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Osteogenic and Biomedical Prospects of Hafnium and Its Compounds: A Scoping Review

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Abstract

The direct engagement of hafnium (Hf) in biological processes or its critical function in living things is not well understood as of now. Unlike key elements like oxygen, carbon, hydrogen, and nitrogen, which are necessary for life, Hf is not known to have any biological activities or functions. It is essential to acknowledge that scientific research is ongoing and that new findings may have been made. This systematic review aimed to aggregate and analyze the studies that discuss biomedical applications of Hf metal. This systematic review was conducted following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement. The following search strategy was used: two independent researchers conducted electronic searches in databases including PubMed, Embase, Cochrane Database of Systematic Reviews, and Google Scholar. The search was conducted up to August 2023 using the Medical Subject Headings (MeSH) terms “transition elements,” “hafnium,” and “biomedical research.” Boolean operators “AND” and “OR” were used to refine the search. Electronic databases, along with hand searches, identified a total of 38 studies. The various database searches resulted in a total of 38 studies, of which 12 were excluded as duplicates, and five were unavailable for full-text data. The remaining 21 full-text articles were then assessed for their eligibility based on the inclusion and exclusion criteria, and finally, a total of 12 studies were included in the present systematic review. Among the 12 chosen studies, six were on cancer-related targeted radiotherapy or chemoradiotherapy, five were on bone or apatite-forming capabilities, and one was on the treatment of inflammatory bowel disease. The common outcome measures included cell proliferation, osteoblast formation, radiotherapy intensification, and immunotherapy. This review outlines an overall picture of the biomedical uses of Hf metal, a transition element, as a potent biomaterial. In conclusion, this transition element, Hf, has some promising scope in the fields of biomedicine, with a special focus in terms of cancer radiotherapy and osteogenic capabilities.

Categories: Dentistry, Radiology, Therapeutics
Keywords: transition metals, radiotherapy (rt), implant osseointegration, hafnium compounds, hafnium, biomedical

Introduction And Background

Transition elements are important facets of dentistry. These classes of metals are valuable in dental products and procedures due to their distinctive features [1,2]. A few metals of this group are titanium, zirconium, cobalt-chromium, nickel-titanium, gold, copper, and silver. These transition elements offer a range of properties that cater to specific dental applications such as restorations, orthodontics, and implants [3,4]. The selection of a particular material depends on factors like the patient's needs, aesthetic preferences, and the functional requirements of the dental restoration or treatment. As dental materials and technology continue to advance, new applications of transition elements may emerge in dentistry.

The transition metal hafnium is renowned for its resistance to corrosion and high melting point. It is employed in nuclear reactors, aerospace alloys, and electronic applications because of its resistance to extreme temperatures and ability to maintain stability in a variety of settings. It is frequently found in zirconium minerals. As noted in the previous literature, lanthanide-series compounds incorporating hafnium have been investigated for potential biomedical applications [5-7]. Typically, the focus of these investigations is on the biocompatibility and security of materials containing hafnium for use in implants, medical devices, and other healthcare applications [8]. As a potential component to improve osseointegration in dental implantology, hafnium shows huge promise [9-11]. It is a desirable choice for covering dental implants because of its special qualities, which include biocompatibility, resistance to corrosion, and the capacity to produce bioactive oxide layers [12].

Even though research is still in progress, hafnium's contribution to osseointegration may have a major positive impact on the efficacy and durability of dental implant procedures. To further investigate the possible uses of hafnium in dentistry and convert research findings into clinical practice, it is essential that material scientists, dental practitioners, and researchers work together. In this context, hafnium has been used in various studies before to check its osseointegration potential and tissue compatibility with other lanthanide metals and showed promising results. This review aims to scrutinize the studies that evaluated

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biomedical applications of hafnium metal.

Review

Material and methodology

This review was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement guidelines [13]. The primary objective of this review was to evaluate the biomedical applications of hafnium. The period of the included studies was extended. An electronic database search identified a total of 38 studies. A strategy was planned for this scoping review, and the research question was formulated (Table *1*).

	Search strategy
Domain	Description
Population	Transition metals
Intervention	Hafnium
Outcome	Biomedical applications

TABLE 1: Search strategy for the research question in this scoping review

Search Strategy

Two researchers independently conducted electronic searches in databases including Embase, Cochrane Database of Systematic Reviews, PubMed, Scopus, Web of Science, and Google Scholar. The search was conducted up to August 2023 with the terms “transition elements,” “hafnium,” and “biomedical research.” “AND” and “OR” Boolean operators were used to refine the search. The search strategy in PubMed yielded 19 articles.

An advanced search of the Cochrane search engine was done, and the search yielded two clinical trials. Three articles were retrieved from the Google Scholar engine, and a hand search yielded 14 results. An initial search was performed with the abovementioned keywords and databases. Duplicates were excluded, and studies were screened further. Titles and abstracts of the non-duplicate citations were independently screened in a standardized manner by two calibrated reviewers (VR and PA) for potential inclusion in this review. The remaining included articles were then obtained in full text and then screened, excluding studies as per the inclusion and exclusion criteria, independently by both reviewers. Cohen’s kappa statistic was used to evaluate the agreement between the two reviewers. Any disagreement between the two reviewers was resolved by discussion. Finally, 12 articles were included for data extraction (Figure *1*).

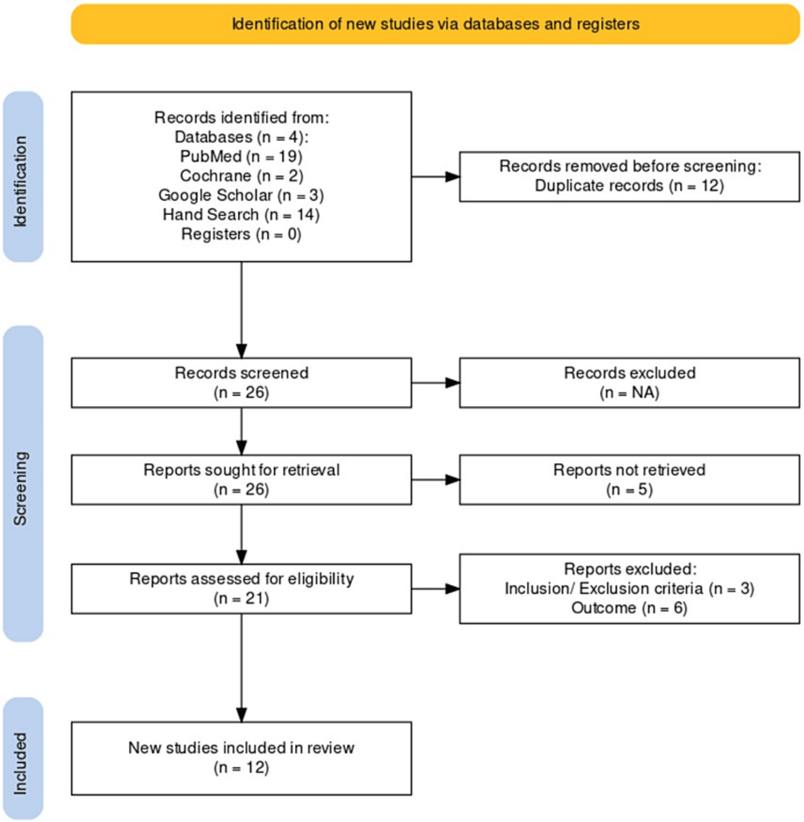


FIGURE 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart describing the inclusion of studies for this systematic review

Inclusion Criteria

This review included studies meeting specific criteria: those that provided results in terms of biomedical applications or biomedical research, published in English, focused on animal studies, and relevant to hafnium and related compounds.

Exclusion Criteria

Excluded were case reports, case series, and reviews or literature articles, studies that do not report biomedical applications, are irrelevant to hafnium, or do not have full text available.

Focused Question

The focused question was, “Does hafnium have biomedical applications or not?”

Statistical Analysis

A meta-analysis could not be performed for this review as the study results were heterogeneous and non-parametric.

Results

The searches in various databases resulted in 38 studies in total, of which 12 were excluded as duplicates, and five were unavailable for full-text data. The remaining 21 articles were then assessed based on exclusion and inclusion criteria for their eligibility (Table *2*), and 12 studies were included in the present review [14-22].

Author, year	Reason for exclusion
Il Song Y et al., 2011 [14]	Outcome: Water and ion penetration in flexible bioelectronic systems
Villa I et al., 2018 [15]	Outcome: Cellular imaging
Reszka P et al., 2019 [16]	Outcome: The materials were assessed for surface morphology.
Verry C et al., 2019 [17]	Review article
Khalladi N et al., 2019 [18]	Exclusion criteria: French article
McGinnity et al., 2021 [19]	Outcome: Synthesis of intervention, not applications
Sebti et al., 2022 [20]	Outcome: Morphological, optical, and photoluminescence properties
Ren HM et al., 2022 [21]	Outcome: Mechanical properties measured
Liu N et al., 2023 [22]	Inclusion criteria: Intervention modified

TABLE 2: Studies excluded in this review and the reason for their exclusion

Among the 12 chosen studies, six were on cancer-related targeted radiotherapy (RT) or chemoradiotherapy, five were on the bone or apatite forming capabilities, and one was on the treatment of inflammatory bowel disease. Most of the studies were based in China; one was a multicenter study, and the other studies were from Japan, Poland, Russia, and India. The common outcome measures included cell proliferation, osteoblast formation, RT intensification, and immunotherapy.

Geographic Distribution

In the current research, the geographic distribution of the study centers is widespread. Of the included studies, five are from China, two studies from Russia and India each, one study from Japan and Poland each, and one from a multicenter study [23,24]. Due to the distribution of studies in a wide geographic range, the results can be extrapolated with minimal risk of bias.

Characterization of Intervention

The articles included in the research studied various forms of hafnium and its compounds. Of these, five studies had hafnium oxide as its intervention, one had hafnium and its alloyed form, one had a coating of hafnium, and the rest had multiple alloyed or compounded forms [15,25]. As this research included all forms of hafnium and its compounds in its intervention, there is no bias regarding the same. Previous studies have had a similar compilation of hafnium and related compounds [26,27].

Outcomes Measured

Among the 12 studies included, six were on targeted RT [28-33] or chemoradiotherapy for cancer, five on the apatite forming abilities, and one on efficacy in the treatment of inflammatory bowel disease. The current research aims to find all the biomedical applications of hafnium and its compounds. Hence, it is justified to have a heterogeneous collection of outcome measures in the included studies. The extracted data characteristics from the included studies were tabulated (Table *3*).

Author, year	Country of study	Intervention	Outcomes	Methods of analysis	Relevant findings
Chao Y et al., 2018 [7]	China	Polyethylene glycol (PEG)-modified nanoscale coordination polymers (NCPs) composed of hafnium (Hf4+) and tetrakis(4-carboxyphenyl) porphyrin (TCPP)	Killing cancer cells, likely owing to the interaction of Hf with γ rays emitted from 99mTc to produce charged particles for radiosensitization	Single-photon emission computed tomography (SPECT) imaging	TCPP-PEG NCPs offer exceptional therapeutic results in eliminating tumors with moderate doses of 99mTc after either local or systemic administration. Importantly, those biodegradable NCPs could be rapidly excreted without much long-term body retention.
Kuang Y et		Cisplatin-loaded Gd2Hf2O7	1) Combined chemo/ photothermal therapy (PTT)/radiotherapy		The less release of Gd showed excellent cytocompatibility, high relaxivity, pH, and dual-sensitive release of loaded cisplatin. The

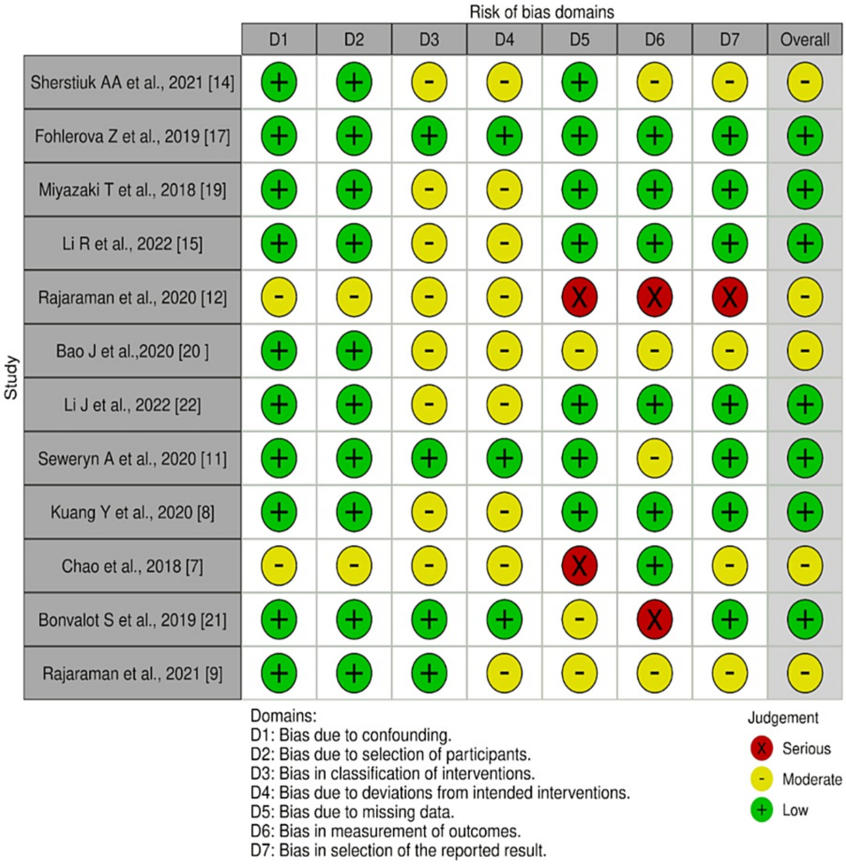
al., 2020 [8]	China	nanoparticles (NPs)	(RT) in vivo; 2) long-term biodistribution; 3) histology analysis in vivo	Intravenous injection into mice	effective PTT/RT ability showed the potential of Gd2Hf2O7@PDA@PEG-Pt-RGD NPs as multimodal theranostic nanoplatform for MRI-guided combined chemo/PTT/RT.
Rajaraman V et al., 2021 [9]	India	Hafnium (Hf)-coated titanium (Ti) and uncoated Ti	Implant stability histologic evaluation of bone formation toxicology	Hematoxylin and eosin (H&E) stain, Masson trichome stain, aspartate aminotransferase (AST), alanine transaminase (ALT), creatinine kinase (CK) assay using enzyme-linked immunosorbent assay (ELISA) kit	Hf coating in the rat mandible showed promising osseointegration with good tissue biocompatibility.
Seweryn A et al., 2020 [11]	Poland	Homogeneous, amorphous layer of Hf(IV) oxide (HfO_2) using atomic layer deposition (ALD) technology	Pre-osteoblast (MC3T3), pre-osteoclasts (4B12), and macrophages cell lines	Immunofluorescence and reverse transcription-quantitative real-time polymerase chain reaction (RT-qPCR)	HfO_2 1) enhanced osteogenesis, 2) reduced osteoclastogenesis, 3) did not elicit an immune response, and 4) exerted anti-inflammatory effects. HfO_2 layer can be applied to cover the surface of metallic biomaterials in order to enhance the healing process of osteoporotic bone fracture.
Rajaraman V et al., 2020 [12]	India	Chitosan NP and Hf metal-based composite	Cytotoxic effect and antimicrobial activity	Brine shrimp lethality assay and the disc diffusion method	This study substantiates the antimicrobial activity and highlights the possible cytotoxicity of the chitosan and Hf composite.
Sherstiuk AA et al., 2021 [23]	Russia	HfO_2 NPs coated with oleic acid and a monomethoxypoly(ethylene gglycol)-poly(-caprolactonelycol)-poly(ε-caprolactone) copolymer shell (nanoplatform)	Targeted delivery of chemotherapeutic compounds, imaging, and an enhanced radiotherapy	Cytotoxicity IC_{50} value	X-ray irradiation of cancer cells loaded with a nanoplatform shows a higher death rate than that for cells without NPs.
Li R et al., 2022 [24]	China	Tannic acid (TA) capped Hf disulfide (HfS_2@TA) nanosheets	Prophylactic and therapeutic effect and potential of oral administration of HfS_2@TA on dextran sulfate sodium (DSS)-induced acute colitis	NCM460 cells Balb/c mice intravenous/oral administration followed by H&E stain and blood work up	HfS_2@TA had excellent therapeutic effects, like repair of the intestinal mucosal barrier, restoration of colonic length, and reduction of proinflammatory factor levels.
Fohlerova Z et al., 2019 [25]	Czech Republic	Flat film and nanostructured anodic Hf-oxide films	Cell culture and cell proliferation	Human osteoblast-like MG-63 cells (European Collection Of Authenticated Cell Cultures (ECACC), Salisbury, UK) were used for in vitro characterization of hafnium oxide (HO) films	Nanostructured Hf film absorbed nine times larger amounts of fibronectin and albumin, relatively better initial attachment and significantly promotes the viability of the cells.
Miyazaki T et al., 2018 [27]	Japan	Pure Hf and Ti-xHf alloy x = 20,40,60,80	Zeta potential indicating negative charge on surface, which indicated apatite-forming abilities in simulated body fluid (SBF)	Electrophoretic light scattering zeta potential analyzer (ELSZ, Otsuka Electronics Co., Osaka, Japan) in a connected box-like quartz cell	1) Pure Hf metal enabled formation of apatite on its surfaces and exhibits bone-bonding potential. 2) The apatite-forming ability of Ti-Hf alloys was low at Ti-60Hf.
Bao J et al., 2020 [28]	China	Folic acid (FA) modified nanoscale metal-organic framework (NMOF) of Hf cluster and Mn(III)-porphyrin	In vivo PTT/RT efficiency	H&E staining was performed on the heart, liver, spleen, lung, kidney, and tumor from one mouse in each group	fHMNM held great clinical application potential for targeting the enhancement of MRI/CT/photoacoustic tomography (PAT) imaging modalities and PTT/RT synergistic treatments of cancer.
Bonvalot S et al., 2019 [29]	Multicenter study	HfO_2 functionalized NP NBTXR3	Proportion of patients with a pathological	Assessed by a central pathology review board following European Organisation for Research and Treatment of Cancer guidelines	NBTXR3 activated by radiotherapy could represent a new treatment option in patients with locally advanced soft-tissue sarcoma of the

			complete response	in the intention-to-treat population full analysis set	extremities or trunk wall
Li J et al., 2022 [33]	China	Metal-phenolic nanosensitizer (Hf-PSP-DTC@PLX) integrated via an acid-sensitive hydrogen sulfide (H_2S) donor (polyethylene glycol-co-polydithiocarbamates, PEG-DTC)	Radiotherapy intensification and immunogenicity	H_2S-reprogrammed oxygen metabolism	Hf-sensitization could fully utilize the well-preserved oxygen to intensify RT efficacy and activate immunogenicity. Such a synergistic strategy for improvement of oxygenation and oxygen utilization would have great potential in optimizing oxygen-dependent therapeutics.

TABLE 3: Characteristics and data of the included studies of this review

Risk of Bias

The risk of bias was assessed using the Risk Of Bias for Non-Randomized Studies: Intervention (ROBINS-I tool) provided in the Cochrane Database of Systematic Reviews (Figure 2).



Risk of bias domains

Study	D1	D2	D3	D4	D5	D6	D7	Overall
Sherstiuk AA et al., 2021 [14]	+	+	-	-	+	-	-	-
Fohlerova Z et al., 2019 [17]	+	+	+	+	+	+	+	+
Miyazaki T et al., 2018 [19]	+	+	-	-	+	+	+	+
Li R et al., 2022 [15]	+	+	-	-	+	+	+	+
Rajaraman et al., 2020 [12]	-	-	-	-	X	X	X	-
Bao J et al.,2020 [20]	+	+	-	-	-	-	-	-
Li J et al., 2022 [22]	+	+	-	-	+	+	+	+
Seweryn A et al., 2020 [11]	+	+	+	+	+	-	+	+
Kuang Y et al., 2020 [8]	+	+	-	-	+	+	+	+
Chao et al., 2018 [7]	-	-	-	-	X	+	-	-
Bonvalot S et al., 2019 [21]	+	+	+	+	-	X	+	+
Rajaraman et al., 2021 [9]	+	+	+	-	-	-	-	-

Domains:
D1: Bias due to confounding.
D2: Bias due to selection of participants.
D3: Bias in classification of interventions.
D4: Bias due to deviations from intended interventions.
D5: Bias due to missing data.
D6: Bias in measurement of outcomes.
D7: Bias in selection of the reported result.

Judgement
X Serious
- Moderate
\+ Low

FIGURE 2: Risk of bias table for the included studies in the systematic review using the ROBINS-I tool by Cochrane Database of Systematic Reviews

Red (X) = serious risk of bias. Yellow (-) = moderate risk of bias. Green (+) = low risk of bias.

Discussion

Titanium is used worldwide as a medical biomaterial in prosthetics. Titanium in dentistry is well-established and used in prosthodontics. From metal frameworks to dental implants, titanium plays a vital role in prosthodontics. Finding alternative biomaterials comparable to this metal would be a challenging task. This said, very few scientists have explored different elements in the periodic table to replace this metal [10]. Hafnium is a promising element as it belongs to the same group in the periodic table as that of gold standard titanium [31]. Since the properties of the same group elements are comparable, newer elements as an alternative to titanium could be explored [31-33].

The current study aims to aggregate and critically analyze the studies that discuss biomedical applications of hafnium metal. Our study has collected scientific evidence from articles that highlight the uses of hafnium in various medical disciplines. The widespread use of this transition metal is researched in targeted RT, chemoradiotherapy, inflammatory bowel disease treatment, and bone tissue regeneration [34,35]. In previous studies on RT, hafnium has proven as a potential biomaterial [23,26, 36].

Functionalized hafnium oxide nanoparticles (NBTXR3) have been synthesized to increase the effects of RT [35]. Hafnium-based nanoparticles are potent contrast enhancement agents for imaging in cancer. They are also used for liquid biopsy in diagnosing cancer [36]. In the past two decades, these nanomaterials have grown to be potential biomaterials for two main fields. One is the CT-guided bioimaging and RT-associated cancer treatment due to their excellent electronic structures and intrinsic physiochemical properties [37].

Hafnium has shown promising tissue response and hence cemented its biocompatibility in the research arena [38-40]. Studies also show osseointegration properties exhibited by hafnium coatings over titanium surfaces [10,27]. Research has been done on chemoradiotherapy and the immune therapeutic properties of hafnium. Our previous research on the lines of bone tissue adhesion over hafnium metal or coated hafnium surfaces also showed moderate success [5,9]. This study adds to the existing evidence and analyzes the overall biomedical applications.

On the whole, the biomedical application of the metal hafnium has been often explored in the past decade. The applications are majorly limited to the therapeutic section, especially on cancer. Minor exploration in the field of dentistry suggested that hafnium is biocompatible with positive results in bone tissue integration to dental implants. This review thus provides an overview of the avenues in which the metal hafnium can be explored and experimented with.

Conclusions

This review outlines an overall bigger picture of the biomedical uses of hafnium metal, a transition element as a potent biomaterial. Various studies conducted in this regard are either primitive or include wider dimensions. Specific research on this metal or its potential applications is in the groundwork. In conclusion, this transition element, hafnium, has some promising scope in the fields of biomedicine with special focus in terms of cancer RT, chemotherapy, and osteogenesis.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Vaishnavi Rajaraman, Padma Ariga, Deepak Pandiar, Karthikeyan Ramalingam

Acquisition, analysis, or interpretation of data: Vaishnavi Rajaraman, Saravanan Sekaran

Drafting of the manuscript: Vaishnavi Rajaraman, Karthikeyan Ramalingam

Critical review of the manuscript for important intellectual content: Vaishnavi Rajaraman, Padma Ariga, Deepak Pandiar, Saravanan Sekaran, Karthikeyan Ramalingam

Supervision: Vaishnavi Rajaraman

Disclosures

Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

References

1. Lautenschlager EP, Monaghan P: Titanium and titanium alloys as dental materials . Int Dent J. 1993, 43:245-

53.
2. Ireland AJ, Sherriff M: Transition metal salt solutions and anaerobic adhesives in dental bonding . Dent Mater. 1999, 15:243-9. 10.1016/s0109-5641(99)00041-x
3. Tanweer T, Rana NF, Khan MJ, et al.: Transition metal doped zinc oxide nanoparticles ameliorates antibacterial potential of dental resin composite in a closed system in-vitro biofilm model. 2022 E-Health and Bioengineering Conference. 2022, 01-04. 10.1109/EHB55594.2022.9991374
4. Su Y, Fu J, Zhou J, et al.: Blending with transition metals improves bioresorbable zinc as better medical implants. Bioact Mater. 2023, 20:243-58. 10.1016/j.bioactmat.2022.05.033
5. Rajaraman V, Nallaswamy D, Ganapathy DM, Kachhara S: Osseointegration of hafnium when compared to titanium-a structured review. Open Dent J. 2011, 15:137. 10.2174/1874210602115010137
6. Jayaraman V, Bhavesh G, Chinnathambi S, et al.: Synthesis and characterization of hafnium oxide nanoparticles for bio-safety. Mater Express. 2014, 4:375-83. 10.1166/mex.2014.1190
7. Chao Y, Liang C, Yang Y, et al.: Highly effective radioisotope cancer therapy with a non-therapeutic isotope delivered and sensitized by nanoscale coordination polymers. ACS Nano. 2018, 12:7519-28. 10.1021/acsnano.8b02400
8. Kuang Y, Zhang Y, Zhao Y, Cao Y, Zhang Y, Chong Y, Pei R: Dual-stimuli-responsive multifunctional Gd(2)Hf(2)O(7) nanoparticles for MRI-guided combined chemo-/photothermal-/radiotherapy of resistant tumors. ACS Appl Mater Interfaces. 2020, 12:35928-39. 10.1021/acsami.0c09422
9. Rajaraman V, Nallaswamy D, Ganapathy D, Rajeshkumar S, Ariga P, Ganesh K: Effect of hafnium coating on osseointegration of titanium implants: a split mouth animal study. J Nanomater. 2021, 1:9. 10.1155/2021/7512957
10. Matsuno H, Yokoyama A, Watari F, Uo M, Kawasaki T: Biocompatibility and osteogenesis of refractory metal implants, titanium, hafnium, niobium, tantalum and rhenium. Biomaterials. 2001, 22:1253-62. 10.1016/s0142-9612(00)00275-1
11. Seweryn A, Alicka M, Fal A, et al.: Hafnium (IV) oxide obtained by atomic layer deposition (ALD) technology promotes early osteogenesis via activation of Runx2-OPN-mir21A axis while inhibits osteoclasts activity. J Nanobiotechnol. 2020, 18:132. 10.1186/s12951-020-00692-5
12. Rajaraman V, Rajeshkumar S, Nallaswamy D, et al.: Cytotoxic effect and antimicrobial activity of chitosan nanoparticles and hafnium metal based composite: two sides of the same coin-an in vitro study. J Pharm Res Int. 2020, 32:122-31. 10.9734/jpri/2020/v32i1930718
13. Moher D, Liberati A, Tetzlaff J, Altman DG: Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J Surg. 2010, 8:336-41. 10.1016/j.ijsu.2010.02.007
14. Il Song Y, Yang CM, Ku Kwac L, Gun Kim H, Ahm Kim Y: Atomic layer coating of hafnium oxide on carbon nanotubes for high-performance field emitters. Appl Phys Lett. 2011, 10:99. 10.1063/1.3650471
15. Villa I, Villa C, Monguzzi A, et al.: Demonstration of cellular imaging by using luminescent and anti-cytotoxic europium-doped hafnia nanocrystals. Nanoscale. 2018, 10:7933-40. 10.1039/c8nr00724a
16. Reszka P, Nowicka A, Dura W, Marek E, Lipski M: SEM and EDS study of TotalFill BC Sealer and GuttaFlow Bioseal root canal sealers. Dent Med Probl. 2019, 56:167-72. 10.17219/dmp/105561
17. Verry C, Porcel E, Chargari C, Rodriguez-Lafrasse C, Balosso J: Use of nanoparticles as radiosensitizing agents in radiotherapy: state of play. Cancer Radiother. 2019, 23:917-21. 10.1016/j.canrad.2019.07.134
18. Khalladi N, Thariat J: Doubling complete histological response in sarcomas with radiation therapy using nanoparticles (hafnium oxide, NBTXR3), a phase III trial. Bull Cancer. 2019, 106:1070-2. 10.1016/j.bulcan.2019.10.002
19. McGinnity TL, Sokolova V, Prymak O, Nallathamby PD, Epple M, Roeder RK: Colloidal stability, cytotoxicity, and cellular uptake of HfO(2) nanoparticles. J Biomed Mater Res B Appl Biomater. 2021, 109:1407-17. 10.1002/jbm.b.34800
20. Sebti Y, Chauveau T, Chalal M, Lalatonne Y, Lefebvre C, Motte L: Assessment of the morphological, optical, and photoluminescence properties of HfO(2) nanoparticles synthesized by a sol-gel method assisted by microwave irradiation. Inorg Chem. 2022, 61:6508-18. 10.1021/acs.inorgchem.2c00277
21. Ren HM, Liu YR, Liu BY, Li ZF, Li G: Comparative studies on the proton conductivities of hafnium-based metal-organic frameworks and related chitosan or Nafion composite membranes. Inorg Chem. 2022, 61:9564-79. 10.1021/acs.inorgchem.2c00809
22. Liu N, Zhu J, Zhu W, et al.: X-ray-induced release of nitric oxide from hafnium-based nanoradiosensitizers for enhanced radio-immunotherapy. Adv Mater. 2023, 35:e2302220. 10.1002/adma.202302220
23. Sherstiuk AA, Tsymbal SA, Fakhardo AF, Morozov VN, Krivoshapkina EF, Hey-Hawkins E, Krivoshapkin PV: Hafnium oxide-based nanoplatform for combined chemoradiotherapy. ACS Biomater Sci Eng. 2021, 7:5633-41. 10.1021/acsbiomaterials.1c00973
24. Li R, Fan Y, Liu L, et al.: Ultrathin hafnium disulfide atomic crystals with ROS-scavenging and colon-targeting capabilities for inflammatory bowel disease treatment. ACS Nano. 2022, 16:15026-41. 10.1021/acsnano.2c06151
25. Fohlerova Z, Mozalev A: Anodic formation and biomedical properties of hafnium-oxide nanofilms . J Mater Chem B. 2019, 7:2300-10. 10.1039/c8tb03180k
26. Liu J, Yang Y, Zhu W, et al.: Nanoscale metal-organic frameworks for combined photodynamic and radiation therapy in cancer treatment. Biomaterials. 2016, 97:1-9. 10.1016/j.biomaterials.2016.04.034
27. Miyazaki T, Sueoka M, Shirosaki Y, Shinozaki N, Shiraishi T: Development of hafnium metal and titanium-hafnium alloys having apatite-forming ability by chemical surface modification. J Biomed Mater Res B Appl Biomater. 2018, 106:2519-23. 10.1002/jbm.b.34068
28. Bao J, Zu X, Wang X, et al.: Multifunctional Hf/Mn-TCPP metal-organic framework nanoparticles for triple-modality imaging-guided PTT/RT synergistic cancer therapy. Int J Nanomedicine. 2020, 15:7687-702. 10.2147/IJN.S267321
29. Bonvalot S, Rutkowski PL, Thariat J, et al.: NBTXR3, a first-in-class radioenhancer hafnium oxide nanoparticle, plus radiotherapy versus radiotherapy alone in patients with locally advanced soft-tissue sarcoma (Act.In.Sarc): a multicentre, phase 2-3, randomised, controlled trial. Lancet Oncol. 2019, 20:1148-1159. 10.1016/S1470-2045(19)30326-2

30. Cao C, Vernon RE, Schwarz WH, Li J: Understanding periodic and non-periodic chemistry in periodic tables . Front Chem. 2020, 8:813. 10.3389/fchem.2020.00813
31. Johnson DA, Williams AF: The gestation and growth of the periodic table . Chimia (Aarau). 2019, 73:144-51. 10.2533/chimia.2019.144
32. Constable EC: Evolution and understanding of the d-block elements in the periodic table . Dalton Trans. 2019, 48:9408-21. 10.1039/c9dt00765b
33. Li J, Xie L, Sang W, et al.: A metal-phenolic nanosensitizer performs hydrogen sulfide-reprogrammed oxygen metabolism for cancer radiotherapy intensification and immunogenicity. Angew Chem Int Ed Engl. 2022, 61:e202200830. 10.1002/anie.202200830
34. Choi E, Landry M, Pennock N, et al.: Nanoscale hafnium metal-organic frameworks enhance radiotherapeutic effects by upregulation of type I interferon and TLR7 expression. Adv Healthc Mater. 2023, 12:e2202830. 10.1002/adhm.202202830
35. Zhang P, Marill J, Darmon A, Mohamed Anesary N, Lu B, Paris S: NBTXR3 radiotherapy-activated functionalized hafnium oxide nanoparticles show efficient antitumor effects across a large panel of human cancer models. Int J Nanomedicine. 2021, 16:2761-73. 10.2147/IJN.S301182
36. Wang J, Pan J, Tang Y, Chen J, Fei X, Xue W, Liu X: Advances of hafnium based nanomaterials for cancer theranostics. Front Chem. 2023, 11:1283924. 10.3389/fchem.2023.1283924
37. Ding S, Chen L, Liao J, Huo Q, Wang Q, Tian G, Yin W: Harnessing hafnium-based nanomaterials for cancer diagnosis and therapy. Small. 2023, 19:e2300341. 10.1002/smll.202300341
38. Mohammadi S, Esposito M, Cucu M, Ericson LE, Thomsen P: Tissue response to hafnium. J Mater Sci Mater Med. 2001, 12:603-11. 10.1023/a:1011237610299
39. Sarraf M, Nasiri-Tabrizi B, Yeong CH, Madaah Hosseini HR, Saber-Samandari S, Basirun WJ, Tsuzuki T: Mixed oxide nanotubes in nanomedicine: a dead-end or a bridge to the future? . Ceram Int. 2021, 47:2917-48. 10.1016/j.ceramint.2020.09.177
40. Zhao T, Li Y, Zhao X, Chen H, Zhang T: Ni ion release, osteoblast-material interactions, and hemocompatibility of hafnium-implanted NiTi alloy. J Biomed Mater Res B Appl Biomater. 2012, 100:646-59. 10.1002/jbm.b.31989