outlines the bone defect area. (e–h) H&E staining at 12 weeks post-surgery. (i–l) Collagen X IHC staining at 12 weeks post-surgery. (m–p) Masson’s trichrome staining at 12 weeks post-surgery. The solid black box represents the enlarged defect area. Blue arrowheads indicate hypertrophic chondrocytes, and black arrowheads represent new trabecular bone formed by endochondral ossification (n = 3/group). Source: Reprinted with permission from ref. 125. Copyright 2019, John Wiley & Sons, Inc.

III. Ce promotes bone marrow mesenchymal stem cells (BMSCs) osteogenic differentiation ex vivo. (a) BMSCs were treated with various concentrations of Ce (0, 0.001, 1, 10 μM) for 7 days and assessed by measuring the alkaline phosphatase (ALP) activity. (b) BMSCs were treated with standard, OS, and OS + Ce medium for 21 days and assessed by alizarin red S staining. (c) Quantitative real time PCR analysis indicated that the mRNA expressions of Runx2, Satb2, and OCN were significantly up-regulated in the BMSCs treated with Ce (0.001 μM) for 7 days compared to the control group. (d) Western blot analysis showed the expressions of RUNX2, Satb2, and OCN proteins were up-regulated after treatment with Ce (0.001 μM) for 7 days. Data are presented as mean ± SD from a representative of three separate experiments. *p < 0.05. Source: Reprinted with permission from ref. 205. IJCEP Copyright 2014.

IV. The TRAP staining of mice skull treated with cerium for 9 days. Source: Reprinted with permission from ref. 79. Copyright 2019, Elsevier. TRAP, tartare resistant acid phosphatase.
The imbalance in the microenvironmental conditions such as changes in pH, necrotic cells, and invasion of microorganisms elevates the ROS levels in bone fracture environments and osteoporotic conditions. Elevated ROS levels hinder the recruitment of osteoblast precursors and delay the healing process. The H$_2$O$_2$ level above 0.3 mmol modulates oxidative stress and inhibits the osteogenic differentiation of odontoblastic cells and preosteoblastic MC3T3-E1 cells via ERK and NFkB pathways. In contrast, the odontoblasts cells treated with H$_2$O$_2$ at concentrations below 0.3 mmol/L display a significant increase in ALP activity and matrix mineralization. Another study demonstrated that H$_2$O$_2$-induced oxidative stress enhances differentiation of calcifying vascular cells and inhibits differentiation of bone cells, which causes either atherosclerosis by the accumulation of lipids in the vessel wall or osteoporosis by lack of osteoblast mineralization. Even though nanoceria acts as an antioxidant, nanoceria also mimics the activity of superoxide dismutase, catalase and nitric oxide synthase maintaining some basal level ROS and redox states, which are mainly dependent on catalytic activity and oxidation potential such Ce$^{3+}$ and Ce$^{4+}$. The catalytic properties and biomedicai applications of cerium oxide nanoparticles were critically reviewed by Walkey et al., the interested readers can be read it for further information. The microenvironmental conditions played a significant role in the production of ROS. Acidic environments like cancer, ceria nanoparticles favor the scavenging of superoxide radical over the hydroxyl peroxide resulting in accumulation of the ROS, which can be used for sensitization of cancer cells. Zhou et al. claimed that elevation of intracellular ROS level by cerium (III) enhances the expression and activity of NADPH oxidase 1, which further activates the RANKL-dependent osteoclasts differentiation, and the cerium (III) activated osteoclasts exhibit higher bone resorption activity. The Figure 1IV depicted the osteoclastogenic effect of cerium by tartare resistant acid phosphatase (TRAP) staining. Another study reported that CeO$_2$ nanoparticles facilitated osteoclast formation at lower concentrations via the RANKL pathway. A higher concentration of CeO$_2$ inhibited osteoclastogenesis by inducing apoptosis in bone marrow-derived macrophages by modulating cellular ROS levels. Recent research attempts with poly(1,8 octanediol-co-citrate), beta-tricalcium phosphate, and CeO$_2$ nanoparticles had developed the porous, biocompatible, bioactive, and free-radical scavenging RE nanomaterials. The Ce$_4$ upconversion nanoparticles act as photosensitizers that excite at 808 nm and convert NIR to visible photon energy. This event generates toxic ROS in cancer cells through the Fenton-like reaction by Fe(OH)$_3$ compound and enhances the tumor treatment efficacy.

### 5.1.2 Angiogenesis and Immunomodulation

Insufficient blood vessel formation is a critical problem that hampers the clinical application of bone grafts. The scaffolds modified with CeO$_2$ nanoparticles improve the proliferation and inhibit the apoptosis of MSCs. Meanwhile, it activates the calcium channel enhancing intracellular free Ca$^{2+}$ level in MSCs, which subsequently augments the stability of hypoxia-inducible factor-1 alpha (HIF-1$\alpha$) and VEGF expression. The improved paracrine signaling of VEGF promotes the proliferation, differentiation, and tube formation ability of endothelial progenitor cells and significantly improves the blood vessel distribution inside of bone scaffolds. Physicochemical properties like Ce$^{3+}$/Ce$^{4+}$ ratio, surface charge, size, and shape of cerium nanoparticles influence the angiogenesis process. The Ce$^{3+}$/Ce$^{4+}$ ratio modulates the intracellular oxygen environment by stabilizing HIF-1$\alpha$ endogenously and promotes angiogenesis. Mesoporous sol–gel glasses substituted with Ce$_2$O$_3$, Ga$_2$O$_3$ (both 0.2% and 1.0%), and ZnO (0.4% or 2.0%), contain well-interconnected ultra-large pores (pores $>400 \mu$m) ideal for vascular ingrowth and proliferation of endothelial cells. The functional nanoconjugates of SmCeO$_2$ trigger endothelial cell proliferation and induce the growth of blood vessels in the chick embryo. The enhanced expression of pro-angiogenic markers (p38MAPK/HIF-1$\alpha$) by these functional nanoconjugates might be the plausible signaling mechanism of the pro-angiogenic property. Endochondral bone regeneration is similar to long bone defect healing, which needs angiogenesis and osteogenesis. The micro emulsion-based alendronate-anchored polyethylene glycol-modified ceria nanoparticles (CNPs) accelerated vascular invasion. They enhanced endochondral ossification-based bone regeneration by activating RNA helicase, DEAH (Asp-Glu-Ala-His) box helicase 15 (DHX15). CNPs enhance the proliferation and hypertrophic differentiation of BMSCs by stimulating the DHX15-p38 MAPK axis. Further inhibition of DHX15 by shRNA affected the expression of hypertrophic genes Runx2, MMP13, and Col10a1, which confirmed the importance of DHX15 in hypertrophic differentiation of BMSCs. The effect of cerium-doped nanoparticles on osteogenesis is shown in Figure 1III.

The aberrant angiogenesis causes lethal effects in some neurodegenerative conditions and cancer metastasis. Nanoceria inhibits the expression of genes associated with inflammation and angiogenesis in the retina of Vldlr null mice representing a novel therapeutic strategy to treat age-related macular degeneration (AMD) and other neurodegenerative diseases. Nanoceria causes inhibition of pro-inflammatory cytokines and pro-angiogenic growth factors and upregulation of several cytokines and anti-angiogenic genes in the Vldlr$^{-/-}$ retina. Nanoceria inhibits the activation of ERK1/2, JNK, p38 MAP kinase, and Akt. Similarly, the water-soluble oligochitosan-coated CeO$_2$ nanoparticle-loaded injectable hydrogel shows biocompatibility and radical-scavenging effect. Furthermore, it downregulates the expression of angiogenic proteins and pro-inflammatory cytokines in AMD cellular models like human retinal pigment epithelium-19 and umbilical endothelium cell lines. It also has been documented that nanoceria alleviates the endometrial lesions induced in the mice model by decreasing oxidative stress and inhibiting angiogenesis.

Moreover, nanoceria was also observed to protect endometriosis-related adverse effects on the oocytes, which is critical for a successful pregnancy. The genotoxicity studies in liver cells revealed that the high dose (1000 mg/kg body weight) of ceria nanoparticles induces DNA damage in peripheral blood leukocytes, micronucleus formation in blood cells, and total cytogenetic changes in the bone marrow. Ceria nanoparticles exhibit higher tissue distribution and greater clearance in large fractions through urine and feces than CeO$_2$ bulk, whereas the maximum amount of micro-sized CeO$_2$ excretes in feces.
significantly inhibits the production of ROS in A2780 ovarian cancer cells. Nanoceria treatment also inhibits VEGF165-induced proliferation, capillary tube formation, activation of VEGFR2 and MMP2 in HUVECs. Thus, nanoceria can be used as an anti-angiogenic therapeutic agent during cancer treatment. This pro-angiogenic and anti-angiogenic potential of ceria-based nanoparticles might be related to the dose of ceria content in the nanoparticles, the cell type, and disease condition. Optimizing the proper dose of cerium in the ceria nanoparticles is crucial for pro-angiogenic effect-mediated bone defect healing.

Plasma spraying technique-based CeO2-coated (CS-10Ce and CS-30Ce) calcium silicate materials have shown good osteogenic responses in bone marrow-derived MSCs (BMSCs) by increasing the expression of osteoinductive molecules BMP2 and TGF-β1. This effect limits inflammatory reactions by up-regulating the expressions of anti-inflammatory M2 macrophage markers (CD206, IL-1ra, and IL-10) in RAW264.7 macrophages. The Ce4+/Ce3+ (i.e., 0.46, 1.23, and 3.23) ratios of CeO2 nanoparticles applied to titanium substrate surfaces by magnetron sputtering elevate the M2 macrophage polarization and anti-inflammatory cytokine secretion resulting in new bone formation and osseointegration. Since immunomodulation plays a vital role in bone defect healing and implant success, the immunomodulatory potential of nanoceria could be applied in bone tissue engineering and implantology. Similarly, the T cells, B cells, neutrophils, and other immune cells participate in the bone regeneration cascade. The effect of RE metal, including cerium-based nanomaterials, on the activation and expansion of the T cells, B cells, neutrophils, and other immune cells during bone defect healing is still unknown.

5.1.3 | Antimicrobial activity

Due to the antioxidant property of ceria, it has been widely used as an antimicrobial agent. Alginate/hyaluronate and Ce (III) ions based hydrogel shows bioactive and antimicrobial ability against Staphylococcus aureus, Staphylococcus epidermidis, Pseudomonas aeruginosa, and Candida albicans without compromising the osteoconductivity. The antimicrobial ability of Ce(III) is observed in Ce3+ ion incorporated hydrogel. A higher Ce(III) concentration in the hydrogel leads to an even stronger antimicrobial activity. The Ce3+ in cerium oxide is the key component of antioxidant activity to overcome free-radical formation during the cellular growth process. Further, nanoceria decreases NO production in macrophages and in tissues of C57BLK6 mice for alleviating the pro-inflammatory response caused by the infectious agents, which could be the mechanism of ROS scavenging ability of nanoceria-mediated anti-inflammation that serves as a treatment for a broad spectrum of inflammatory diseases. The same research group also reported that ceria inclusion in the graphene hydroxyapatite (GR-HA) matrix induces antimicrobial resistance against S. aureus, S. epidermidis, and P. aeruginosa of the composite. Antioxidant ceria and antibacterial silver reinforce HA composite with enhanced mechanical and cytocompatible properties and show antibacterial efficacy of ~61% for Escherichia coli and ~53% for S. aureus. Plasma-sprayed CeO2-incorporated calcium silicate coating in dental implants shows better biocompatibility, upregulates mRNA expression levels of ALP, OCN, and bone sialoprotein (BSP), and intensifies antimicrobial activity against Enterococcus faecalis.

5.1.4 | Osteogenesis

Unique biological properties of ceria nanoparticles such as antioxidation, anti-inflammatory, pro-angiogenic, and antimicrobial nature suggest ceria as an appropriate biomaterial for bone tissue engineering applications. The ceria nanoparticles on the poly-L-lactide scaffold surface promote hMSCs and osteoblast proliferation, migration, and adhesion. The antioxidant properties of the CeO2-incorporated HA coatings maintained intracellular SOD activity, reduced oxidative injury, and enhanced the osteogenic differentiation of BMSCs, probably through Wnt/β-catenin signaling. The cerium ions influence the formation and structure of HA, as indicated by the apatite structure maintained by Ce4+ ions. The cerium has shown dose-dependent osteogenic effects on MC3T3-E1 cells. Cerium at concentrations of 0.0001, 0.001, 0.01, 0.1, or 1 μM promotes the proliferation and osteogenic differentiation of MC3T3-E1 cells, as displayed by the upregulation of RUNX2 and BMP2 ALP, BSP, collagen I (COLI), and OCN. Whereas 1000 μM ceria inhibits osteogenic differentiation. Similarly, exposure to 1% ceria reduces ALP activity in MC3T3-E1 cells, and cerium trichloride (CeCl3) stimulates MC3T3-E1 cell proliferation. These results from the literature indicate that loading the proper dose of ceria in biomaterials is crucial for effective bone regeneration. The plasma-sprayed CeO2+ coating with higher Ce4+ concentration elicits more significant effects than the CeO2 coating with Ce3+ concentration. The osteogenic differentiation is activated by RUNX2 expression and enhanced through increased ALP and OCN expression in BMSCs through the Smad-dependent BMP signaling pathway. The nanoceria-mediated osteogenic differentiation of BMSCs is dose-dependent between 24 and 72 h. Prolonged incubation with nanoceria, that is, 14 days, inhibits the osteogenic differentiation. In contrast, nanoceria inhibits the adipogenic differentiation of BMSCs on Day 17, which conferred that the biomaterial doped with ceria should not give prolonged release and should be optimized for a better bone regenerative effect. Melt quench technique-based bioactive borate (13-93B3) glass powders containing up to 5 wt% Ce2O3 and Ga2O3 increases chemical durability, exhibits a good in vitro bioactive response, and has high in vitro HA forming ability making them promising candidates for bone tissue engineering applications. Ceria promotes osteogenic differentiation in MSCs by interacting with BMP receptors and activates TGF-β/BMP signaling pathway by upregulation of RUNX2, which further up-regulates osteoblast marker genes COLI and BMP2 at early stages, ALP, and OCN at later stages of differentiation further inhibits the adipogenic differentiation of MSCs by downregulation of an adipocyte marker PPARγ. Smad-dependent BMP signaling plays a vital role in the migration and osteogenic differentiation of BMSCs. Ceria promotes the phosphorylation of Smad1/5/8 and translocating to the nucleus via...
increased BMP2 expression. The activity of p-Smad1/5/8 increases stromal cell-derived factor-1 (SDF-1) and RUNX2 expression levels in BMSCs. The foamed ceria made up of CeO2 and bovine hydroxyapatite (BHA) composites show potential free-radical scavenging ability for developing orthopedic biomaterial. Ceria-stabilized zirconia/alumina nanocomposite exhibits an elastic and flexible property equivalent to a cobalt-chromium alloy used as a mandibular implant. Intramuscular injections of CeO2 enhance muscle mass, glycogen, ATP content, and type I fiber ratio, resulting in higher muscle endurance. The cerium/zirconia/alumina composite enhances the osteogenic response in vitro and in vivo. Nano CeO2-containing calcium sulfate hemihydrate composite with 5% w/w shows a higher bone regenerative potential. Freeze-dried CeO2 nanoparticles-modified bioglass scaffolds rapidly promote the
proliferation and osteogenic differentiation of human BMSCs. The enhanced osteoinductivity of ceria-bioglass scaffolds is mainly related to the activated ERK pathway. Rat cranial defect model revealed that ceria-bioglass scaffolds accelerate collagen deposition, osteocalcification formation, and bone regeneration compared to bioglass scaffolds. Nanocrystalline CeO₂ promotes dentinogenesis in the damaged teeth root. All aforementioned osteogenic properties of cerium-doped innovative nanomaterials indicate the potential applications of cerium in bone tissue engineering and implantology.

5.2 | Europium

Europium is the least dense, the softest, and the most volatile member of the lanthanide series. The europium element was discovered in 1901 by French chemist Eugène-Anatole Demarçay and was named for Europe. Europium occurs in minute amounts in many RE minerals such as monazite and bastnasite. The primary use of europium is in optical displays, TV screens, and fluorescent lamps. Europium is also used in scintillators for X-ray tomography and as a source of blue color in light-emitting diodes. The bio labeling property of europium ions has been used to synthesize the cyclen-based europium (III) complex as a lanthanide luminescent contrast agent for bone structure analysis by incorporating the iminodiacetate functionalities as selective Ca(II) binding motifs. This agent selectively visualizes the damaged bone structure (microcracks).

The gold nanoparticles conjugated with the europium luminescent probe and the peptide (pHLIP•Eu•Li•Au) target the platelets in low pH 6.5 and translocate the pHLIP across the membrane. H₂O₂ a redox signaling molecule generated by europium hydroxide nanoparticles, activates the endothelial nitric oxide synthase that promotes nitric oxide production in a PI3K (phosphoinositide 3-kinase)/Akt-dependent manner, eventually triggering angiogenesis. The molecular mechanisms underlying the europium hydroxide nanorods (EHNs) induced angiogenesis are given in Figure 2IV. It has been further evidenced that microwave-assisted synthesized europium (III) hydroxide nanorods exert pro-angiogenic properties through ROS generation and activation of the MAPK pathway. On the other hand, Gd₂O₃:Eu³⁺ nanotubes generate excessive ROS injury to the mitochondria and DNA in BMSCs, and the release of cathepsin B by lysosomal rupture triggered cell death necrosis. The nanotubes of Gd₂O₃:Eu³⁺ remarkably enhance the bone mineral density and bone biomechanics as indicated by high ALP activity, mineralization and promoted the expression of osteogenesis genes in MC3T3-E1 cells through activation of the BMP signaling pathway. Mesoporous bioactive glass (MBG) incorporated europium scaffolds by an in situ co-template methods have highly interconnective large pores (300–500 μm), high specific surface area (140–290 m²/g), and well-ordered mesopores (5 nm) as well as uniformly distributed europium elements. Incorporating 2–5 mol% europium toward MBG scaffolds with luminescent property stimulates new bone formation (Figure 2III) in osteoporotic bone defects in OVX rats.

Figure 2I showed that the morphology of europium-doped mesoporous silica nanospheres (Eu-MSNs) stimulated the pro-inflammatory response in macrophages, osteogenic differentiation of BMSCs, and angiogenic activity human umbilical vein endothelial cells (HUVECs). Further, the Eu-MSNs accelerate the new bone formation in the critical-sized cranial defect site via immunomodulatory effect. The overall mechanism is provided in Figure 2IV. Europium-doped bioactive glass nanoparticles (BGNEu) significantly enhance human MSCs (hMSCs) osteogenic differentiation (ALP activity and COLI secretion) by activating osteogenic marker ALP, COLI, OPN, and RUNX2. Nanohydroxyapatite (nHAp) doped with Li⁺ ions (5 mol% Li⁺:nHAp) and co-doped with lanthanide ions like samarium (III) (Sm³⁺) and europium (III) (Eu³⁺) ions enhance the luminescent property. Further, these composite improve osteogenic differentiation of human adipose-tissue-derived stem cells (hASCs) by a decrease in the expression of glycogen synthase kinase 3β (GSK3β) and an increase in β-catenin mRNA level.

**FIGURE 2** I. SEM images of pure MSNs (a), europium-doped mesoporous silica nanospheres (1Eu-MSNs) (b), 2Eu-MSNs (c), and 3Eu-MSNs (d) show uniformly spherical morphology with a size of 280–300 nm, and the inserted TEM images show the abundant mesoporous structure of nanoparticles. EDS mapping analysis (e) shows homogeneous element distribution of Si, O, and Eu in 2Eu-MSNs typically. Source: Reprinted with permission from ref. 215. Copyright 2017, Elsevier. II. The effect of Eu-MSNs on the in vivo osteogenesis. Representative micro-CT images of new bone formation (the gray background represents normal skull, the black holes represent the cranial defect created by surgical operation with a diameter of 5 mm, and the red part represents the newly formed bone at the defect site, analyzed by CTAn software of micro-CT) (a) in cranial defect at 6 weeks and 12-week show larger new bone area in Eu-MSNs-polymer film (indicated as Eu-P in figure) group. Immunofluorescent imaging (b) by VG stain in the cranial defects show that more new bone (red) was formed at the cross section of the defect in Eu-P groups at 6 weeks and 12 weeks, indicating similar results as micro-CT analysis (pure polymer film as Poly, MSNs-polymer composite films as M-P, and Eu-MSNs-polymer composite films with as Eu-P), scale bar = 1 mm. Source: Reprinted with permission from ref. 215. Copyright 2017, Elsevier. III. Osteogenic effect of EHNs. (a) Histological analysis and histomorphometric measurements of in vivo bone formation ability for MBG, 2Eu-MBG, and 5Eu-MBG scaffolds after implanted in the osteoporotic femur defects of OVX rats at 4 and 8 weeks. The scale bar is 100 μm. Source: Reprinted with permission from ref. 128. Copyright 2016, American Chemical Society. IV. Graphical representation of the hypothesized molecular mechanisms underlying the EHNs induced angiogenesis mediated through ROS-NO-cGMP signaling axis. Source: Republished with permission of Royal Society of Chemistry, 2015, permission conveyed through Copyright Clearance Center, Inc. V. The prepared Eu-MSNs showed an inflammatory stimulation on macrophages, which further induced the osteogenic differentiation of bone marrow mesenchymal stem cells (BMSCs) via upregulating the gene expression of COL-I, OCN, ALP, and RUNX2 as well as the angiogenic differentiation of HUVECs via upregulating the gene expression of CD31, MMP9, VEGFR, and PDGFR. The particles were then applied for in vivo experiments and showed a satisfactory effect on the bone repair of cranial defect and neovascularization. Source: Reprinted with permission from ref. 215. Copyright 2017, Elsevier.
FIGURE 3  I. Schematic illustration of GdPO₄·H₂O and GdPO₄ nanobundles synthesis and their application in biodegradable bone implants for MR and CT tracing. Source: Reprinted with permission from ref. 171. Copyright 2016, John Wiley & Sons, Inc. II. The structural property of the Gd-BG scaffold. (a) SEM image and (b) TEM image of Gd-BGS microspheres. (c) Nitrogen adsorption–desorption isotherm, (d) Barrett–Joyner–Halenda (BJH) pore-size distribution curve of mesoporous Gd-BGS microspheres. (e) The X-ray diffraction patterns of samples: (I) Gd-Bg microspheres and (II) Gd-BG scaffolds. (f) The Fourier transform infrared spectra of samples: (I) Gd-BG microspheres and (II) Gd-BG scaffolds. Source: Reprinted with permission from ref. 217. Copyright 2019, Elsevier. III. Micro-CT of rat cranial defects implanted with BG and Gd₁/₃-BG scaffolds at 8 weeks after implantation. The images of reconstruction of micro-CT for the bone regeneration of the defect area at Week 8. Source: Reprinted with permission from ref. 217. Copyright 2019, Elsevier. IV. Gd nanoparticle-mediated bone tissue regeneration. Fluorochrome-labeling analysis characterizing the new bone formation within MCS/CTS, Gd₁/₅MCS/CTS, and Gd₁/₃MCS/CTS scaffolds. Tetracycline (yellow), calcein (green), and alizarin red (red) were injected in rats at Weeks 3, 6, and 9. Source: Reprinted with permission from ref. 173. Copyright 2019, Elsevier. V. Schematic illustration of Gadolinium-doped mesoporous calcium silicate/chitosan scaffolds enhanced bone regeneration ability. Source: Reprinted with permission from ref. 173. Copyright 2019, Elsevier. VI. Gadolinium phosphate/chitosan scaffolds promote new bone regeneration via Smad/Runx2 pathway. Source: Reprinted with permission from ref. 172. Copyright 2019, Elsevier. TEM, transmission electron microscope
5.3 Gadolinium

Gd occurs in many minerals and other RE materials, but it is obtained primarily from bastnasite. It was discovered by a Finnish chemist Johan Gadolin. Gd is known for its high potential in MRI. Nevertheless, its MRI applications are overshadowed by their large sizes resulting in poor organ/tumor targeting. Hsiao et al. used Gd as a dopant in fluorescein isothiocyanate mesoporous silica nanoparticles that possess green fluorescence and paramagnetism for labeling hMSCs via endocytosis. These labeled hMSCs can proliferate and differentiate into adipocytes, osteocytes, and chondrocytes.

Further radiolabeled arginine-glycine-aspartic acid (RGD)-functionalized E3/Yb3-co-doped NaGdF4 upconversion nanoparticles (UCNPs) had been developed to specifically target the αvβ3 integrin-expressing U87MG tumor cells and xenografted tumor models for tumor angiogenesis. Metallofullerenol Gd@C82(OH)22 effectively inhibits MMP-2 activity by blocking the Zn21-catalytic site directly or the S19 loop indirectly and inhibits the proteolysis of MMP-9 via allosteric modulation with high antitumor efficacy. The biocompatible dextran-coated ultrafine sub-10 nm Gd-based nanoparticles are found particularly capable of determining the tumor boundary with clearly enhanced tumor angiogenesis.

Solvothermal synthesized GdPO4·H2O nanobundles incorporated HA and PLGA serve as a biodegradable and traceable bone implant for MRI and X-ray tracing; this unique biomaterial promotes OCN expression in MC3T3-E1 cells and bone mineralization in vivo rabbit radius defects (Figure 3I). GdPO4/chitosan scaffolds prepared by the lyophilization method improve the osteoconductivity, resulting in admired cell spreading and in vivo bone tissue in-growth. GdPO4 nanoparticles in the GdPO4/CTS scaffolds robustly promote osteogenic differentiation by upregulating the levels of ALP, RUNX2, OCN, and COLI expression in rabbit BMSCs via activation of the Smad/ RUNX2 signaling pathway (Figure 3IV). Gd-doped MCS/CTS scaffolds show anabolic effects on rabbit BMSCs cell proliferation and osteogenic differentiation through the activation of the Wnt/β-catenin signaling pathway (Figure 3IV). Gd-BG scaffolds promote the proliferation and osteogenic differentiation of human BMSCs via the Akt/GSK3β signaling pathway (Figure 3III,III). Gd is a widely accepted contrast agent in MRI, cardiac applications such as effective MR angiography.

Gd ethoxybenzyl diethylenetriamine pentaacetic acid (Gd-EOB-DTPA) is the liver-specific contrast enhancement agent presently used for diagnosing HCC. MRI with Gd-EOB-DTPA enhancement is superior to enhanced CT and conventional contrast-enhanced MRI in diagnosing small liver lesions and differentiating benign and malignant nodules. Gd-EOB-DTPA excretes into the biliary tract through multidrug resistance-associated protein 2 (MRP2) on the biliary tract. The period of this phase is called the hepatobiliary specific period or hepatobiliary phase. The remaining contrast agent, similar to Gd-DTPA, can be excreted through the kidney. This dual clearance pathway can compensate for each other when the liver or kidney function is damaged, thereby ensuring higher safety. Compared with conventional hepatobiliary MRI, enhanced MRI by Gd-BOPTA combined with ultrasound has good diagnostic value in determining HCC. Gd(III) complexes containing a polydentate carboxylate ligand exhibit good MRI contrast properties. PEGGd2O3 NPs presented longer half-life, similar acute toxicity and histological influence, more negligible effect on hepatic and renal functions, and stronger contrast enhancement in the tumor. Gd2O3-assembled mesoporous silica MCM-41 nanocomposite has been identified both in vitro and in vivo as a safe MRI contrast medium with better efficacy than its commercially available counterpart Gd-DTPA. An ultrasmall, theranostic (3.0 ± 1.0 nm size) Gd-based nanoparticle (AGuIX NPs) are used to improve radiographic delineation and increase the intratumoral dose-effect delivered by the particles.

Further, it has been used as an MRI or X-ray contrast agent of the osteoblasts applied in biodegradable HA/PLGA bone implants in vivo, providing a practical approach for recognizing the implants or the newly formed bone tissues. 171 GD MRI enhancer-based dynamic contrast-enhanced (DCE) MR examinations at 3 T assess perfusion in healthy carpal bones in a patient with osteonecrosis and Kienbock’s disease. The results suggested that areas of healthy bone show low perfusion. DCE-MRI at 3 T diagnoses altered perfusion in patients with Kienbock’s disease. RE element Gd-doped magnesium scaffold (CaP-coated Mg-Zn-Gd) enhances orthotopic reconstruction of large-sized orbital bone defect healing in canines. The scaffolds triggered trigeminal neurons via CGRP promote endomucin expression in endothelial cells, facilitating angiogenesis and osteogenesis. Gd (III) oxide nanoparticles (70 nm size) synthesized via the polyl method and surface functionalized with a bisphosphonate (BP) derivative (GBCAs)-BP show a strong affinity towards calcium phosphate. The CPC-GBCAs-BP functional material is longitudinally monitored after in vivo implantation in a condyle defect rat model. The BP functionalization prolongs the residence of the contrast agent within the CPC to allow long-term follow-up imaging studies. Heat shock protein 16.5 (Hsp16.5) and peptide conjugated Gd (III) nanocages detect neuropilin-1-positive cells in genetically engineered mouse models.

5.4 Neodymium

Neodymium is a ductile and malleable silvery-white metal. Austrian chemist Carl Auer von Welsbach discovered neodymium in 1885. Neodymium occurs in the least amount in the rocks of Earth’s crust. The major application of neodymium is in high-strength permanent
magnets used in high-performance electric motors and generators, the electronics industry, and the ceramics industry for glazes and color glass in various shades from pink to purple. Neodymium-stabilized yttrium aluminum garnet (YAG) is a component of many modern lasers, and neodymium glasses are used in fiber optics. Neodymium is used in a laser oscillator to irradiate the specimen. Nd:YVO₄ laser oscillator has a threshold average laser power of 160 mW required to drill through a 0.75-mm thick cortical bone with a peak intensity of 1.3 GW/cm². Nd-YAG laser irradiation in the near-infrared ray (NIR) area has been reported to promote bone healing via the expression of ALP, RANKL, and OPG. It indicated that osteoblast-like cells activate genes related to bone metabolism by combining mechanical

**FIGURE 4**  I. Photoemission spectra of BNPs: (a) survey spectra and high-resolution spectra of (b) Ag 3d (c) Nd 3d.  
II. Emission spectra of Ag–Nd BNPs on excitation with 808 nm reveals mission ability in the NIR (750–1600 nm) region, with strong emission in the region of the second biological window, which is more transparent for deep tissue penetration. III. Fluorescence images of treated cells (scale bar = 100 μm). 
Source: Reprinted with permission from ref. 279. Copyright 2017, Elsevier. IV. Bimodal imaging by rare-earth nanoparticles. Multiphoton microscopy images of fibroblast cells with PMAO coated GdF₃:Nd³⁺ nanoparticles. (a) Image of the DAPI-stained nuclei (blue channel) and phalloidin-stained cytoplasm (red channel). (b) Observed emission of the nanoparticles under 488 nm excitation. The green color denotes emission correlated with the cytoplasm, and the light blue color denotes emission correlated with the nuclei. (c) Images of the DAPI, phalloidin, and fluorescent channels together. Source: Reprinted with permission from ref. 280. Republished with permission of Royal Society of Chemistry, 2013, permission conveyed through Copyright Clearance Center, Inc. V. The angiogenic property of Nd nanopolymorphs assessed using the chorioallantoic membrane (CAM) chick egg model. PC, positive control (20 ng VEGF-treated CAM), NC, negative control (200 μM thalidomide-treated CAM), NHH, Nd nanoparticles, NBA, Nd nanocubes, NBC, Nd nanorods. Source: Reprinted with permission from ref. 18. Copyright 2019, Elsevier
stimulation and laser irradiation. Nd:YAG laser irradiation stimulates cell growth in the nonsensitized osteoblasts and induces the expression of osteopontin, ALP, and RUNX2 in osteoblasts, type I COL1 in fibroblasts, and vinculin in endothelial cells in low pulse energy levels. Nd:YAG laser treatment improves zirconia bioactivity by increasing human osteoblast’s cell viability, proliferation, and expression of COL1 and ALP activity. Nd:YAG is frequently used as an alternate nonsurgical mechanical debridement of peri-implant diseases. Single time Nd:YAG laser treatment effectively decreases the peri-implant inflammatory parameters plaque index, bleeding on probing, and probing depth indicated that Nd:YAG laser-assisted nonsurgical MD is more effective in reducing peri-implant soft tissue inflammatory parameters than MD alone in the short term but not in long term. The major challenge for orthodontic treatments lies in moving the tooth and shortening the time. Nd:YAG laser irradiation on orthodontic tooth movement with 1064 nm stimulates osteoblasts via producing ROS and nitric oxide. A higher RANKL/OPG ratio leads to the activation of osteoclasts. Higher RANKL expression was noticed in the prolonged laser irradiation side, while no change was noticed in the expression of OPG. It has been found that the Nd: YAG laser irradiation of bone for the long term severely delays bone healing as compared to positive control bur osteotomy sites and in patients with osteopenia or osteoporosis. So the slight modification of Nd:YAG laser with silicon carbide on titanium-6 aluminum-4 vanadium (Ti6Al4V) alloys had been prepared to promote the osteoblast cell growth effectively. To exterminate the delayed bone healing induced by Nd:YAG, Kim et al. used high-power, low-power Nd: YAG laser, which increases osteoblast activity very efficiently, accelerating the mineral deposition via activation of the BMP-2-related signaling pathway in MC3T3-E1 osteoblasts. A pulsed Nd:YAG laser is an effective physiotherapy modality used as a Class IV high-intensity laser therapy combined with exercise, which effectively increases lumbar and total hip BMD after 24 weeks of treatment, with effects lasting up to 1 year. High-intensity, pulsed, and high-power laser irradiation applied once every 2 days for 2 weeks effectively enhanced bone regeneration in an osseous defect in rats. The power magnitude did not affect the osseous regeneration process but was presumed to be more efficient at the dose of 0.75 W, lower than 3 W. These data indicated that the Nd:YAG laser light could heal local bone loss after surgical treatment.

Enamel matrix proteins (EMPs) are widely used in periodontal surgery for the regeneration of periodontal tissues. The use of Nd:YAG laser with EMP heals the intrabony defects of periodontal disease. This treatment approach decreases the probing depth and increases the clinical attachment level compared to baseline values. Similarly, Nd:YAG laser in combination with scaling and root planning (SRP) alleviates periodontal inflammatory parameters plaque index, gingival index, and probing pocket depth, as well as reduces marginal bone loss compared to treatment by SRP alone. The nanophosphors of GdF3:Nd2+ coated with poly(maleic anhydride-alt-1-octadecine) (PMAO) have no significant cellular toxicity for concentrations up to 200 mg ml−1. Furthermore, the incorporation of Gd into the nanocrystalline structure makes an ideal structure for use as MRI contrast agents (Figure 4IV). Rocha et al. found that neodymium-doped LaF3 core/shell nanoparticles emerge as relevant sub-tissue optical probes for bioimaging. Further experiments from their team reported that Nd3+-doped LaF3 (Nd3+:LaF3) nanoparticles exhibit fluorescence in three main emission channels of Nd3+ ions like 910, 1050, and 1330 nm, respectively. The optimal fluorescence of Nd3+:doped LaF3 nanoparticles in terms of relative emission intensities, penetration depths, and sub tissue optical dispersion is higher in 4F5/2−→4I11/2 (1050 nm in the second biological window) than the 4F5/2−→4F7/2 (910 nm, in the first biological window).

Nano-sized neodymium oxide (Nd2O3) arrests the S-phase of the cell cycle, disrupts mitochondrial membrane potential, and inhibits proteasome activity, leading to autophagy in non-small cell lung cancer NCI-H460 cell. Microwave-assisted polyol-based chitosan-functionalized silver-neodymium bimetallic nanoparticles (Ag-Nd BNPs, 10 nm) exhibit fluorescence in the NIR region and magnetic properties (Figure 4II). Ag-Nd BNPs have excellent biocompatibility and also promoted the loading of the anticancer drug paclitaxel. The synergistic effect of paclitaxel and the photothermal property enables Ag-Nd BNPs to destroy cancer cells in vitro at a low dose compared to single therapy (Figure 4III). Nd-diethylene triamine penta acetic acid (Nd-DTPA) complex shows bright narrow-band emission at 1330 nm for in vivo NIR-II bioimaging with rapid renal excretion and high biocompatibility and optical-guided small tumor (down to ~3 mm) detection. Polyacrylic acid (PAA)-modified NaLuF4:Gd/Nd nanorods are used in tiny tumor detection. The NIR-II emission at 1056 nm and 1328 nm with high photostability of Nd can utilize for NIR-II optical imaging of small tumor (5 mm) diagnosis and small blood vessel with a high resolution (~105 μm). Recently, Ma et al. prepared implantable multifunctional material of Nd-Ca-Si silicate glasses and glass/alginate composite hydrogels, which have photothermal properties with unique temperature monitoring, photothermal function, and wound healing bioactivity that can be used for localized thermal therapy for cancer treatment. Besides, the composite hydrogel has bioactivity to repair heat damage-caused wounds by PTT due to the bioactive silicate components. These findings demonstrate that the explored lanthanide-based probes are promising NIR contrast agents for future biomedical applications, such as early diagnosis of a small tumor, vascular-related disease imaging, angiogenesis, and diagnosis. Recently Ansari et al. reported that surface-modified mesoporous silica micro-coconoon with neodymium hydroxide (Nd(OH)3) shows good cell viability even at high concentrations and hydrophilic conditions. These nontoxic cocoon-shaped microstructures could be potentially suitable candidates for optical bio-probes and drug delivery applications. Nd2O3 exposure on human bronchial epithelial cells (16HBE) initiates an inflammatory response via the p-STAT3 pathway. Nd2O3-treated 16HBE cells release the pro-inflammatory cytokines IL-6 and IL-8 and upregulate circRNA 0039411 (circ_0039411) by sponging miR-93-5p. These anticancer applications of RE smart nano-biomaterials might be helpful to combine with the osteogenic treatment during cancer metastasis-induced bone loss.

Our previous research revealed that neodymium nanoparticles exhibit a redox-mediated angiogenic response in a shape-dependent manner (Figure 4V). The redox signaling perceived via PKM2-NOX4
Figure 5

I. Representative TEM images of nanoparticles with proangiogenesis activity. (a) Eu rods, (b) Eu spheres, (c) Tb rods, and (d) Tb spheres. Source: Republished with permission of Royal Society of Chemistry. Reprinted with permission from ref. 295. Copyright 2016, Copyright Clearance Center, Inc.

II. Yb(3+/Ho(3+)) co-doped apatite upconversion nanoparticles to distinguish implanted material from bone tissue. (a) The light image of the Masson's stained histological section of new bone tissue (matured: blue, growing: red). (b) The upconversion green fluorescent image of the implanted FA:10Yb3+/0.5Ho3+ particles. (c) Their overlap image after 4 months. (d) The light image of the stained new bone tissue after 6 months. (e) Overlapping image of the light image and the upconversion green fluorescent image of the implanted FA:10Yb3+/0.5Ho3+ particles. (f) The superposition of the red fluorescent image of the new bone tissue under 561 nm laser excitation and the green fluorescent image of the FA:10Yb3+/0.5Ho3+ particles under 980 nm NIR excitation. The confocal superposition images of FA:10Yb3+/0.5Ho3+ particles (green) and new bone tissue (red) at 2 (g), 4 (h), and 6 (i) months after implantation. Source: Reprinted with permission from ref. 220. Copyright 2016, American Chemical Society.

III. Schematic diagram showing the overall strategy and methodology of our experiments illustrating Tg(flk: EGFP) transgenic primary cell and whole embryo-based high-throughput screening for nanomaterials with proangiogenesis activity. Source: Reprinted with permission from ref. 295. Copyright 2016, Royal Society of Chemistry.

IV. Lanthanide nanoparticles could recover circulation in VRI pretreated zebrafish embryos. Zebrafish embryos at 72 hpf. (i) Blank control, (ii) 100 µg ml⁻¹ Eu rods, (iii) 100 µg ml⁻¹ Eu spheres, (iv) 100 µg ml⁻¹ Tb rods, and (v) 100 µg ml⁻¹ Tb spheres. The green channel represents the blood vessels, while the red channel represents the mature blood cells. The merged pictures indicate that the embryonic circulation in the ISV region has recovered after the treatment of nanoparticles in this method. Source: Republished with permission of Royal Society of Chemistry, 2016, Copyright Clearance Center, Inc. SEM, scanning electron microscope; TEM, transmission electron microscope.
signaling pathways activates the pro-angiogenic factors, namely, VE-cadherin, HIF1α, VEGF, and VEGFR2, to facilitate the angiogenic process in EA. Hy 926 cells.18 The static magnetic field of neodymium is helpful to promote the bone formation faster after the bone is wounded. The implant stability quotient values and tissue response after implant placement under the influence of the magnetic field are significantly higher than on the nonmagnetic side. A positive correlation has existed between the magnetic field and osseointegration.287 Nd:YAG laser irradiation significantly enhances the amount of orthodontic tooth movement, the expressions of ALP and RANKL at the pressure site, and no difference in OPG expression.228 These effects stimulate osteoclast and osteoblast activation and accelerate bone metabolism during tooth movement. The laser melting method alloyed neodymium with Mg-5.6, Zn-0.5, and zirconia enhances corrosion resistance and exhibits excellent biocompatibility.288 Shreds of evidence revealed that microorganisms play the chief role in causing peri-implantitis. Short pulse laser-induced by Nd:YAG Q-switch laser in nanoseconds cleans contaminated implant surfaces to treat peri-implantitis significantly.229

Besides the application in laser irradiation, bone healing, and bioimaging, the nanoparticles of neodymium (III) hexacyanoferrate (II) (NdHCF) coated on the surface of carbon paste electrode are used for sensing the glucose by enzymatic reaction of the glucose oxidase (GOx) with NdHCF.289 Pourjavid et al. developed the highly selective Nd(III) PVC-based membrane sensor with sodium tetraphenylborate in nanoseconds cleans contaminated implant surfaces to treat peri-implantitis significantly.229

5.5 Lanthanum and other RE metal-doped nanobiomaterials

Lanthanum is the second most reactive and malleable silvery-white rare-earth metal. Lanthanum was discovered in 1839 by Carl Gustaf Mosander. Lanthanum occurs in the rare-earth minerals monazite and bastnasite. Lanthanum compounds are used as hosts for phosphors in fluorescent lighting and X-ray detectors.292 Lanthanum and other RE metal-doped nano-biomaterials are reported sporadically. Radiolabeled arginine-glycine-aspartic acid (RGD)-functionalized Er3+/Yb3+ co-doped NaGdF4 upconversion nanophosphors (UCNPs) had been developed to specifically target the αvβ3 integrin-expressing U87MG tumor cells and xenografted tumor models for tumor angiogenesis.168 It has been reported that Eu III(OH)2 and TbIII(OH)3 promote angiogenesis in the transgenic zebrafish model. (Figure 5I,III,IV)295 Zou et al. reported that the one-pot hydrothermal carbonization method synthesized praseodymium co-doped carbon quantum dots (Ce/Pr-C GR-HA) enhance hydroxyl radical scavenging property with favorable biocompatibility and negligible cytotoxicity. These carbon dots are readily internalized into the cytoplasm and decrease ROS level.186

Further radiolabeled arginine-glycine-aspartic acid (RGD)-functionalized Er3+/Yb3+ co-doped NaGdF4 UCNPs had been developed to specifically target the αvβ3 integrin-expressing U87MG tumor cells and xenografted tumor models for tumor angiogenesis.168 Samarium-doped YVO4 nanoparticles (20–50 nm) show significant toxicity in RAW 264.7 macrophages at concentrations of 25 mg/ml than erbium-doped YVO4.188 Ethylenediamine tetramethylene phosphonic acid (EDTMP), and technetium-99m-labeled samarium nanoparticles accumulate in the bone tissue for extended periods (150 min), resulting in the prolonged release of EDTMP at the target site. This prolonged release may be a more optimal treatment for the management of cancer bone metastasis-related pain.189 Morais et al. fabricated samarium (Sm3+)-doped P2O5 glass-reinforced HA-based bone composites, which enhance the F-actin cytoskeleton organization and cell proliferation and expression of relevant osteoblastic genes. Also, Sm3+ doping reduces the adhesion of S. aureus and S. epidermidis on bone substitutes. The
improved osteoblastic behavior and the antibacterial effects are dependent on the amount of samarium in the composite.\textsuperscript{231} Augustine et al. reported that Y\textsubscript{2}O\textsubscript{3} nanoparticles incorporated polycaprolactone scaffolds promote the expression of cell proliferation and angiogenesis-related markers such as VEGF and endothelial growth factor receptor (EGFR) in fibroblasts (L-929) and osteoblast-like cells UMR-106.\textsuperscript{232}

Erbium:YAG (Er:YAG) laser-assisted bone irradiation promotes inflammatory cell infiltration, fibroblastic reaction, and revascularization adjacent to the irradiated bone surface.\textsuperscript{296} Even though Er:YAG is being used in clinical practice, the water content of bone usually changes with the position. At the same time, the amount of water spray in the process of laser irradiation is also uncertain. In order to avoid this problem, Huang et al. used optical coherence tomography (OCT) to characterize the roughness and thickness of the heterogeneous layer on the cortical bone surface with different moisture contents that led to different ablation effects. The results from their study showed that OCT could quickly and accurately evaluate the differences between the moisture content, as compared to histology and scanning electron microscope (SEM).\textsuperscript{233} Na\textsubscript{1}YF\textsubscript{4}:Yb, Er@CaF\textsubscript{2} nanoparticles with a small size (10–13 nm) robustly enhance (ca. 300 times) upconversion emission compared with the pristine nanoparticles. The CaF\textsubscript{2} shell protects the rare-earth ions from leaking when the nanoparticles are exposed to the buffer solution and ensure biological safety for the potential bio probe applications.\textsuperscript{13} Nanoparticle-based in vivo imaging is hindered by the autofluorescence of the host cells and tissues. This issue could be addressed by the use of HA:Yb/Ho as an upconversion material. Ytterbium (Yb) and holmium (Ho) co-doped HA matrix favors by its bright fluorescence under NIR irradiation and enhances bone formation.\textsuperscript{297} Another study conducted by Nethi et al. extensively studied the pro-angiogenic properties of terbium hydroxide nanorods. They reported that the pro-angiogenic property of Tb enhances wound healing in mouse models.\textsuperscript{191}

6 | CHALLENGES OF RE ELEMENTS AND THEIR USE IN BONE REGENERATION

RE elements hold unique biological properties required for effective bone regeneration, such as pro-angiogenic, immunomodulatory, antimicrobial, and osteogenic.\textsuperscript{18,129,197,280} The various biological processes and signaling molecules involved in RE material-mediated bone defects healing are depicted in Figure 6. The advances in RE nanobiomaterials for bone tissue engineering and implantology are aforementioned in this review. Overall, potential applications of RE materials in bone tissue engineering and implantology are depicted in Figure 7. RE materials in bone tissue engineering and bone defect healing in the clinic are still a long way to go. One of the major

![FIGURE 6](image-url)
challenges in RE material-based bone regeneration is progenitor cells’ recruitment and biological activity. Some RE nanomaterials are engaged in recruiting immature progenitor cells like MSCs and stimulating them to develop osteoblasts, mediated by a cascade of signals and the activations of several extra and intracellular receptors. The recruitment of progenitor cells is mainly regulated via epigenetic, cellular reprogramming, cell metabolism, and autophagy.\textsuperscript{298} It has been reported that decreased level of autophagy in human MSCs reduces osteoblast differentiation.\textsuperscript{299} The molecular mechanisms involved in RE material-induced autophagy in bone cells are not yet fully elucidated. The recruitment and activation of immune cells are essential for effective and accelerated bone fracture healing. RE nanomaterials had been reported to modulate macrophage polarization during bone defect healing. However, the effect of RE nanomaterials on the expansion and activation of various immune cells regulating bone homeostasis, including T cells, B cells, and neutrophils, has not been investigated yet.

Furthermore, in the bone fracture microenvironment, the ROS levels are abundantly high and affect bone reconstruction.\textsuperscript{300} Excessive ROS production can induce osteoclastogenesis,\textsuperscript{57} whereas
hydrogen peroxide suppresses the osteoblastic differentiation process in primary mouse BMSCs.\textsuperscript{301} There is an opposing role of RE materials in producing reactive oxygen species and altering the redox states in the bone defect site. Thereby, it is inevitable to tune or modulate the redox signaling intersecting the current problem. Most of these studies lack the in-depth investigation on local and systemic adverse effects of in vivo applied RE nano-biomaterials in long-term use. Therefore, designing suitable graft materials and optimizing the proper dose of RE material to stimulate biological functions required for bone regeneration is the most challenging. The clinical usage of rare-earth-based materials in the tissue engineering field is restricted by a lack of site specificity and sustained delivery of RE elements. Direct injection of nanomaterials in the minor defects and fracture sites and systemic injection targeting osteoporotic bone/defect sites are under investigation.\textsuperscript{302–304} Whereas nonunion fractures and critical-sized bone defects need specialized treatment modalities. Mainstream reports from the literature had indicated the in vitro and in vivo osteogenic properties of RE nanoparticles. However, literature has indicated the inhibitory effect of RE nanoparticles on cell viability and osteogenic properties.\textsuperscript{302} This inhibitory effect was mainly related to the dose of RE metals and the duration of the incubation period in vitro.

7 | PROSPECTS OF RE METALS IN BONE TISSUE ENGINEERING AND IMPLANTOLOGY

Bone regeneration is a complex process involving numerous factors, including the recruitment of progenitor cells, inflammation, early angiogenesis, and osteogenesis. RE nanomaterials have autophagy augmenting potential,\textsuperscript{305} whereas RE materials can induce autophagy, but there is no adequate evidence to prove this phenomenon. In order to intersect the role of RE materials induced autophagy would open up the new vistas in bone tissue engineering that can be applied to induce bone regenerative potential. RE nanomaterials contribute to sustaining mild ROS levels, which could modulate the redox state via autophagy in the MSCs to regulate the osteogenic processes effectively and eventually heal the bone defect.

Effective bone regeneration requires a continuous blood supply. Coordination between osteogenesis and angiogenesis is crucial for proper bone regeneration.\textsuperscript{306–308} Osteogenesis, angiogenesis, and osseointegration are essential for the successful restoration of bone mass. Tuning of such factors by designing with RE nano biomaterials is critical for bone tissue engineering.\textsuperscript{306,309} In recent years, great attention has been drawn to coupling angiogenesis and osteogenesis to promote type H vessel formation. Type H vessels are a subtype of the capillary with high expression of CD31 and endomucin and promote osteogenesis. Type H vessels can actively direct bone formation by producing factors that stimulate the proliferation and differentiation of osteoprogenitors in the bone marrow.\textsuperscript{310–312} Type H vessel-inducing potential of rare-earth-based nanomaterials is not adequately studied. Understanding the role of RE-based materials on type H vessel formation may open up new vistas in the bone tissue engineering field.

Osteocytes play a vital role in bone modeling, remodeling, and homeostasis. The primary function of osteocytes is to convert mechanical stimuli to biological signalings that regulate the functions of osteoblasts, osteoclasts, and immune cells. The effect of RE nanomaterials on osteocytes function has not been reported yet. Future research should focus on designing RE smart nano-biomaterials that can modulate osteocyte function and promote bone regeneration. Similarly, immunomodulation regulation-based bone tissue engineering is currently a hot research topic. Investigating the use of RE nanomaterials on spatial temporal control of macrophage polarization and infiltration of various immune cells, including T cells, B cells, and neutrophils, would lead to the applicability of RE-immunoengineering approaches in bone tissue.

The majority of cancer easily metastasized in the bone. The cancer metastasized to the bone is very difficult to treat and causes excessive osteolysis. Scientists are desperately trying to develop therapeutic approaches to treat cancer metastasized in bone and simultaneously rescue bone loss. RE nano-biomaterials have bone regenerative and anti-cancer properties. RE nano-biomaterials has the potential to be used for in vivo imaging of cancer during diagnosis and treatment. Similarly, RE nano-biomaterials have shown the potential for imaging the newly formed and osteoporotic bone. Therefore, the prospect should be focused on designing RE innovative nano-biomaterials-based targeted therapy that can treat cancer metastasized in bone, rescue metastasis-induced bone loss, and simultaneously visualize the remaining cancer mass and newly formed bone.

In-depth analysis of local and systemic adverse effects of RE-nanobiomaterials in large animal models close to humans is another prospect that streamlines the clinical application of RE nano-bio materials. The clinical complication can be minimized by using rare-earth nanomaterials as a co dopant in new scaffold-based mechanics like 3D printing or electrospinning.\textsuperscript{313–315} Electrospinning is the most practical and widely explored technique for synthetic membranous grafts. Biopolymers like collagen, silk, and synthetic polymers like polyethylene glycol (PEG) and poly(lactic acid) (PLLA) have been designed for tissue regeneration purposes.\textsuperscript{316,317} Using the RE-based nanomaterials with these techniques may yield a remarkable outcome in accelerating bone defect healing with structural and mechanical stability. RE materials doped electrosprun or 3D-printed scaffolds may aid to warrant the sustained release and site-specific delivery of RE elements based on their physicochemical properties.

8 | CONCLUSIONS

In summary, this review portrayed the technological innovations of RE-based materials in bone tissue engineering. The intriguing features of RE materials such as biocompatibility, narrow band upconversion fluorescence property for deep tissue penetration, and excellent biological properties imply the promising potential of RE materials in biomedical applications. RE materials’ antioxidant, immunomodulatory, angiogenic, and osteogenic properties could be utilized to fabricate cost-effective bone grafts and implants. The mechanism of RE-material-based recruitment of progenitor cells,
induction of early angiogenesis, and osteogenesis should be studied thoroughly. The role of RE materials on immunomodulation, autophagy machinery in osteoblasts and MSCs, type H vessel formation, osteocytes function, and endothelial regulations need to be thoroughly investigated. Nevertheless, dose optimization, mode of delivery, and local/systemic adverse effects should be thoroughly investigated in large animal models to guarantee the bench-to-bed translation. Overall, RE smart nano-bio materials hold promising potential to substantiate the global demand for cost-effective biomaterials for bone tissue engineering and implantology in the future.

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CONFLICT OF INTERESTS

All authors have no conflicts of interest.

AUTHOR CONTRIBUTIONS

Duraiapandy Natarajan: Conceptualization (lead); formal analysis (lead); investigation (lead); methodology (lead); writing – original draft (lead); writing – review and editing (lead). Zhitong Ye: Software (equal); visualization (equal). Linhu Ge: Funding acquisition (equal); project administration (equal); resources (equal); supervision (equal). Janak Lal Pathak: Conceptualization (lead); funding acquisition (lead); methodology (lead); project administration (equal); resources (equal); supervision (lead); validation (lead); writing – review and editing (lead).

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