The biological functions of europium-containing biomaterials: A systematic review

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ABSTRACT

The biological functions of rare-earth elements (REEs) have become a focus of intense research. Recent studies have demonstrated that ion doping or alloying of some REEs can optimize the properties of traditional biomaterials. Europium (Eu), which is an REE with low toxicity and good biocompatibility, has promising applications in biomedicine. This article systematically reviews the osteogenic, angiogenic, neuritogenic, antibacterial, and anti-tumor properties of Eu-containing biomaterials, thereby paving the way for biomedical applications of Eu. Data collection for this review was completed in October 2022, and 30 relevant articles were finally included. Most articles indicated that doping of Eu ions or Eu-compound nanoparticles in biomaterials can improve their osteogenic, angiogenic, neuritogenic, antibacterial, and anti-tumor properties. The angiogenic, antibacterial, and potential neuritogenic effects of $Eu(OH)_3$ nanoparticles have also been demonstrated.

1. Introduction

Rare-earth elements (REEs) are of great interest in materials science. Some studies have shown that doping REEs in biomaterials can improve their biological properties [1–4]. For example, doping of cerium (Ce) and Gallium (Ga) can promote bone regeneration and antibacterial activity [5–9].

Europium (Eu) is the softest, most volatile, and most active REE. It generally exists in the trivalent form [10]. This element is primarily used in industrial applications [11,12]. Indeed, the fluorescence of Eu was the first aspect exploited for medical applications. Eu has been widely used as a fluorescent agent for cell imaging [13–17], monitoring of drug release behavior [10,18–21], and quantitative detection [22–24]. Certain materials doped with Eu ions can also be used as photo-inducers for therapy and pH or temperature biosensors [25–30].

It's indicated that Eu-containing biomaterials possess osteogenic, angiogenic, neuritogenic, antibacterial, and anti-tumor properties. The excellent biological functions of Eu have increased interest therein for biomedical applications. The osteogenic and angiogenic properties of Eu deposited in bone renders it suitable for bone tissue engineering [13, 31–34]. In 2016, it was demonstrated that Eu-doped mesoporous bioactive glasses (Eu-MBGs) promoted osteogenesis *in vivo* [35]. The neuritogenic properties of Eu are another reason why it is of interest in tissue engineering [36,37]. Europium-doped hydroxyapatite (Eu-HAp) can increase neurite length [38]. The antibacterial properties of Eu, which are concentration-dependent, are also important [39–44]. Its antibacterial behavior has promoted the development of antibiotic-free antibacterial agents exploiting antibacterial ion release, which helps to reduce the risk of infection. In addition, a few studies have also mentioned the possibility of using Eu-doped materials in anticancer therapy [45–51].

The biological functions of europium-containing biomaterials are of increasing interest. This systematic review summarizes studies on the osteogenic, angiogenic, neuritogenic, antibacterial, and anti-tumor properties of Eu-doped biomaterials and Eu compounds, and discusses the possible mechanisms underlying its biological functions, to lay a solid foundation for the application of Eu in biomedicine in future.

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2. Materials and methods

2.1. Objective of the study

The objective of this review was to systematically review the published literature concerning the osteogenic, angiogenic, neuritogenic, antibacterial, and anti-tumor properties of Eu, to pave the way for in-depth research and exploration of the mechanisms and application of Eu in biomedicine.

2.2. Inclusion and exclusion criteria

2.2.1. Inclusion criteria

- Articles analyzing the relationships among Eu-doped biomaterials (Eu ions, Eu oxide, and Eu hydroxide), Eu compounds and their osteogenic, angiogenic, neuritogenic, antibacterial, and anti-tumor properties.
- Evaluation of Eu-doped biomaterials through comparison with matched Eu-undoped biomaterials.

2.2.2. Exclusion criteria

- Reviews, books, meetings, patents, letters, and literature updates.
- Duplicate studies.
- Studies with no control group.
- Articles without full text.

2.3. Search strategy

The following databases were searched: Embase, PubMed, and Web of Science (from 2002 to July 2022). The search field was "title or abstract", and the search terms were as follows: (Europium) AND ((antibacterial) OR (osteogenesis) OR (angiogenesis) OR (tissue regeneration) OR (neuritogenic) OR (neurodegenerative) OR (nerve regeneration) OR (anti-tumor) OR (anticancer)). A total of 303 articles (PubMed, n = 63; Embase, n = 86; Web of Science, n = 154) were identified. The references of the included studies were also examined.

2.4. Article screening method

Duplicate articles, reviews, books, meetings, patents, letters, and literature updates were removed, and the titles and abstracts of the remaining hits were screened based on the inclusion and exclusion criteria. Then, the full texts of the selected articles were read for more detailed screening. The references of the included articles were also examined. The final review included 30 articles. The detailed screening process is presented in Fig. 1.

2.5. Quality assessment

The risk of bias was assessed according to the Methodological Index for Non-Randomized Studies (MINORS) scale [52,53]. The 12 evaluation items [54] were scored from 0 to 2. A non-comparative study with a score >16 was considered ideal.

3. Results

3.1. Study selection and results

In total, 303 articles were retrieved from the three databases, 145 of which were duplicates and were thus excluded. After removing patents, reviews, and books, 119 articles remained. After full-text screening, 28 articles remained. Two articles were added on the basis of the assessment of the reference sections of the included articles. Ultimately, 30 studies were included; their details are provided in Tables 1–8. The results shown that doping of Eu ions or Eu-compound nanoparticles in biomaterials can improve their osteogenic, angiogenic, neuritogenic, antibacterial, and anti-tumor properties (Fig. 2). The researches on this field have increased year by year and gradually become a research hotspot (Fig. S1).

3.2. Europium and osteogenesis

Promoting bone regeneration is a crucial aspect of tissue engineering. Doping an appropriate amount of Eu ions can improve the osteogenic properties of bioactive materials, such as bioactive glasses (BGs) [13,35, 33], HAp [55], and calcium polyphosphate scaffolds [31]. Details of the included studies concerning the relationship between Eu and osteogenesis are presented in Tables 1 and 2

Bioactive glasses have been widely used in bone tissue engineering [64,65]. Doping of Eu can improve the osteogenic property of BGs [13, 35,33]. Europium can up-regulate the expression of osteogenic genes and induce the osteogenic differentiation of mesenchymal stem cells (MSCs) *in vitro*. *In vivo* experiments have shown that Eu-doped biomaterials can promote new bone formation. Wu et al. proposed that the doping of Eu
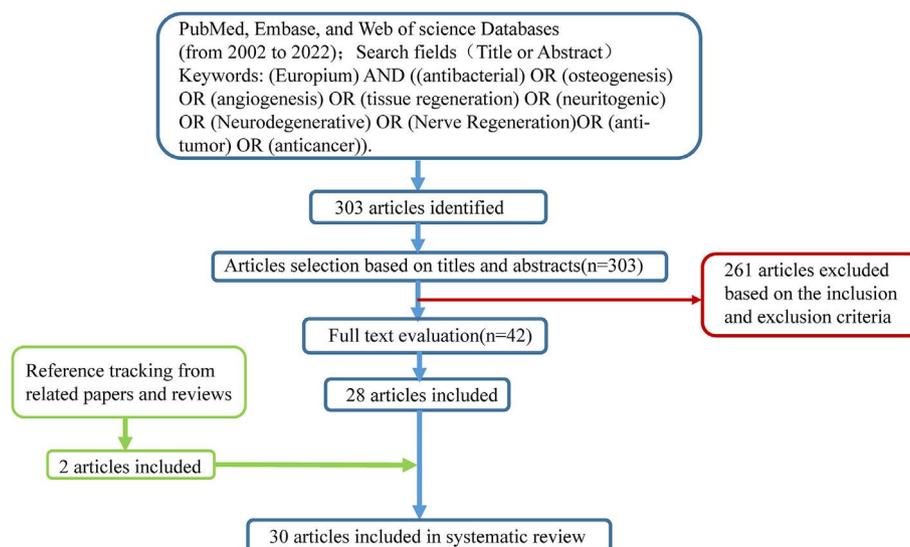

Fig. 1. Details of the study selection process.

Table 1
Osteogenic properties of europium *in vitro*.

Biomaterial	The form of europium	Experimental group	Control group	Cell type	Cell proliferation assessment	Cell osteogenic differentiation assessment	Results	Reference
Europium-doped calcium polyphosphate	Eu^{3+} ($EuPO_4$)	CCP 1, 3, 5, 7% EuCCP (1% europium/calcium molar ratio 1:99)	Blank control group	MC3T3-E1	CCK-8 assay	ELISA: ALP, OPN, osteoprotegerin/NF-kB receptor activator ligand ratio	Increased secretion of osteogenesis-related proteins. The greatest response: 5% group.	2022 [31]
nHAp/PLLA@Eu^{3+}	Eu^{3+} ($Eu(NO_3)_3$)	10 wt% nHAp/PLLA@3 mol% Eu^{3+}	10 wt% nHAp/PLLA@0 mol% Eu^{3+}	hASCs	BrdU incorporation assay	Alizarin Red staining; p-NPP hydrolysis; ELISA; RT-qPCR; Western blot	Increased osteogenesis-related markers. The greatest response: 3 mol% Eu^{3+} group.group.	2020 [55]
Eu-BGNs	Eu_2O_3	Eu-BGN (1, 3, 5%)	BGN	hMSCs	MTT assays	ALP staining; COL I staining; RT-PCR	Increased expression of the osteogenic genes. Better group: 3 mol% group.	2018 [33]
Eu-MSNs	Eu^{3+} ($Eu(NO_3)_3$)	2Eu-MSN (Eu: 2 mol%, 200 μg/mL)	MSN	Rat BMSCs; RAW 264.7	MTT assays	RT-qPCR; Western blot; Alizarin Red S staining	Increased osteogenesis-related markers.	2017 [13]
Eu-MBG	Eu^{3+} ($Eu(NO_3)_3$)	1, 2, 5 Eu-MBG; Different concentrations of 5Eu-MBG (6.25, 25, 100 mg/mL)	MBG	BMSCs	MTT assays	RT-qPCR	Increased expression of osteogenic genes. Better group: 12.5–100 mg/mL 5Eu-MBG.	2016 [35]

CCP, calcium polyphosphate; EuCCP, europium-doped calcium polyphosphate; MC3T3-E1, mouse embryonic osteoblast precursor cells; ALP, alkaline phosphatase; OPN, osteopontin; NF-kB, nuclear factor-k-gene binding; nHAp/PLLA@Eu^{3+}, polylactic acid with nano-hydroxyapatite doped with europium (III) ions; hASCs, human adipose-derived stromal cells; BrdU, 5-bromo-2-deoxyuridine; p-NPP, 4-Nitrophenyldihydrogenphosphate; ELISA, Enzyme-linked Immunosorbent Assay; RT-qPCR, Real Time Quantitative Polymerase Chain Reaction; Eu-BGNs, Eu-doped bioactive glass nanoparticles; MTT, 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2-H-tetrazolium bromide; COL I, human collagen type I; MSCs, mesenchymal stem cells; Eu-MSNs, Eu-doped mesoporous silica nanospheres; Eu-MBG, Eu-doped mesoporous bioactive glasses; BMSCs, bone marrow mesenchymal stem cells.

Table 2
Osteogenic properties of europium *in vivo*.

Biomaterial	The form of europium	Experimental group	Control group	Animal model	Evaluation method	Results	Reference
Eu-MSNs	Eu^{3+} ($Eu(NO_3)_3$)	M-P; Eu–P	Polymer	Sprague–Dawley rats; male; 10 weeks; full-thickness cranial defects (diameter: 5 mm)	Micro-CT, BV/TV, VG staining	Eu–P group: increased new bone formation.	2017 [13]
Eu-MBG	Eu^{3+} ($Eu(NO_3)_3$)	1, 2, 5Eu-MBG (0, 1, 2, 5 mol%)	MBG	OVX rats: femur defects; Monocortical bone defects (diameter: 3.5 mm; depth: 5 mm)	SEM; Micro-CT; BV/TV; Trabecular thickness; VG staining.	5Eu-MBG possesses the best osteogenic effect.	2016 [35]

Eu-MSNs, Eu-doped mesoporous silica nanospheres; M − P, MSNs + polymer film; Eu–P, Eu-doped M-P; BV/TV, bone volume fraction, bone volume/total volume; VG, Van Gieson; Eu-MBG, Eu-doped mesoporous bioactive glasses; OVX, ovariectomized; SEM, scanning electron microscope.

ions into mesoporous bioactive glass (MBG) scaffolds can promote osteogenesis. Compared with undoped MBGs, Eu-MBGs can up-regulate the expression of most osteogenic genes in bone marrow mesenchymal stem cells (BMSCs). In an ovariectomized (OVX) rat model of femoral defects, Eu-MBG scaffolds significantly promoted the formation of new bone in bone defect sites. The bone volume fraction (BV/TV) of the 5Eu-MBG (Eu: 5 mol%) group (47.71 ± 4.01%) was higher than that of the MBG group (26.81 ± 4.41%), and the 5Eu-MBG group (27.15 ± 4.31% and 46.53 ± 3.44%) had a more extensive area of new bone area than the other groups (MBG group, 13.36 ± 1.76% and 25.80 ± 3.48%; 2Eu-MBG group, 21.73 ± 2.59% and 36.58 ± 3.19%) [35]. Studies on hMSCs and rat MSCs (rMSCs) reported that Eu-doped bioactive glasses (Eu-BGs) can stimulate the osteogenic differentiation of hMSCs and enhance the expression of osteogenic genes. A 25% Eu-BG extract significantly stimulated the proliferation of rMSCs [33,66]. A study on Eu-MBGs reported that appropriate doping of Eu ions induced apatite mineralization, and an increased doping level changed the morphology from sheet to rod [10]. Compared with mesoporous silica nanospheres (MSNs), Eu-doped MSNs (Eu-MSNs) can induce pro-inflammatory responses of macrophages, which modulate the immune microenvironment. The modulated microenvironment can further induce the

osteogenic differentiation of BMSCs and significantly up-regulate the expression of osteogenic genes, such as osteocalcin (OCN). An *in vivo* study confirmed that Eu-doped MSNs can better promote bone formation of critically sized cranial defects compared with MSNs alone [13,67].

Hydroxyapatite has been widely explored in the context of bone tissue engineering [68,69]. Hydroxyapatite crystals can combine with many materials or ions without any change in its geometric structure. Eu ions can replace calcium (Ca) ions, thereby changing material properties. Marycz et al. demonstrated that doping of 3% mol Eu^{3+} into 10 wt% polylactic acid with nano-hydroxyapatite (10 wt% nHAp/PLLA@3% Eu^{3+}) scaffolds improved the survival rate of adipose-derived stromal cells (ASCs) and shortened the population doubling time of ASCs. Scaffolds of 10 wt% nHAp/PLLA@3% Eu^{3+} induced marked accumulation of Coll-1 in hASCs, facilitated the secretion of OCN, and increased the mRNA levels of BMP-2 and BMP-7. These findings confirmed that Eu-doped scaffolds are osteoinductive [55]. Europium-doped fluorapatite (Eu-FHAp) nanorods promoted the growth of BMSCs. However, Eu did not affect the ability of Eu-FHAp to promote osteogenic differentiation of BMSCs [16].

Multifunctional Eu-doped calcium polyphosphate scaffolds are currently attracting particular interest. Compared with pure calcium

Table 3
Angiogenic properties of europium *in vitro*.

Biomaterial	The form of europium	Experimental group	Control group	Cell type	Cell proliferation assessment	Cell angiogenic differentiation assessment	Results	Possible mechanism	Reference
Europium-doped calcium polyphosphate	Eu^{3+} ($EuPO_4$)	CCP 1, 3, 5, 7% EuCCP	Blank control group	HUVECs	CCK-8 assay	ELISA	Increased secretion of angiogenesis-related proteins. The best group: 5% group.		2022 [31]
Eu-MSNs (Eu: 1, 2, 3 mol%)	Eu^{3+} ($Eu(NO_3)_3$)	2Eu-MSNs (200 μg/mL)	MSNs	HUVECs		RT-qPCR	Increased expression of angiogenic genes.		2017 [13]
Polyphenol–europium assembly enabled functional poly(l-lactic acid) nanofiber mats	Eu^{3+} ($Eu(NO_3)_3$)	PLLA-(TA/Eu)$_n$ (n = 1, 3, 5; n: the number of deposition cycles)	PLLA	HUVECs	CCK-8 assay	RT-qPCR、Western blot	Increased angiogenesis-related markers. The best group: n=5		2021 [32]
EHNs	$Eu(OH)_3$	EHNs (10 μg/mL), Cd (20 μM), Cd + EHNs	Control, Spermine NONOate (SPNO, 10 μM); positive control	EA. hy926 cells, NIH 3T3 cells	Methyl-[3H]-thymidine incorporation assay	Scratch wound healing assay; Boyden chamber assay; Annexin V staining-flow cytometry; Griess assay; Western blot	EHN promotes the proliferation and migration of endothelial cells and decreases the apoptosis of them.	Activation of NO signal pathway; Anti-apoptosis	2020 [56]
Eu(OH)$_3$ nanorods	$Eu(OH)_3$	Eu(OH)$_3$ nanorods (Eu-20, 50, 100 μg/mL)	Untreated control; VEGF (10 ng/mL)	HUVECs	[3H]-thymidine incorporation assay	Western blot: MAPK activation analysis; Cell-cycle analysis; Apoptosis assay (TUNEL)	Dose-dependent increase in endothelial cell proliferation at 20–50 μg/mL; Less cell proliferation at 100 μg/mL	Reactive oxygen species (ROS); MAPK	2008 [57]
EHNPs	$Eu(OH)_3$	EHNPs 100 μg/mL	Black control; Positive control (VEGF)	Tg(flk:EGFP) zebrafish embryonic primary cells		High throughput screening; Fluorescence intensity	EHNPs increased GFP-positive cells.	ROS: H_2O_2	2016 [58]
Dextran- capped Eu(OH)$_3$ nanoclusters	$Eu(OH)_3$	50 μg/mL Eu(OH)$_3$ nanoclusters	TE buffer	HUVECs	MTT assay	Western blot; RT-qPCR	Increased proliferation of HUVECs and the expression of miR199a-3p	Up-regulate the expression of miR-199a-3p, which can directly target ZHX1; MAPK	2018 [59]
PCL scaffolds embedded with EHNs	$Eu(OH)_3$	PCL-EHNs-0.25, 0.5, 1, 2% (0.25, 0.5, 1, 2% EHNs) w/w	PCL	HUVECs		Western blot	Phosphorylation of Akt protein and VEGFR2 increased. Better group: EHNs (0.5% w/w)	VEGFR2/Akt-dependent.	2017 [60]

CCP, calcium polyphosphate; EuCCP, europium-doped calcium polyphosphate; HUVECs, Human umbilical vein endothelial cells; ELISA, Enzyme-linked Immunosorbent Assay; Eu-MSNs, Eu-doped mesoporous silica nanospheres; RT-qPCR, Real Time Quantitative Polymerase Chain Reaction; PLLA-(TA/Eu)$_n$, poly(l-lactic acid)-(tanic acid/europium)$_n$; EHNs, Eu(OH)$_3$ nanorods; VEGF, vascular endothelial growth factor; EHNPs, Eu(OH)$_3$ nanoparticles; GFP, green fluorescent protein; TE buffer, Tris-EDTA buffer; ZHX1, zinc fingers and homeoboxes protein 1; PCL, Polycaprolactone; VEGFR2, vascular endothelial growth factor receptor 2; ROS, reactive oxygen species; Akt, protein kinase B; MAPK, mitogen-activated protein kinase.

Table 4
Angiogenic properties of europium *in vivo*.

Biomaterials	The form of europium	Experimental group	Control group	Animal model	Evaluation method	Results	Possible mechanism	Reference
EHNs	$Eu(OH)_3$	EHNs: 5 mg/kg	Sham group (nonischemic; surgical control); Control (ischemic; TE buffer treatment)	Wistar rats; Hind limb ischemia (intraperitoneal injection)	Moor LDI2-HR laser Doppler imager; H&E staining; Immunofluorescence (Ki67, α-SMA); Serum NO estimation	Blood perfusion of ischemic rats treated with EHN increased rapidly over time. Increased angiogenesis-related markers. Increased NO level.	ROS mediated, PI3K/Akt dependent, NO signaling pathway	2021 [34]
EHNs	$Eu(OH)_3$	EHNs (10 μg/mL), Cd + EHNs, Cd (20 μM),	Control, Spermine NONOate (SPNO 10 μM)-positive control	Developing chick embryo (fertile eggs of Vanaraja chicken variety)	CEA assay; Measurement of blood vessel growth (AngioQuant software); Chick aortic arch tube formation assay.	Better angiogenic effect in EHN + Cd group than in Cd group. The best group: EHNs (10 μg/mL) group.	Enhanced NO production through eNOS activation. Anti-apoptosis	2020 [56]
EHNs	$Eu(OH)_3$	EHNs: 1 and 10 μg	TE buffer; VEGF-A (50 ng)	CAM	CAM sprouting assays.	$Eu(OH)_3$ nanorods significantly promoted vascular germination.	ROS , activation of MAPK	2008 [57]
EHNPs	$Eu(OH)_3$	100 μg/mL EHNPs	Blank control group	Transgenic line Tg(flk:EGFP) zebrafish live embryos	Axioskop 2 Plus microscope, AxioCam camera, OpenLab 4.0 software	Sprouts extended from the dorsal aorta. Head vessels recovered (> 50%).	ROS	2016 [58]
FHAEs (0.5, 1, and 2 mg/mL; Eu_2O_3 nanorods: 0.5, 1, and 2 mg/mL)	Eu_2O_3	FHAE hydrogel (50 μL)	Blank control group, 3 M group (commercial dressing)	Female mice (25–30 g, 4 weeks old): full-thickness skin wounds on dorsum (diameter: 7 mm)	HE staining; Immunohistochemical method	Increased angiogenesis-related markers Decreased inflammatory markers. Better group: FHAE-0.5. (Eu_2O_3:25 μg)	ROS	2021 [61]
Eu-MSNs (Eu: 1, 2, and 3 mol%)	Eu^{3+} ($Eu(NO_3)_3$)	Polymer, M − P, Eu–P	Control	Diabetic mice (female C57BL/6); full-thickness wound on dorsal (diameter: 8 mm)	Counting the number of vessels; Immunofluorescence; Masson's trichrome stain	Eu–P group: the capillary network around the wound center was tighter, and collagen deposition, re-epithelialization and blood vessel density were significantly higher.		2017 [13]
PCL scaffolds embedded with EHNs	$Eu(OH)_3$	PCL-EHNs-0.25, 0.5, 1, 2	PCL	Fertilized eggs of the Vanaraja strain chicken variety	AngioQuant software	Various angiogenesis parameters (junctions, length and size) improved. Better group: 0.5% EHNs group.	ROS	2017 [60]
PLLA-(TA/Eu)$_n$	Eu^{3+} ($Eu(NO_3)_3$)	PLLA-(TA/Eu)$_n$ (n = 3, 5)	Blank control group (normal saline treatment), PLLA	SD rats; Full-thickness skin defect mode (diameter:1 cm)	Wound size reduction (%); H&E staining; Masson staining; Immunohistochemical staining	The wound healing effect increased with increasing numbers of TA/Eu deposition cycles (n).		2021 [32]

EHNs, $Eu(OH)_3$ nanorods; TE buffer, Tris-EDTA buffer; CEA, Chick embryo Angiogenesis; α-SMA, α-smooth muscle actin; ROS, reactive oxygen species; PI3K, Phosphatidylinositol 3-kinase; Akt, protein kinase B; MAPK, mitogen-activated protein kinase; eNOS, endothelial nitric oxide synthase; VEGF-A, vascular endothelial growth factor-A; CAM, Chick chorioallantoic membrane; EHNPs, $Eu(OH)_3$ nanoparticles; FHAEs, europium oxide nanorod-reinforced nanocomposites; Eu-MSNs, Eu-doped mesoporous silica nanospheres; M − P, MSNs + polymer film; Eu–P, Eu-doped M-P; PCL, Polycaprolactone; PLLA-(TA/Eu)$_n$, poly(l-lactic acid)-(tanic acid/europium)$_n$; SD rats, Sprague–Dawley rats.

Table 5
Neuritogenic properties of europium.

Biomaterial	The form of europium	Experimental group	Control group	Cell type	Methods	Results	Reference
EHNs	Eu(OH)$_3$	EHNs (50 mg/mL)	Trehalose (100 mM), TE buffer	PC12, Neuro 2a and HeLa cells	Western blot; TEM	EHNs promoted the conversion from LC3-I to LC3-II and increased the LC3-II/GAPDH ratio; the level of p62/SQSTM1 decreased.	2014 [37]
Eu-CeO$_2$ nanoparticles	EuCeO$_2$	Eu-CeO$_2$ nanoparticles (100 ng/mL)	Lipid nanoparticles without CeO$_2$	BV2 cells	Western blot; ELISA; RT-qPCR	EuCeO$_2$ nanoparticles reduced Aβ1–42 levels and LPS-induced IL-6 and IL-1β expression.	2022 [36]
Li$^+$/Eu^{3+}-doped nHAp	Eu^{3+}	nHAp: Li$^+$/Eu^{3+}	nHAp: Li$^+$;	Neuron-like cells (SH-SY5Y and PC12 after differentiation)	Length of neurites	nHAp:Li$^+$/Eu^{3+} group had longer average neurite length than nHAp:Li$^+$ group. (Statistically significant at 2.5–20 μg/mL)	2021 [38]

EHNs, Eu(OH)$_3$ nanorods; TE buffer: Tris-EDTA buffer solution; TEM, transmission electron microscope; LC3, light chain 3; GAPDH, glyceraldehyde phosphate dehydrogenase; SQSTM1, Sequestosome 1; ELISA, Enzyme-linked Immunosorbent Assay; RT-qPCR, Real Time Quantitative Polymerase Chain Reaction; LPS, lipopolysaccharide; Aβ, amyloid beta; HAp, hydroxyapatite.

polyphosphate, the proliferation and migration of mouse embryonic osteoblast precursor cells (MC3T3-E1 osteoblasts) cultured on Eu-doped calcium polyphosphate scaffolds was superior, especially at the 5% doping level. These scaffolds enhanced the secretion of alkaline phosphatase (ALP), which promoted the proliferation and differentiation of osteoblasts. Notably, 5 mol% Eu^{3+}-doped calcium polyphosphate simultaneously inhibited bone resorption. Hence, such scaffolds can significantly promote osteogenesis [31].

At appropriate concentrations, Eu has positive effects on cell proliferation and osteogenesis, but these effects are inhibited by high Eu concentrations [70,71]. Most articles concluded that in the presence of Eu^{3+} at the concentration of 3 or 5 mol%, the biomaterials showed better osteogenic effect [35,31,33,55]. Only one article showed that the best concentration of Eu^{3+} was 2 mol% [13]. In summary, the concentration range of 1 mol% to 7 mol% can promote osteogenesis according to the included studies.

3.3. Europium and angiogenesis

Some Eu-doped biomaterials can effectively promote angiogenesis *in vitro* and *in vivo*. Yuchong et al. conducted a study on the angiogenic ability of Eu-doped calcium polyphosphate scaffolds. The surface roughness of the scaffolds promoted cell adhesion and spreading. Human umbilical vein endothelial cells (HUVECs) seeded on the scaffolds exhibited better proliferation and migration, and the secretion of VEGF was enhanced by the scaffolds [31]. *In vitro* experiments established that PLLA-(TA/Eu)$_n$ nanomaterials cocultured with HUVECs stimulated angiogenesis by increasing the expression of angiogenic genes (e.g., CD31, FGF, and VEGF). The results of *in vivo* experiments confirmed that PLLA-(TA/Eu)$_n$ nanomaterials can promote angiogenesis and enhance antioxidant properties, which in turn promotes wound healing. The wound closure rates of PLLA-(TA/Eu)$_3$ (70.46%) and PLLA-(TA/Eu)$_5$ groups (75.14%) were higher than that of control (58.32%) and PLLA groups (66.14%) [32]. Shi et al. reported that Eu-MSNs can regulate the immune microenvironment, enhance the expression of angiogenic genes (e.g., CD31, VEGFR1, and VEGFR2), and promote angiogenesis in HUVECs. *In vivo* experiments further indicated that Eu-MSNs could promote angiogenesis, as well as the deposition of collagen and reattachment of epithelial cells at skin lesions; the Eu-MSNs had stronger angiogenic ability than MSNs alone and effectively promoted skin healing [13]. Europium oxide nanorod-reinforced nanocomposites (FHAEs) can significantly inhibit early inflammation, enhance the expression of CD31 and α-SMA, and promote angiogenesis. *In vivo* experiments showed that the material significantly promoted the healing of tissues and wounds, and the regeneration of skin appendages [61,72].

Numerous *in vivo* and *in vitro* studies have demonstrated that Eu(OH)$_3$ nanorods (EHNs) possess good angiogenic activity [34,56–60,73]. For example, Nethi et al. evaluated their therapeutic effect on ischemic rats. They reported enhanced blood flow of the ischemic part of rats treated with EHNs. The motility of the rats also improved, and the expression of angiogenic factors increased [34]. Key findings of the studies are provided in Tables 3 and 4

All the included articles suggested that EHNs promoted angiogenesis at appropriate amount. R. Bhattacharya et al. reported EHNs caused a dose-dependent increase in endothelial cell proliferation at concentrations of 20–50 μg/mL. While at the concentration of 100 μg/mL, there existed less cell proliferation [57]. Other studies confirmed that proliferation of endothelial cells was stimulated under EHNs concentrations of 10 or 50 μg/mL [56,59]. H. Zhao et al. confirmed that Eu(OH)$_3$ nanoparticles (EHNPs) promoted the endothelial differentiation of zebrafish embryonic primary cells at the concentration of 100 μg/mL [58]. The researches on Eu-doped biomaterials have demonstrated that the concentration range of Eu (1–5 mol%) promoting angiogenesis is similar to that of Eu promoting osteogenesis [13,31].

Table 6
Antibacterial properties of europium.

Biomaterial	The form of europium	Experimental group	Control group	Methods	Bacteria	Results	Reference
Bare and APTES-coated Eu$_2$O$_3$ nanoparticles	Eu$_2$O$_3$	50 μL of bare and APTES-coated Eu$_2$O$_3$ nanoparticles (100, 250, 500, 1000 ppm)	Sterile distilled water	Effective zone of inhibition	*E. coli*, *P. aeruginosa*, *S. aureus* and *S. typhi*	Bare Eu$_2$O$_3$ nanoparticles: good antibacterial activity against the texted bacteria.	2018 [62]
Eu(OH)$_3$ nanorods	Eu(OH)$_3$	2000 μg/mL Eu(OH)$_3$ nanorods	Ciprofloxacin (CIP-5 μg), rifampicin (RS-5 μg), and fluconazole (25 μg/mL)	Disc diffusion assay; MIC assay	*S. aureus*, *P. aeruginosa*, *E. coli* and C. albicans (fungus)	Good antibacterial effect.	2022 [41]
Eu(OH)$_3$ nanoparticles	Eu(OH)$_3$	0.1 mg/mL of Eu(OH)$_3$	0.1 mg/mL of ampicillin	Disk diffusion assay	*E. coli*	Eu(OH)$_3$/RGO suspension exhibited the highest *E. coli* growth inhibition	2021 [42]
Eu:HAp	Ca$_{10-x}$Eu$_x$(PO$_4$)$_6$(OH)$_2$	Eu:HAp (0 ≤ xEU ≤0.2; x = 0.05, 0.1, 0.2)	Eu:HAp groups compared with each other	Disk diffusion method	*S. aureus*, *P. aeruginosa*, *E. faecalis*, *E. coli* and C. albicans (fungus)	No antibacterial activity was observed against *E. coli*. The antibacterial properties were Eu concentration-dependent.	2013 [39]
Eu-HAp	Eu^{3+}	Eu-HAp ((Ca + Eu)/P = 1.67)	HAp	Well diffusion	*S. aureus* and *E. coli*	Eu-HAp possesses higher diameter of the growth inhibition zone. (50, 100 μg/mL)	2022 [63]
Eu^{3+}-doped HAp nanopowders	Eu^{3+}	Eu^{3+}-doped hydroxyapatite nanopowders (2, 5 mol % Eu^{3+})	HAp nanopowders	Microdilution	*E. coli* and *K. pneumoniae*	Differences were nonsignificant.	2020 [43]
Eu^{3+}-doped Ca$_{10}$(PO4)$_6$Cl$_2$ nanoparticles	Eu^{3+}	Eu^{3+}-doped Ca$_{10}$(PO4)$_6$Cl$_2$ nanoparticles (2 mol%)	Positive controls: saline solution. Negative controls: apatite saline diluent	Microdilution	*P. aeruginosa*, *E. coli* and *K. pneumoniae*	Eu^{3+}-doped Ca$_{10}$(PO$_4$)$_6$Cl$_2$ did not exhibit antibacterial properties.	2015 [44]
Eu(III)-2-thioacetate benzothiazole complexes	Eu^{3+}(Eu(TAB)$_2$Cl)	Eu(III)-2-thioacetate benzothiazole complexes	2-thioacetic acid benzothiazole	MIC assay	*E. coli* and Salmonella	The Eu-doped complexes had stronger antibacterial effects.	2012 [51]

APTES, 3-aminopropyltriethoxysilane; *P. aeruginosa*, Pseudomonas aeruginosa; *E. coli*, *Escherichia coli*; *S. aureus*, *Staphylococcus aureus*; *K. pneumoniae*, *Klebsiella pneumoniae*; *S. typhi*, Salmonella typhi; TAB, thioacetate benzothiazole; MIC, minimum inhibitory concentration; C. albicans, Candida Albicans; HAp, hydroxyapatite.

3.4. Nerve regeneration and treatment of neurodegeneration

Nerve regeneration is another important aspect of tissue engineering. Current research mainly focuses on the treatment of neurodegenerative diseases and axonal injury, which mainly involves autophagy and the enhancement of antioxidant capacity. All neuro-related experiments were conducted *in vitro* and involved nanomaterials [36–38]. Many areas about the potential neuritogenic properties of europium remain to be explored and further *in vivo* experiments are needed. Details of the reviewed researches are provided in Table 5.

Autophagy, which is beneficial for the treatment of neurodegeneration, accelerates the clearance of protein aggregates. Wei et al. confirmed that EHNs can up-regulate the expression of autophagy-related protein and reduce the expression of related substrate receptors. Accordingly, these nanorods can reduce the aggregation of huntingtin protein through the induction of autophagy [37]. Alzheimer's disease is the most well-known neurodegenerative disease. The main pathological manifestations of Alzheimer's disease are neurofibrillary tangles and Aβ (amyloid beta) plaque deposition. These changes may lead to microglial neuroinflammation and neurodegeneration. Machhi et al. found that EuCeO$_2$ nanoparticles increased the expression of the CD36 receptor, and subsequently improved Aβ phagocytic microglial capabilities and enhanced Aβ degradation. These nanoparticles also inhibited the inflammatory response of microglia, and could potentially be deployed as immunomodulators of Alzheimer's disease [36].

Wiatrak et al. reported that nHAp-induced mitochondrial activity elevation corresponded to increased neurite length. They studied potential nerve regenerative and neurite-protective effects in neuron-like cells. They also found that doping Eu ions into nHAp enhanced its antioxidant properties. Europium ions influenced neuronal features even more strongly than doping with Li alone [38].

3.5. Antibacterial properties of europium

The antibacterial properties of Eu help reduce the risk of infection. The literature reviewed herein focused primarily on Pseudomonas aeruginosa (*P. aeruginosa*), *Escherichia coli* (*E. coli*), *Staphylococcus aureus* (*S. aureus*), *Klebsiella pneumoniae* (*K. pneumoniae*), and Salmonella typhi (*S. typhi*) bacteria [39,41–44,51,62,63]. The most commonly used methods for evaluating the antimicrobial properties of Eu were the disk diffusion method and minimum inhibitory concentration (MIC) assay. Details of the studies are provided in Table 6.

Most studies have established that Eu-containing biomaterials exert antibacterial effects mainly on *P. aeruginosa*, *E. coli*, and *S. aureus* at appropriate concentrations. For example, Iconaru et al. reported that the antibacterial properties of Eu-doped HAp nanomaterials depended on the concentration of Eu ions. Moreover, at the concentration from 0.031 mg/mL to 1 mg/mL, the Eu-doped HAp nanomaterials possessed antibacterial effect. When the concentration of Eu-doped HAp was in the range of 0.125–1 mg/mL, the inhibitory effect on *P. aeruginosa* was better [39]. In most cases, for dopants at 5 mol% ratio, the Eu^{3+}-doped hydroxyapatite nanoparticles had better antibacterial effect against Gram-negative bacteria such as *K. pneumoniae*, *E. coli* and *P. aeruginosa*. But this effect is related to species and strains [43]. However, Iconaru et al. [39], Wiglusz et al. [44], and Szyszka et al. demonstrated that Eu-doped HAp nanopowders did not have antibacterial effects on *E. coli* [43,74], but the specific mechanism was still unclear. Interestingly, the combination of Eu^{3+} and Ag $^+$ ions had a synergistic antibacterial effect, reducing the bacterial number by 100%. The europium ion Eu^{3+} is readily reduced to Eu^{2+} in air; the reported antibacterial activity may be related to the interaction between Eu^{2+} and Ag $^+$ ions [44].

The formation of bacterial biofilm is one of the important difficulties in anti-infection therapy. The biofilm inhibition rate of Eu(OH)$_3$

Table 7

Anti-tumor activity of europium *in vitro*.

Biomaterials	The form of europium	Experimental group	Control group	Cell type	Methods	Results	Reference
Europium (III)-2-thioacetate benzothiazole	$Eu^{3+}(Eu(TAB)_2Cl)$	Europium (III)-2-thioacetate benzothiazole (1, 5, 10, 25, 50 mM)	Cisplatin	MCF7, hepG2, and EAC cell lines	Cell viability curves; IC50 values.	Significant cytotoxic activity against HepG2 and MCF7 cell lines.	2012 [51]
Bis(acridine-9-carboxylate)-nitro-europium dihydrate complex	bis(acridine-9-carboxylate)-nitro-europium(III) dihydrate complex	Bis(acridine-9-carboxylate)-nitro-europium dihydrate complex	Cisplatin; 9-acridine carboxylic acid	EAC cell line	MTT assay	Cell viability decreased with increasing concentrations of the complex.	2013 [45]
Europium selenide nanoparticles	$Eu^{3+}(EuCl_3)$	Europium selenide nanoparticles (1, 5, 10, 30, 50, 100, 300, 500, 1,000, 2000 μM)	Untreated cells	HeLa, SKOV-3, and 293 T cells	MTT assay	Cell viability decreased.	2016 [50]
Eu-nHAp	Eu^{3+}	Eu-nHAp (Eu/(Ca + Eu): 5%)	Routinely cultured group	HUVECs	MTT assay; Lactate dehydrogenase activity assay	Time- and dose-dependent inhibitory effects on HUVECs (0.3, 3, and 30 μg/mL); Stimulation of LDH in a dose-dependent manner.	2016 [49]
Eu^{3+}: nHAp @PLLA	Eu^{3+}	10 wt%, 3 mol% Eu^{3+}: nHAp @PLLA	Polystyrene	Saos-2, U-2 OS, and MG-63 cells	Confocal/scanning electron microscopy; MTS test; RT-qPCR.	High cytotoxicity to all OSA cell lines.	2019 [48]

TAB, thioacetate benzothiazole; MCF7, human breast carcinoma cell line; hepG2, human liver carcinoma cell line; EAC, mouse Ehrlich ascites carcinoma; IC50, half maximal inhibitory concentration; HAp, hydroxyapatite; HUVECs, Human umbilical vein endothelial cells; LDH, lactate dehydrogenase; PLLA, polylactic acid; Saos-2, U-2 OS, MG-63, human osteosarcoma cell lines; MTS, 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium; RT-qPCR, Real Time Quantitative Polymerase Chain Reaction; OSA, osteosarcoma.

Table 8

Anti-tumor activity of europium *in vivo*.

Biomaterials	The form of europium	Experimental group	Control group	Animal models	Methods	Results	Reference
Europium(III)- 2-thioacetate benzothiazole	$Eu^{3+}(Eu(TAB)_2Cl)$	Europium(III)- 2-thio-acetate benzothiazole (4 mg/kg IP)	Vehicle injection (DMSO in PBS)	Swiss albino mice weighing 20–25 g	DNA extraction; Immunohistochemistry; Tumor mass	Anti-angiogenic activity against EACs. Reduction in solid tumor mass.	2012 [51]
Bis(acridine-9-carboxylate)-nitro-europium dihydrate complex	Bis(acridine-9-carboxylate)-nitro-europium(III) dihydrate complex	Bis(acridine-9-carboxylate)-nitro-europium dihydrate complex (5 mg/kg IP), 100 μL	Vehicle injection (DMSO in PBS); 9-acridine carboxylic acid	Swiss albino mice weighing 20–25 g	DNA extraction; Immunohistochemistry; Tumor mass	Reduction in tumor mass, number of EAC cells, and microvessel density. Formation of nucleosomes of DNA fragments.	2013 [45]

TAB, thioacetate benzothiazole; IP, intraperitoneal injection; DMSO, dimethyl sulfoxide; PBS, phosphate buffered saline; DNA, Deoxyribonucleic Acid; EAC, mouse Ehrlich ascites carcinoma cells.
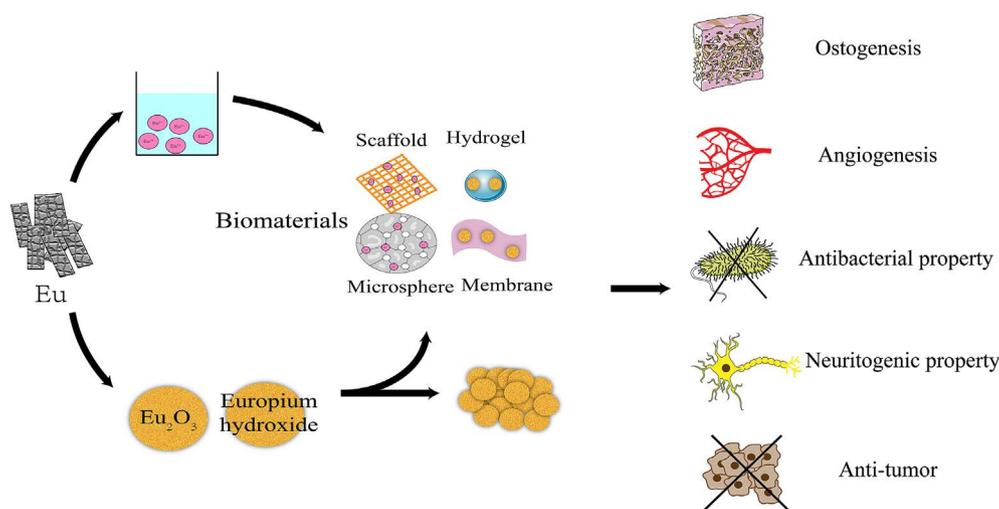

Fig. 2. Biological effects of europium. Europium (Eu)-containing biomaterials possess osteogenic, angiogenic, neuritogenic, antibacterial, and anti-tumor properties.

nanorods against *Pseudomonas aeruginosa* (77.5 ± 0.43%) was the highest, which could be considered as potential candidates to prevent the formation of biofilm [41].

3.6. Anti-tumor properties of europium

Tumors are very harmful to human health, and producing safe and effective anti-tumor drugs has long been a focus of research. Europium has potential anti-tumor activity [45,47–51], but more studies are needed to validate this.

Hussein et al. synthesized a new complex, Eu(III)-2-thioacetate benzothiazole, which displayed anti-tumor properties when combined with DNA. Their research indicated that the complex exserted anti-tumor effects via its anti-angiogenic activity; the density of microvessels and expression of Flk-1 (VEGF receptor type-2) were reduced [51]. *In vivo* experiments by Azab et al. demonstrated that the bis(acridine-9-carboxylate)-nitro-europium dihydrate complex significantly increased the level of caspase-3 compared with the complex containing the simpler acridine ligand, which also exerted anti-angiogenic effects by reducing Flk-1 [45]. There have been few studies on the relationship between Eu ion and anti-tumor activity; the most recent publication among those reviewed herein concerned the interaction between Eu and DNA. Studies reported a strong interaction between Eu_2O_3 and dsDNA, and that binding was independent of the ion concentration in the surrounding area. Gel electrophoresis showed that Eu_2O_3 did not interfere with drug intercalation into the double-helix structure [47]. Various studies have demonstrated that Eu has the potential to interact with nucleic acids, which could inform the design of future metal-based anticancer drugs. Details of the studies are given in Tables 7 and 8

3.7. Quality assessments

Table 9 lists the results of the quality evaluation. All of the included studies had scores >16, indicating a low risk of bias.

4. Discussion

Combining traditional biomaterials with REEs has been a focus of research for many decades. Europium is a potential therapeutic ion that can act ionically or exert effects in the form of EHNPs. In most Eu-containing biomaterials, Eu is added in the form of salt or hydroxide, and occasionally in the form of oxide. Some Eu^{3+}-doped biomaterials and EHNPs possess angiogenic, antibacterial, and neuritogenic properties. Furthermore, doping with Eu ions can enhance the osteogenic and anti-tumor properties of biomaterials. Promoting the regeneration of bone, blood vessels, and nerves is beneficial for tissue defect healing. In conclusion, Eu has great potential in biomedicine due to its osteogenic, angiogenic, potential neuritogenic, antibacterial, and anti-tumor properties.

4.1. The osteogenic property of europium

Researches have demonstrated that doping an appropriate amount of Eu ions can improve the osteogenic properties of some bioactive materials, such as BGs, HAp, and calcium polyphosphate scaffolds. Most included studies have confirmed that the appropriate doping of Eu can up-regulate the expression of some osteogenic markers, such as ALP, human collagen type I (COL I), OPN, and runt-related transcription factor 2 (Runx2). The concentration range of 1 mol% to 7 mol% can promote osteogenesis according to the included studies. The results suggest that

Table 9
MINORS bias scale.

Evaluation	[31]	[32]	[34]	[61]	[56]	[55]	[59]	[33]	[13]	[60]	[58]	[35]	[57]	[63]
Prospective collection of data	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Contemporary groups	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Clearly stated aim	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Test group: Eu content in the materials: 0 (not reported), 1 (materials coated with Eu or approximate mixing ratio of Eu), 2 (precise mixing ratio of Eu)	2	1	2	2	2	2	2	2	2	2	2	2	2	2
Sample randomization	0	0	0	1	0	0	0	0	0	0	0	2	0	0
Condition of the samples during measurements	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Standardized measurements standardization	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Unbiased assessment of the study endpoint	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Measurements method	2	2	2	2	2	2	2	2	2	2	2	2	2	1
Endpoints appropriate to the aim of the study	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Adequate statistical analyses	2	2	2	2	2	2	2	2	2	2	2	2	2	1
Baseline equivalence of groups	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Total score	20	19	20	21	20	20	20	20	20	20	20	21	20	18
Evaluation	[41]	[42]	[43]	[62]	[44]	[39]	[51]	[37]	[36]	[38]	[47]	[48]	[49]	[50]
Prospective collection of data	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Contemporary groups	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Clearly stated aim	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Test group: Eu content in the materials: 0 (not reported), 1 (materials coated with Eu or approximate mixing ratio of Eu), 2 (precise mixing ratio of Eu)	2	1	2	2	2	2	2	2	2	1	2	2	2	2
Sample randomization	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Condition of the samples during measurements	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Standardized measurements	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Unbiased assessment of the study endpoint	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Measurement methods	2	2	2	1	2	1	1	2	2	2	1	2	1	1
Endpoints appropriate to the aim of the study	2	2	2	2	2	2	2	2	1	2	2	2	2	2
Adequate statistical analyses	2	2	2	1	1	2	1	2	2	2	2	2	2	2
Baseline equivalence of groups	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Total score	20	19	20	18	19	19	18	20	19	19	19	20	19	19
Sample randomization	0	0	0	0	0	0	0	0	0	0	0	0	0	0

0, not reported; 1, inadequately reported; 2, sufficiently reported.

there is an optimal Eu concentration that will have the strongest growth-promoting effect. Moreover, due to the variety of methods for doping Eu, it is difficult to determine the optimal concentration. The effect of Eu on osteogenesis needs to be further explored for future biomedicine applications. Current research on osteogenesis is mainly focused on Eu-doped functional biomaterials, while the osteogenic properties of Eu compounds and Eu alloys deserve further exploration.

The biological characteristics of Eu are mainly based on the similarity between its structure and that of Ca. The radius of an Eu ion is close to that of a Ca ion. Because Eu has larger ionic potential than Ca, Eu ions are more likely to occupy Ca sites in biomaterials, which act as inhibitors or biochemical probes of Ca ions [10]. Europium can potentially treat bone mineral density disorders by functionally mimicking Ca and affecting the bone remodeling cycle. However, the specific mechanism of osteogenesis remains unclear. It is possible to affect the osteogenesis of biomaterials by modulating Ca ion release, thereby changing the conformation of HAp during the deposition of new bone and influencing the expression of osteogenesis-related genes. Some studies have proposed that osteogenic mechanisms for other REEs, such as Ce and lanthanum, might be related to activation of the TGF signal pathway [75,76]. However, whether TGF signaling is relevant to Eu remains to be verified.

Europium is rarely distributed in bone; thus, it could be applied locally (by local injection or doping into stents) or be combined with bone-targeting drugs (e.g., by combining it with bisphosphonates [77]) to repair bone defects [78]. Systemic application of bone-targeted drugs is beneficial to the treatment of bone mineral density disorders such as osteoporosis. Europium can also be incorporated into scaffolds for the repair of local tissue defects [13,35]. The controlled release of Eu merits further exploration, too. Alloying with appropriate amount of Europium can enhance the mechanical properties of biodegradable metals, improve the corrosion behavior and reduce the hemolysis rate, which is beneficial to the application of biodegradable metals in bone tissue engineering [71,79]. The osteogenic property of europium alloy can be further studied in the future.

4.2. The angiogenic property of europium

$Eu(OH)_3$ nanoparticles promote angiogenesis at appropriate amount. The researches on Eu-doped biomaterials have demonstrated that the concentration range of Eu (1–5 mol%) promoting angiogenesis is similar to that of Eu promoting osteogenesis, which means that the biomaterials containing Eu are conducive to promoting the generation of vascularized bone in the application of bone tissue engineering.

The mechanism underlying the angiogenic properties of Eu has been explored but remains unclear. It was reported that the angiogenic properties of $Eu(OH)_3$ arose from to formation of ROS, especially H_2O_2 [72, 58,80–83]. Nethi et al. reported that EHNPs can promote the production of H_2O_2, which in turn activates endothelial nitric oxide synthase (eNOS) and promotes the production of NO through a PI3K-dependent pathway, ultimately promoting angiogenesis [84]. Augustine et al. found that PCL scaffolds embedded within EHNs enhanced the angiogenic properties of HUVECs via a VEGFR2/Akt-mediated signaling pathway, as indicated by protein expression [60]. The research of Li et al. on EHNPs confirmed that up-regulated Mir-199a-3p is a key modulator of pro-proliferative activity and can target zinc fingers and homeoboxes protein 1 (ZHX1) [59,85,86]. This finding points to a potential strategy for treating ischemic diseases, i.e., by combining nanomedicine and gene therapy (Fig. 3).

Europium is promising for the treatment of ischemic diseases in the future. Angiogenesis disorder is one of the important causes of coronary and ischemic heart disease. Conventional treatments such as angioplasty have several limitations, such as thrombosis and fibrosis [87–89]. Compared with the control group, the blood flow of ischemic limbs increased in Wistar rats after intraperitoneal injection of EHNs [34]. After thorough biosafety studies, europium-containing biomaterials are expected to be developed as a possible alternative treatment strategy. Eu can promote angiogenesis and wound healing, which is potential to be used in tissue engineering. However, before being explored in clinics, the biosafety, immune response, biological distribution, metabolic effect and bioavailability of Eu need to be investigated in detail in larger animals.
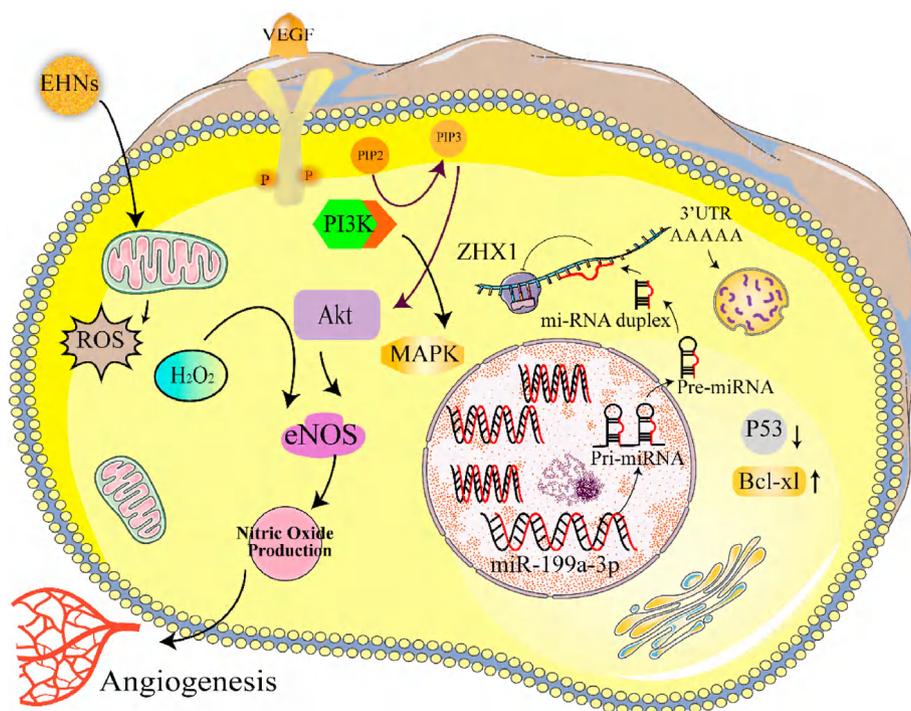

Fig. 3. Mechanism underlying the angiogenic properties of $Eu(OH)_3$ nanoparticles. EHNs, $Eu(OH)_3$ nanorods; ROS, reactive oxygen species; VEGF, vascular endothelial growth factor; PI3K, Phosphatidylinositol 3-kinase; Akt, protein kinase B; MAPK, mitogen-activated protein kinase; eNOS, endothelial nitric oxide synthase.

4.3. The neuritogenic property of europium

There are few researches concerning the neuritogenic property of Eu. As noted above, enhancing autophagy is beneficial for the treatment of neurodegenerative diseases. Wei et al. revealed that EHNs did not induce autophagy through the classical AMPK and AKT-mTOR signaling pathways, but rather activated the MEK/ERK1/2 signaling pathway. This study also found that the combination of two autophagy inducers with different mechanisms can stimulate autophagy through different signaling pathways and enhance the clearance of intracellular protein aggregates, which is conducive to better treatment of neurodegenerative disorders [90]. Some studies have also shown that the ability of Eu to promote neurite growth may be related to its antioxidant capacity. The existing researches are limited to *in vitro* researches. Studies have shown that Eu had a potential application in the treatment of axonal injury and neurodegeneration. However, further primary neuron cultures and *in vivo* experiments are still needed.

4.4. The antibacterial property of europium

Composite materials with long-term antibacterial effects have potential utility for many medical devices. Studies have established that Eu-containing biomaterials exert antibacterial effects mainly on *P. aeruginosa*, *E. coli*, and *S. aureus* at appropriate concentrations.

There are few studies on the antibacterial mechanism of Eu. Kolmas et al. advanced a hypothesis for the antibacterial mechanism of metal ions. When entering bacterial cells, metal ions affect ATP production and DNA replication. The aggregation of ions in the cell membrane can affect its permeability and transport function. The ions also induce the production of ROS, which can have various effects on bacterial cells. This could explain the antibacterial effects of Eu ions [74,91]. Shih et al. found that the antimicrobial activity of EHNs was related to electrostatic attraction between nanorods and cell membranes, nanorod size, and the release of Eu ions [42]. Eu ions can penetrate into cells and kill bacteria through the electrostatic interaction between cell walls and nanorods [91] (Fig. 4). All of these mechanisms are important for the eradication of bacterial infections.

P. aeruginosa is more common in infected wounds, especially in patients with diabetes. Eu can promote wound healing, possess antibacterial against many bacteria such as *P. aeruginosa* and antibiofilm activity, which suggests that Eu has great potential to be used as wound dressing materials. The antibacterial properties of Eu-containing biomaterials render them suitable for combination with bacteria-targeted molecules to yield targeted bactericides; these could be incorporated into scaffolds to promote tissue healing while also playing an anti-infection role [92–94]. The bacterial microenvironment is acidic, hypoxic, and highly reductive, and contains a large amount of ROS [95]. Microenvironment-sensitive drug delivery systems can be constructed for targeted antibacterial delivery.

4.5. The anti-tumor properties of europium

Few studies have been reported concerning the mechanism of anti-tumor effects of Eu. Genetic factors are among the most important; drugs interacting with DNA or RNA are used in anticancer, antivirus, and antibacterial therapy [96,97]. Eu_2O_3 interacts strongly with dsDNA, which strongly suggests that Eu could be considered in the design of future metal-based anti-tumor drugs. Other research reported that single-strand DNA had affinity for Eu [98].

Considering the osteogenic ability of europium and its potential anti-tumor properties, Eu-doped bioactive stents can be used for the treatment of bone defects after tumor surgery. The controlled release of Eu may have the potential to prevent the further growth of cancer cells. Europium provides a new idea for the development of new antineoplastic drugs. The combination of Eu with tumor-targeted groups or drugs can reduce the damage to the healthy tissue.

4.6. Biological safety of europium

Good biological safety is a prerequisite for biomedical applications. Europium has better biocompatibility than other low solutions REEs. It has an LD50 of 550 mg/kg, induces relatively few inflammatory factors from macrophages, and possesses good hemocompatibility and biocompatibility [99]. The research done by Jenkins et al. showed that Eu had
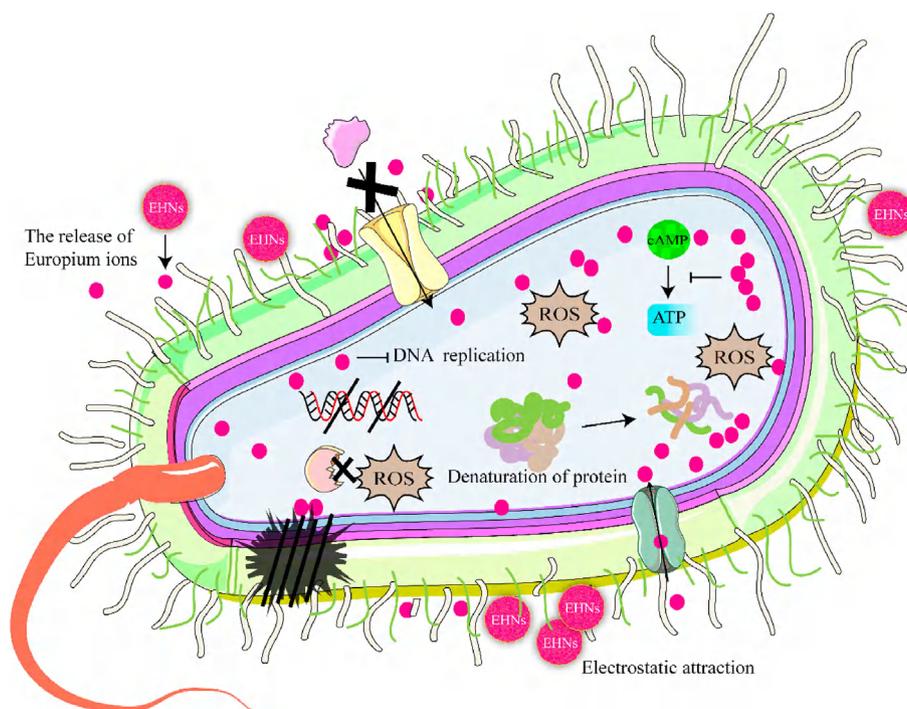

Fig. 4. Mechanism of the antibacterial properties of Eu(OH)$_3$ nanoparticles. EHNs, Eu(OH)$_3$ nanorods; ROS, reactive oxygen species; ATP, adenosine triphosphate; cAMP, cyclic adenosine 3′,5′-monophosphate.

stimulatory effect on human keratinocytes at 1–10 μM and inhibitory effect at 50–100 μM [100]. Luo, Meng et al. have demonstrated that the Eu_2O_3 NRs possess a better anti-inflammatory at 100 μg/mL, but exhibit pro-inflammatory effects at 150 μg/mL by evaluating the TNF-α expression levels of L929 cells [61]. However, there is a paucity of reported research on the biological safety of Eu with long-term exposure, which are important issues with respect to the biomedical applications of Eu.

Europium hydroxide nanorods were mildly toxic in C57BL/6 mice, even at high doses [73]. Other research reported that inflammation or damage to major organs was not obvious after exposure to 2 mg/kg of EHNPs; indexes of liver function and renal function were largely normal [101]. According to other studies on EHNPs, Eu is mainly distributed in the liver, spleen, kidneys, and lungs [34,102]. Nethi et al. reported that the EHNPs were cleared from the body via the kidney and can be excreted from the body [34]. However, acute exposure to europium chloride increased the liver lipid content, and long-term intragastric administration caused structural changes in the gastrointestinal mucosa of rats, thereby reducing their appetite [103]. In summary, the biological safety of Eu appears to be relatively high at low concentrations. The negative effects of Eu increase with dose, administration rate, and time.

4.7. Publication bias

Experiments with positive results are more likely to be published. Studies not including unpublished negative or neutral results may overstate their positive results.

4.8. Limitations of this study

Generally, research on the osteogenic, angiogenic, neuritogenic, antibacterial, and anti-tumor properties of Eu is immature, and unified evaluation criteria and normative models are lacking. Among the studies included in this review, the outcome measures were highly heterogeneous, as were the research methods, animal models, cell types, types and compositions of materials, Eu concentrations, and results. Moreover, in some cases the results were qualitative. Future research should collect quantitative data to allow systematic analysis and evaluation.

5. Conclusion

This systematic review summarizes the relevant literature concerning the osteogenic, angiogenic, neuritogenic, antibacterial, and anti-tumor properties of Eu, to provide a basis for further study of Eu and facilitate its biomedical application. Europium, as a low-toxic REE with good biocompatibility, has great promise in biomedicine. The antibacterial properties of Eu-containing materials can be used in some drugs and implants to prevent infection. They can also promote osteogenesis, angiogenesis, and nerve regeneration, suggesting the potential for tissue engineering and regenerative medicine. However, many challenges remain, although these may be overcome in the near future as biomedicine develops.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

Acknowledgments

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mtbio.2023.100595.

References

[1] D. Natarajan, Z. Ye, L. Wang, L. Ge, J.L. Pathak, Rare earth smart nanomaterials for bone tissue engineering and implantology: advances, challenges, and prospects, Bioeng Transl Med 7 (1) (2022), e10262, https://doi.org/10.1002/btm2.10262.

[2] J. Huang, Z. Lv, Y. Wang, Z. Wang, T. Gao, N. Zhang, M. Guo, H. Zou, P. Zhang, Vivo MRI and X-ray bifunctional imaging of polymeric composite supplemented with GdPO4 ·H2 O nanobundles for tracing bone implant and bone regeneration, Adv Healthc Mater 5 (17) (2016) 2182–2190, https://doi.org/10.1002/adhm.201600249.

[3] U. Pantulap, M. Arango-Ospina, A.R. Boccaccini, Bioactive glasses incorporating less-common ions to improve biological and physical properties, J. Mater. Sci. Mater. Med. 33 (1) (2021) 3, https://doi.org/10.1007/s10856-021-06626-3.

[4] F. Liao, X.Y. Peng, F. Yang, Q.F. Ke, Z.H. Zhu, Y.P. Guo, Gadolinium-doped mesoporous calcium silicate/chitosan scaffolds enhanced bone regeneration ability, Mater Sci Eng C Mater Biol Appl 104 (2019), 109999, https://doi.org/10.1016/j.msec.2019.109999.

[5] F. Kurtuldu, N. Mutlu, A.R. Boccaccini, D. Galusek, Gallium containing bioactive materials: a review of anticancer, antibacterial, and osteogenic properties, Bioact. Mater. 17 (2022) 125–146, https://doi.org/10.1016/j.bioactmat.2021.12.034.

[6] E. Varini, S. Sánchez-Salcedo, G. Malavasi, G. Lusvardi, M. Vallet-Regí, A.J. Salinas, Cerium (III) and (IV) containing mesoporous glasses/alginate beads for bone regeneration: bioactivity, biocompatibility and reactive oxygen species activity, Mater Sci Eng C Mater Biol Appl 105 (2019), https://doi.org/10.1016/j.msec.2019.109971.

[7] S. Ren, Y. Zhou, K. Zheng, X. Xu, J. Yang, X. Wang, L. Miao, H. Wei, Y. Xu, Cerium oxide nanoparticles loaded nanofibrous membranes promote bone regeneration for periodontal tissue engineering, Bioact. Mater. 7 (2022) 242–253, https://doi.org/10.1016/j.bioactmat.2021.05.037.

[8] F. Kurtuldu, N. Mutlu, M. Michálek, K. Zheng, M. Masar, L. Liverani, S. Chen, D. Galusek, A.R. Boccaccini, Cerium and gallium containing mesoporous bioactive glass nanoparticles for bone regeneration: bioactivity, biocompatibility and antibacterial activity, Mater Sci Eng C Mater Biol Appl 124 (2021), 112050, https://doi.org/10.1016/j.msec.2021.112050.

[9] A.M. Deliormanlı, Synthesis and characterization of cerium- and gallium-containing borate bioactive glass scaffolds for bone tissue engineering, J. Mater. Sci. Mater. Med. 26 (2) (2015) 67, https://doi.org/10.1007/s10856-014-5368-0.

[10] Y. Zhang, M. Hu, X. Wang, Z. Zhou, Y. Liu, Design and evaluation of europium containing mesoporous bioactive glass nanospheres: doxorubicin release kinetics and inhibitory effect on osteosarcoma MG 63 cells, Nanomaterials 8 (11) (2018), https://doi.org/10.3390/nano8110961.

[11] Y. Wang, X. Yin, J. Chen, Y. Wang, Z. Chai, S. Wang, Gleaming uranium: an emerging emitter for building X-ray scintillators, Chemistry (Weinheim an der Bergstrasse, Germany) 26 (9) (2020) 1900–1905, https://doi.org/10.1002/chem.201904409.

[12] R. Devi, S. Vaidyanathan, Narrow band red emitting europium complexes and their application in smart white LEDs and vapoluminescent sensors, Dalton transactions (Cambridge, England 49 (19) (2020) 6205–6219, https://doi.org/10.1039/d0dt00519c, 2003.

[13] M. Shi, L. Xia, Z. Chen, F. Lv, H. Zhu, F. Wei, S. Han, J. Chang, Y. Xiao, C. Wu, Europium-doped mesoporous silica nanosphere as an immune-modulating osteogenesis/angiogenesis agent, Biomaterials 144 (2017) 176–187, https://doi.org/10.1016/j.biomaterials.2017.08.027.

[14] F. Chen, P. Huang, Y.J. Zhu, J. Wu, C.L. Zhang, D.X. Cui, The photoluminescence, drug delivery and imaging properties of multifunctional Eu3+/Gd3+ dual-doped hydroxyapatite nanorods, Biomaterials 32 (34) (2011) 9031–9039, https://doi.org/10.1016/j.biomaterials.2011.08.032.

[15] M. Liu, M. Shu, J. Yan, X. Liu, R. Wang, Z. Hou, J. Lin, Luminescent net-like inorganic scaffolds with europium-doped hydroxyapatite for enhanced bone reconstruction, Nanoscale 13 (2) (2021) 1181–1194, https://doi.org/10.1039/d0nr05608a.

[16] H. Zeng, X. Li, F. Xie, L. Teng, H. Chen, Dextran-coated fluorapatite nanorods doped with lanthanides in labelling and directing osteogenic differentiation of bone marrow mesenchymal stem cells, J. Mater. Chem. B 2 (23) (2014) 3609–3617, https://doi.org/10.1039/c4tb00303a.

[17] L. Zhang, L. Tian, Z. Ye, B. Song, J. Yuan, Preparation of visible-light-excited europium biolabels for time-resolved luminescence cell imaging application, Talanta 108 (2013) 143–149, https://doi.org/10.1016/j.talanta.2013.02.065.

[18] H. Li, C. Xie, R. Lan, S. Zha, C.F. Chan, W.Y. Wong, K.L. Ho, B.D. Chan, Y. Luo, J.X. Zhang, G.L. Law, W.C.S. Tai, J.G. Bunzli, K.L. Wong, A smart europium-ruthenium complex as anticancer prodrug: controllable drug release and real-time monitoring under different light excitations, J. Med. Chem. 60 (21) (2017) 8923–8932, https://doi.org/10.1021/acs.jmedchem.7b01162.

[19] B.D. Kevadiya, C. Woldstad, B.M. Ottemann, P. Dash, B.R. Sajja, B. Lamberty, B. Morsey, T. Kocher, R. Dutta, A.N. Bade, Y. Liu, S.E. Callen, H.S. Fox, S.N. Byrareddy, J.M. McMillan, T.K. Bronich, B.J. Edagwa, M.D. Boska, H.E. Gendelman, Multimodal theranostic nanoformulations permit magnetic resonance bioimaging of antiretroviral drug particle tissue-cell biodistribution, Theranostics 8 (1) (2018) 256–276, https://doi.org/10.7150/thno.22764.

[20] B.M. Ottemann, A.J. Helmink, W. Zhang, I. Mukadam, C. Woldstad, J.R. Hilaire, Y. Liu, J.M. McMillan, B.J. Edagwa, R.L. Mosley, J.C. Garrison, B.D. Kevadiya, H.E. Gendelman, Bioimaging predictors of rilpivirine biodistribution and antiretroviral activities, Biomaterials 185 (2018) 174–193, https://doi.org/10.1016/j.biomaterials.2018.09.018.

[21] P. Yang, Z. Quan, C. Li, X. Kang, H. Lian, J. Lin, Bioactive, luminescent and mesoporous europium-doped hydroxyapatite as a drug carrier, Biomaterials 29 (32) (2008) 4341–4347, https://doi.org/10.1016/j.biomaterials.2008.07.042.

[22] X. Yin, B. Chen, M. He, B. Hu, Simultaneous determination of two phosphorylated p53 proteins in SCC-7 cells by an ICP-MS immunoassay using apoferritin-templated europium(III) and lutetium(III) phosphate nanoparticles as labels, Mikrochim. Acta 186 (7) (2019) 424, https://doi.org/10.1007/s00604-019-3540-4.

[23] R.L. Liang, Q.T. Deng, Z.H. Chen, X.P. Xu, J.W. Zhou, J.Y. Liang, Z.N. Dong, T.C. Liu, Y.S. Wu, Europium (III) chelate microparticle-based lateral flow immunoassay strips for rapid and quantitative detection of antibody to hepatitis B core antigen, Sci. Rep. 7 (1) (2017) 14093, https://doi.org/10.1038/s41598-017-14427-4.

[24] X.H. Lai, R.L. Liang, T.C. Liu, Z.N. Dong, Y.S. Wu, L.H. Li, A fluorescence immunochromatographic assay using europium (III) chelate microparticles for rapid, quantitative and sensitive detection of creatine kinase MB, J. Fluoresc. 26 (3) (2016) 987–996, https://doi.org/10.1007/s10895-016-1786-3.

[25] H. Yue, J.Y. Park, Y. Chang, G.H. Lee, Ultrasmall europium, gadolinium, and dysprosium oxide nanoparticles: polyol synthesis, properties, and biomedical imaging applications, Mini Rev. Med. Chem. 20 (17) (2020) 1767–1780, https://doi.org/10.2174/1389557520666200604163452.

[26] C.U. Lenora, F. Carniato, Y. Shen, Z. Latif, E.M. Haacke, P.D. Martin, M. Botta, M.J. Allen, Structural features of europium(II)-Containing cryptates that influence relaxivity, Chemistry 23 (61) (2017) 15404–15414, https://doi.org/10.1002/chem.201702158.

[27] W. Lee, M. Jeon, J. Choi, C. Oh, G. Kim, S. Jung, C. Kim, S.J. Ye, H.J. Im, Europium-diethylenetriaminepentaacetic acid loaded radioluminescence liposome nanoplatform for effective radioisotope-mediated photodynamic therapy, ACS Nano 14 (10) (2020) 13004–13015, https://doi.org/10.1021/acsnano.0c04324.

[28] B. Ghaemi, O. Mashinchian, T. Mousavi, R. Karimi, S. Kharrazi, A. Amani, Harnessing the cancer radiation therapy by lanthanide-doped zinc oxide based theranostic nanoparticles, ACS Appl. Mater. Interfaces 8 (5) (2016) 3123–3134, https://doi.org/10.1021/acsami.5b10056.

[29] W. Zhang, Y.G. Abou El-Reash, L. Ding, Z. Lin, Y. Lian, B. Song, J. Yuan, X.D. Wang, A lysosome-targeting nanosensor for simultaneous fluorometric imaging of intracellular pH values and temperature, Mikrochim. Acta 185 (12) (2018) 533, https://doi.org/10.1007/s00604-018-3040-y.

[30] J.Y.R. Silva, Y.G. Proenza, L.L. da Luz, S.d.S. Araujo, M.A. Gomes Filho, S. Alves Junior, T.A. Soares, R.L. Longo, A thermo-responsive adsorbent-heater-thermometer nanomaterial for controlled drug release: (ZIF-8,EuxTby)@AuNP core-shell, Materials Science & Engineering C-Materials for Biological Applications 102 (2019) 578–588, https://doi.org/10.1016/j.msec.2019.04.078.

[31] W. Yuchong, P. Xu, Y. Xixun, Osteogenesis, angiogenesis and anti-aseptic loosening of europium-doped calcium polyphosphate bone tissue engineering scaffold, Chinese Journal of Tissue Engineering Research 26 (28) (2022) 4458–4465, https://doi.org/10.12307/2022.298.

[32] K. Wu, X. Wu, J. Guo, Y. Jiao, C. Zhou, Facile polyphenol–europium assembly enabled functional poly(l-lactic acid) nanofiber mats with enhanced antioxidation and angiogenesis for accelerated wound healing, Advanced Healthcare Materials 10 (19) (2021), https://doi.org/10.1002/adhm.202100793.

[33] F. Li, M. Wang, G. Pi, B. Lei, Europium doped monodispersed bioactive glass nanoparticles regulate the osteogenic differentiation of human marrow mesenchymal stem cells, J. Biomed. Nanotechnol. 14 (4) (2018) 756–764, https://doi.org/10.1166/jbn.2018.2504.

[34] S.K. Nethi, A.K. Barui, P. Jhelum, P. Basuthakur, V.S. Bollu, B.R. Reddy, S. Chakravarty, C.R. Patra, Europium hydroxide nanorods mitigate hind limb ischemia in wistar rats, Advanced Therapeutics 4 (6) (2021), https://doi.org/10.1002/adtp.202100016.

[35] C. Wu, L. Xia, P. Han, L. Mao, J. Wang, D. Zhai, B. Fang, J. Chang, Y. Xiao, Europium-containing mesoporous bioactive glass scaffolds for stimulating in vitro and in vivo osteogenesis, ACS Appl. Mater. Interfaces 8 (18) (2016) 11342–11354, https://doi.org/10.1021/acsami.6b03100.

[36] J. Machhi, P. Yeapuri, M. Markovic, M. Patel, W. Yan, Y. Lu, J.D. Cohen, M. Hasan, M.M. Abdelmoaty, Y. Zhou, H. Xiong, X. Wang, R.L. Mosley, H.E. Gendelman, B.D. Kevadiya, Europium-doped cerium oxide nanoparticles for microglial amyloid beta clearance and homeostasis, ACS Chem. Neurosci. 13 (8) (2022) 1232–1244, https://doi.org/10.1021/acschemneuro.1c00847.

[37] P.F. Wei, L. Zhang, S.K. Nethi, A.K. Barui, J. Lin, W. Zhou, Y. Shen, N. Man, Y.J. Zhang, J. Xu, C.R. Patra, L.P. Wen, Accelerating the clearance of mutant huntingtin protein aggregates through autophagy induction by europium hydroxide nanorods, Biomaterials 35 (3) (2014) 899–907, https://doi.org/10.1016/j.biomaterials.2013.10.024.

[38] B. Wiatrak, P. Sobierajska, M. Szandruk-Bender, P. Jawien, M. Janeczek, M. Dobrzynski, P. Pistor, A. Szelag, R.J. Wiglusz, Nanohydroxyapatite as a biomaterial for peripheral nerve regeneration after mechanical damage-in vitro study, Int. J. Mol. Sci. 22 (9) (2021), https://doi.org/10.3390/ijms22094454.

[39] S.-L. Iconaru, M. Motelica-Heino, D. Predoi, Study on europium-doped hydroxyapatite nanoparticles by fourier transform infrared spectroscopy and their antimicrobial properties, Journal of Spectroscopy 2013 (2013) 1–10, https://doi.org/10.1155/2013/284285.

[40] J.T.B. Ratnayake, M. Mucalo, G.J. Dias, Substituted hydroxyapatites for bone regeneration: a review of current trends, J. Biomed. Mater. Res. B Appl. Biomater. 105 (5) (2017) 1285–1299, https://doi.org/10.1002/jbm.b.33651.

[41] E. Çinar Avar, K.E. Türkmen, E. Erdal, E. Loğoğlu, H. Katircioğlu, Biological activities and biocompatibility properties of Eu(OH)(3) and Tb(OH)(3) nanorods: evaluation for wound healing applications, Biol. Trace Elem. Res. (2022), https://doi.org/10.1007/s12011-022-03264-w.

[42] K.Y. Shih, S.C. Yu, Microwave-assisted rapid synthesis of Eu(OH)3/RGO nanocomposites and enhancement of their antibacterial activity against Escherichia coli, Materials 15 (1) (2021), https://doi.org/10.3390/ma15010043.

[43] K. Szyszka, J. Rewak-Soroczynska, A. Dorotkiewicz-Jach, K.A. Ledwa, A. Piecuch, M. Giersig, Z. Drulis-Kawa, R.J. Wiglusz, Structural modification of nanohydroxyapatite Ca10(PO4)6(OH)2 related to Eu3+ and Sr2+ ions doping and its spectroscopic and antimicrobial properties, J. Inorg. Biochem. 203 (2020), https://doi.org/10.1016/j.jinorgbio.2019.110884.

[44] R.J. Wiglusz, Z. Drulis-Kawa, R. Pazik, K. Zawisza, A. Dorotkiewicz-Jach, J. Roszkowiak, J.M. Nedelec, Multifunctional lanthanide and silver ion co-doped nano-chlorapatites with combined spectroscopic and antimicrobial properties, Dalton Trans. 44 (15) (2015) 6918–6925, https://doi.org/10.1039/c5dt00046g. Cambridge, England : 2003.

[45] H.A. Azab, B.H.M. Hussein, M.F. El-Azab, M. Gomaa, A.I. El-Falouji, Bis(acridine-9-carboxylate)-nitro-europium(III) dihydrate complex a new apoptotic agent through Flk-1 down regulation, caspase-3 activation and oligonucleosomes DNA fragmentation, Bioorg. Med. Chem. 21 (1) (2013) 223–234, https://doi.org/10.1016/j.bmc.2012.10.020.

[46] A.K. Barui, P. Jhelum, S.K. Nethi, T. Das, D. Bhattacharya, B. Vinothkumar, S. Karri, S. Chakravarty, C.R. Patra, Potential therapeutic application of zinc oxide nanoflowers in the cerebral ischemia rat model through neuritogenic and neuroprotective properties, Bioconjugate Chem. 31 (3) (2020) 895–906, https://doi.org/10.1021/acs.bioconjchem.0c00030.

[47] J.A.D. Batista, L. Oliveira, T.A. Moura, V.C. Dos Anjos, M.J.V. Bell, M.S. Rocha, On the use of Europium (Eu) for designing new metal-based anticancer drugs, Biochem. Biophys. Res. Commun. 531 (3) (2020) 372–376, https://doi.org/10.1016/j.bbrc.2020.07.080.

[48] M. Sikora, K. Marcinkowska, K. Marycz, R.J. Wiglusz, A. Smieszek, The potential selective cytotoxicity of poly (L- lactic acid)-based scaffolds functionalized with nanohydroxyapatite and europium (III) ions toward osteosarcoma cells, Materials 12 (22) (2019), https://doi.org/10.3390/ma12223779.

[49] X. Ma, Y. Liu, X.M. Wu, C. Wang, Q. Li, T. Fu, Synthesis of europium-doped nanohydroxyapatite and its cytocompatibility with endothelial cells in vitro, Mater. Technol. 31 (2016) 23–27, https://doi.org/10.1080/10667857.2016.1232644.

[50] E.B. Kim, J.M. Seo, G.W. Kim, S.Y. Lee, T.J. Park, In vivo synthesis of europium selenide nanoparticles and related cytotoxicity evaluation of human cells, Enzym. Microb. Technol. 95 (2016) 201–208, https://doi.org/10.1016/j.enzmictec.2016.08.012.

[51] B.H.M. Hussein, H.A. Azab, M.F. El-Azab, A.I. El-Falouji, A novel anti-tumor agent, Ln(III) 2-thioacetate benzothiazole induces anti-angiogenic effect and cell death in cancer cell lines, Eur. J. Med. Chem. 51 (2012) 99–109, https://doi.org/10.1016/j.ejmech.2012.02.025.

[52] K. Slim, E. Nini, D. Forestier, F. Kwiatkowski, Y. Panis, J. Chipponi, Methodological index for non-randomized studies (minors): development and validation of a new instrument, ANZ J. Surg. 73 (9) (2003) 712–716, https://doi.org/10.1046/j.1445-2197.2003.02748.x.

[53] R.S. Leão, S.L.D. Moraes, J.M.L. Gomes, C.A.A. Lemos, B. Casado, B. Vasconcelos, E.P. Pellizzer, Influence of addition of zirconia on PMMA: a systematic review, Materials science & engineering. C, Materials for biological applications 106 (2020), 110292, https://doi.org/10.1016/j.msec.2019.110292.

[54] S. Wang, R. Li, D. Xia, X. Zhao, Y. Zhu, R. Gu, J. Yoon, Y. Liu, The impact of Zn-doped synthetic polymer materials on bone regeneration: a systematic review, Stem Cell Res. Ther. 12 (1) (2021) 123, https://doi.org/10.1186/s13287-021-02195-y.

[55] K. Marycz, A. Smieszek, S. Targonska, S.A. Walsh, K. Szustakiewicz, R.J. Wiglusz, Three dimensional (3D) printed polylactic acid with nano-hydroxyapatite doped with europium(III) ions (nHAp/PLLA@Eu3+) composite for osteochondral defect regeneration and theranostics, Materials Science & Engineering C-Materials for Biological Applications 110 (2020), https://doi.org/10.1016/j.msec.2020.110634.

[56] A. Roy, S.K. Nethi, N. Suganya, M. Raval, S. Chatterjee, C.R. Patra, Attenuation of cadmium-induced vascular toxicity by pro-angiogenic nanorods, Materials Science & Engineering C-Materials for Biological Applications 115 (2020), https://doi.org/10.1016/j.msec.2020.111108.

[57] C.R. Patra, R. Bhattacharya, S. Patra, N.E. Vlahakis, A. Gabashvili, Y. Koltypin, A. Gedanken, P. Mukherjee, D. Mukhopadhyay, Pro-angiogenic properties of europium(III) hydroxide nanorods, Adv. Mater. 20 (4) (2008) 753, https://doi.org/10.1002/adma.200701611.

[58] H. Zhao, O.J. Osborne, S. Lin, Z. Ji, R. Damoiseux, Y. Wang, A.E. Nel, S. Lin, Lanthanide hydroxide nanoparticles induce angiogenesis via ROS-sensitive signaling, Small 12 (32) (2016) 4404–4411, https://doi.org/10.1002/smll.201600291.

[59] L. Zhang, W. Hu, Y. Wu, P. Wei, L. Dong, Z. Hao, S. Fan, Y. Song, Y. Lu, C. Liang, L. Wen, Microwave-assisted facile synthesis of Eu(OH)(3) nanoclusters with pro-proliferative activity mediated by miR-199a-3p, ACS Appl. Mater. Interfaces 10 (37) (2018) 31044–31053, https://doi.org/10.1021/acsami.8b10543.

[60] R. Augustine, S.K. Nethi, N. Kalarikkal, S. Thomas, C.R. Patra, Electrospun polycaprolactone (PCL) scaffolds embedded with europium hydroxide nanorods (EHNs) with enhanced vascularization and cell proliferation for tissue engineering applications, J. Mater. Chem. B 5 (24) (2017) 4660–4672, https://doi.org/10.1039/c7tb00518k.

[61] M. Luo, W. Wang, W. Niu, M. Chen, W. Cheng, L. Zhang, C. Xie, Y. Wang, Y. Guo, T. Leng, X. Zhang, C. Lin, B. Lei, Injectable self-healing anti-inflammatory europium oxide-based dressing with high angiogenesis for improving wound healing and skin regeneration, Chem. Eng. J. 412 (2021), https://doi.org/10.1016/j.cej.2021.128471.

[62] S. Chaudhary, P. Sharma, S. Kumar, S.A. Alex, R. Kumar, S.K. Mehta, A. Mukherjee, A. Umar, A comparative multi-assay approach to study the toxicity behaviour of Eu2O3 nanoparticles, J. Mol. Liq. 269 (2018) 783–795, https://doi.org/10.1016/j.molliq.2018.08.082.

[63] R. Raji, S. Elangomannan, R. Subramani, K. Louis, M. Periasamy, G. Dhanaraj, Calotropis gigantea fiber-A biogenic reinforcement material for europium substituted hydroxyapatite/poly(3,4-propylenedioxythiophene) matrix: a novel ternary composite for biomedical applications, ACS Omega 7 (7) (2022) 6024–6034, https://doi.org/10.1021/acsomega.1c06372.

[64] K. Zheng, W. Niu, B. Lei, A.R. Boccaccini, Immunomodulatory bioactive glasses for tissue regeneration, Acta Biomater. 133 (2021) 168–186, https://doi.org/10.1016/j.actbio.2021.08.023.

[65] A.A. El-Rashidy, J.A. Roether, L. Harhaus, U. Kneser, A.R. Boccaccini, Regenerating bone with bioactive glass scaffolds: a review of in vivo studies in bone defect models, Acta Biomater. 62 (2017) 1–28, https://doi.org/10.1016/j.actbio.2017.08.030.

[66] G. Miao, X. Chen, C. Mao, X. Li, Y. Li, C. Lin, Synthesis and characterization of europium-containing luminescent bioactive glasses and evaluation of in vitro bioactivity and cytotoxicity, J. Sol. Gel Sci. Technol. 69 (2) (2014) 250–259, https://doi.org/10.1007/s10971-013-3209-0.

[67] M. Shi, Y. Zhou, J. Shao, Z. Chen, B. Song, J. Chang, C. Wu, Y. Xiao, Stimulation of osteogenesis and angiogenesis of hBMSCs by delivering Si ions and functional drug from mesoporous silica nanospheres, Acta Biomater. 21 (2015) 178–189, https://doi.org/10.1016/j.actbio.2015.04.019.

[68] H. Zhou, J. Lee, Nanoscale hydroxyapatite particles for bone tissue engineering, Acta Biomater. 7 (7) (2011) 2769–2781, https://doi.org/10.1016/j.actbio.2011.03.019.

[69] F. Yu, R. Lian, L. Liu, T. Liu, C. Bi, K. Hong, S. Zhang, J. Ren, H. Wang, N. Ouyang, L.J. Du, Y. Liu, L. Zhou, Y. Liu, B. Fang, Y. Li, S.Z. Duan, L. Xia, Biomimetic hydroxyapatite nanorods promote bone regeneration via accelerating osteogenesis of BMSCs through T cell-derived IL-22, ACS Nano 16 (1) (2022) 755–770, https://doi.org/10.1021/acsnano.1c08281.

[70] X. Song, L. Chang, J. Wang, S. Zhu, L. Wang, K. Feng, Y. Luo, S. Guan, Investigation on the in vitro cytocompatibility of Mg-Zn-Y-Nd-Zr alloys as degradable orthopaedic implant materials, J. Mater. Sci. Mater. Med. 29 (4) (2018) 44, https://doi.org/10.1007/s10856-018-6050-8.

[71] H. Li, P. Wang, G. Lin, J. Huang, The role of rare earth elements in biodegradable metals: a review, Acta Biomater. 129 (2021) 33–42, https://doi.org/10.1016/j.actbio.2021.05.014.

[72] C.R. Patra, J.H. Kim, K. Pramanik, L.V. d'Uscio, S. Patra, K. Pal, R. Ramchandran, M.S. Strano, D. Mukhopadhyay, Reactive oxygen species driven angiogenesis by inorganic nanorods, Nano Lett. 11 (11) (2011) 4932–4938, https://doi.org/10.1021/nl2028766.

[73] V.S. Bollu, S.K. Nethi, R.K. Dasari, S.S. Rao, S. Misra, C.R. Patra, Evaluation of in vivo cytogenetic toxicity of europium hydroxide nanorods (EHNs) in male and female Swiss albino mice, Nanotoxicology 10 (4) (2016) 413–425, https://doi.org/10.3109/17435390.2015.1073398.

[74] J. Kolmas, E. Groszyk, D. Kwiatkowska-Rozycka, Substituted hydroxyapatites with antibacterial properties, BioMed Res. Int. 2014 (2014), 178123, https://doi.org/10.1155/2014/178123.

[75] X.Y. Peng, M. Hu, F. Liao, F. Yang, Q.F. Ke, Y.P. Guo, Z.H. Zhu, La-Doped mesoporous calcium silicate/chitosan scaffolds for bone tissue engineering, Biomater. Sci. 7 (4) (2019) 1565–1573, https://doi.org/10.1039/c8bm01498a.

[76] D.D. Liu, J.C. Zhang, Q. Zhang, S.X. Wang, M.S. Yang, TGF-β/BMP signaling pathway is involved in cerium-promoted osteogenic differentiation of mesenchymal stem cells, J. Cell. Biochem. 114 (5) (2013) 1105–1114, https://doi.org/10.1002/jcb.24451.

[77] L. Zheng, Z. Zhuang, Y. Li, T. Shi, K. Fu, W. Yan, L. Zhang, P. Wang, L. Li, Q. Jiang, Bone targeting antioxidative nano-iron oxide for treating postmenopausal osteoporosis, Bioact. Mater. 14 (2022) 250–261, https://doi.org/10.1016/j.bioactmat.2021.11.012.

[78] C.R. Patra, S.S.A. Moneim, E. Wang, S. Dutta, S. Patra, M. Eshed, P. Mukherjee, A. Gedanken, V.H. Shah, D. Mukhopadhyay, Vivo toxicity studies of europium hydroxide nanorods in mice, Toxicol. Appl. Pharmacol. 240 (1) (2009) 88–98, https://doi.org/10.1016/j.taap.2009.07.009.

[79] J. Liu, D. Bian, Y. Zheng, X. Chu, Y. Lin, M. Wang, Z. Lin, M. Li, Y. Zhang, S. Guan, Comparative in vitro study on binary Mg-RE (Sc, Y, La, Ce, Pr, Nd, Sm, Eu, Gd, Tb, Dy, Ho, Er, Tm, Yb and Lu) alloy systems, Acta Biomater. 102 (2020) 508–528, https://doi.org/10.1016/j.actbio.2019.11.013.

[80] M. Zhang, A.C. Brewer, K. Schroder, C.X. Santos, D.J. Grieve, M. Wang, N. Anilkumar, B. Yu, X. Dong, S.J. Walker, R.P. Brandes, A.M. Shah, NADPH oxidase-4 mediates protection against chronic load-induced stress in mouse hearts by enhancing angiogenesis, Proc. Natl. Acad. Sci. U. S. A. 107 (42) (2010) 18121–18126, https://doi.org/10.1073/pnas.1009700107.

[81] E.L. Page, D.A. Chan, A.J. Giaccia, M. Levine, D.E. Richard, Hypoxia-inducible factor-1alpha stabilization in nonhypoxic conditions: role of oxidation and intracellular ascorbate depletion, Mol. Biol. Cell 19 (1) (2008) 86–94, https://doi.org/10.1091/mbc.e07-06-0612.

[82] C. Xia, Q. Meng, L.Z. Liu, Y. Rojanasakul, X.R. Wang, B.H. Jiang, Reactive oxygen species regulate angiogenesis and tumor growth through vascular endothelial growth factor, Cancer Res. 67 (22) (2007) 10823–10830, https://doi.org/10.1158/0008-5472.CAN-07-0783.

[83] A. Ostman, J. Frijhoff, A. Sandin, F.D. Bohmer, Regulation of protein tyrosine phosphatases by reversible oxidation, J. Biochem. 150 (4) (2011) 345–356, https://doi.org/10.1093/jb/mvr104.

[84] S.K. Nethi, V. Veeriah, A.K. Barui, S. Rajendran, S. Mattapally, S. Misra, S. Chatterjee, C.R. Patra, Investigation of molecular mechanisms and regulatory pathways of pro-angiogenic nanorods, Nanoscale 7 (21) (2015) 9760–9770, https://doi.org/10.1039/c5nr01327e.

[85] X. Ma, M. Huang, Z. Wang, B. Liu, Z. Zhu, C. Li, ZHX1 inhibits gastric cancer cell growth through inducing cell-cycle arrest and apoptosis, J. Cancer 7 (1) (2016) 60–68, https://doi.org/10.7150/jca.12973.

[86] Z. Wang, X. Ma, Q. Cai, X. Wang, B. Yu, Q. Cai, B. liu, Z. Zhu, C. Li, MiR-199a-3p promotes gastric cancer progression by targeting ZHX1, FEBS Lett. 588 (23) (2014) 4504–4512, https://doi.org/10.1016/j.febslet.2014.09.047.

[87] P. McKavanagh, B. Yanagawa, G. Zawadowski, A. Cheema, Management and prevention of saphenous vein graft failure: a review, Cardiology and therapy 6 (2) (2017) 203–223, https://doi.org/10.1007/s40119-017-0094-6.

[88] J. Withrow, C. Murphy, Y. Liu, M. Hunter, S. Fulzele, M.W. Hamrick, Extracellular vesicles in the pathogenesis of rheumatoid arthritis and osteoarthritis, Arthritis Res. Ther. 18 (1) (2016) 286, https://doi.org/10.1186/s13075-016-1178-8.

[89] T. Johnson, L. Zhao, G. Manuel, H. Taylor, D. Liu, Approaches to therapeutic angiogenesis for ischemic heart disease, Journal of molecular medicine (Berlin, Germany) 97 (2) (2019) 141–151, https://doi.org/10.1007/s00109-018-1729-3.

[90] P.F. Wei, P.P. Jin, A.K. Barui, Y. Hu, L. Zhang, J.Q. Zhang, S.S. Shi, H.R. Zhang, J. Lin, W. Zhou, Y.J. Zhang, R.Q. Ruan, C.R. Patra, L.P. Wen, Differential ERK activation during autophagy induced by europium hydroxide nanorods and trehalose: maximum clearance of huntingtin aggregates through combined treatment, Biomaterials 73 (2015) 160–174, https://doi.org/10.1016/j.biomaterials.2015.09.006.

[91] E. Hoseinizadeh, P. Makhdoumi, P. Taha, H. Hossini, J. Stelling, M.A. Kamal, G.M. Ashraf, A review on nano-antimicrobials: metal nanoparticles, methods and mechanisms, Curr. Drug Metabol. 18 (2) (2017) 120–128, https://doi.org/10.2174/1389200217666161201111146.

[92] X. Peng, L. Zhu, Z. Wang, X. Zhan, Enhanced stability of the bactericidal activity of nisin through conjugation with gellan gum, Int. J. Biol. Macromol. 148 (2020) 525–532, https://doi.org/10.1016/j.ijbiomac.2020.01.164.

[93] Y. Gao, J. Wang, D. Hu, Y. Deng, T. Chen, Q. Jin, J. Ji, Bacteria-targeted supramolecular photosensitizer delivery vehicles for photodynamic ablation against biofilms, Macromol. Rapid Commun. 40 (4) (2019), e1800763, https://doi.org/10.1002/marc.201800763.

[94] L. Li, P. Gu, M. Hao, X. Xiang, Y. Feng, X. Zhu, Y. Song, E. Song, Bacteria-targeted MRI probe-based imaging bacterial infection and monitoring antimicrobial therapy in vivo, Small 17 (44) (2021), e2103627, https://doi.org/10.1002/smll.202103627.

[95] Z. Wang, F.J. Xu, B. Yu, Smart polymeric delivery system for antitumor and antimicrobial photodynamic therapy, Front. Bioeng. Biotechnol. 9 (2021), 783354, https://doi.org/10.3389/fbioe.2021.783354.

[96] P. Krishnamoorthy, P. Sathyadevi, A.H. Cowley, R.R. Butorac, N. Dharmaraj, Evaluation of DNA binding, DNA cleavage, protein binding and in vitro cytotoxic activities of bivalent transition metal hydrazone complexes, Eur. J. Med. Chem. 46 (8) (2011) 3376–3387, https://doi.org/10.1016/j.ejmech.2011.05.001.

[97] Z. Chen, R. Cao, B. Shi, L. Guo, J. Sun, Q. Ma, W. Fan, H. Song, Synthesis and biological evaluation of 1,9-disubstituted β-carbolines as potent DNA intercalating and cytotoxic agents, Eur. J. Med. Chem. 46 (10) (2011) 5127–5137, https://doi.org/10.1016/j.ejmech.2011.08.027.

[98] S.F. Xue, X.Y. Han, Z.H. Chen, Q. Yan, Z.Y. Lin, M. Zhang, G. Shi, The chemistry of europium(III) encountering DNA: sprouting unique sequence-dependent performances for multifunctional time-resolved luminescent assays, Anal. Chem. 90 (17) (2018) 10614–10620, https://doi.org/10.1021/acs.analchem.8b03010.

[99] F. Feyerabend, J. Fischer, J. Holtz, F. Witte, R. Willumeit, H. Drucker, C. Vogt, N. Hort, Evaluation of short-term effects of rare earth and other elements used in magnesium alloys on primary cells and cell lines, Acta Biomater. 6 (5) (2010) 1834–1842, https://doi.org/10.1016/j.actbio.2009.09.024.

[100] G. Pagano, M. Guida, F. Tommasi, R. Oral, Health effects and toxicity mechanisms of rare earth elements-Knowledge gaps and research prospects, Ecotoxicol. Environ. Saf. 115 (2015) 40–48, https://doi.org/10.1016/j.ecoenv.2015.01.030.

[101] L. Zhang, W. Hu, Y. Wu, P. Wei, L. Dong, Z. Hao, S. Fan, Y. Song, Y. Lu, C. Liang, L. Wen, Microwave-assisted facile synthesis of Eu(OH)(3) nanoclusters with pro-proliferative activity mediated by miR-199a-3p, ACS Appl. Mater. Interfaces 10 (37) (2018) 31044–31053, https://doi.org/10.1021/acsami.8b10543.

[102] H. Liu, Y. Jin, K. Ge, G. Jia, Z. Li, X. Yang, S. Chen, M. Ge, W. Sun, D. Liu, J. Zhang, Europium-doped Gd2O3 nanotubes increase bone mineral density in vivo and promote mineralization in vitro, ACS Appl. Mater. Interfaces 9 (7) (2017) 5784–5792, https://doi.org/10.1021/acsami.6b14682.

[103] W. Weng, A. Biesiekierski, Y. Li, M. Dargusch, C. Wen, A review of the physiological impact of rare earth elements and their uses in biomedical Mg alloys, Acta Biomater. 130 (2021) 80–97, https://doi.org/10.1016/j.actbio.2021.06.004.