Hydroxyapatite is a Next-Generation Theranostic Probe for Tissue Engineering and Biomedical Application

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Abstract

Hydroxyapatite (HAp), a synthetic analog of biogenic apatite, has several physicochemical characteristics that make it a desirable choice for disease diagnostics, therapy, and enhancement of biological tissues. In this article, we discuss remarkable recent research on HAp that could serve as the foundation for several novel medical applications. The review's content is organized into various HAp synthesis routes, HAp structure, and HAp-based medical application modes, such as bioimaging, controlled medication administration, gene treatments, and tissue engineering. This discussion highlights several benefits of HAp over the existing biomaterials, such as facile synthesis with tailored morphologies, biocompatibility, bioactivity, functionalization and adaptive surface modification, drug conjugation and delivery applications, etc. The novelty of this chapter is the investigation of particulate HAp's safety as a component of parenterally administered drugs, and their potential biomedical applications are covered.

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4.1 Introduction

The main component of mammalian hard tissues is hydroxyapatite (HAp), $Ca_{10}(PO_4)_6(OH)_2$, a naturally occurring biological nanomaterial (Mondal et al. 2018a). HAp could be found in enamel with a diameter of 20–40 nm or in dentin and bone as 5–20-nm-thick flakes. Additionally, it permits the integration of various cations and anions in its arrangement, which facilitates the functionalization of the system (Kim et al. 2018a; Park et al. 2022a). HAp is a wonderful and distinctive option for multiple applications in the field of nanomedicine since it differs from other ceramic nanoparticles while sharing several similar characteristics with them (Uskoković 2015). The calcium phosphate (CaP) family of biomaterials includes HAp, which is the most stable material. Dentists, orthopedic surgeons, and bone tissue engineers were the first to notice the exceptional biocompatibility and bioactivity of HAp nanoparticles. Since then, HAp's range of possible uses has widened beyond these particular industries. Today, it is understood that HAp possesses a variety of physicochemical traits that make it a desirable candidate for medical applications such as diagnostics, therapy, and tissue augmentation. According to the numerous publications on HAp's uses that have been published, the main use for HAp is in the field of tissue engineering, namely, for the regeneration and repair of bone deformities. However, the primary mechanical issues associated with the use of HAp in hard tissue engineering include inadequate fracture toughness, failure owing to fatigue, and brittleness. Like a natural bone, an ideal bone substitute should progressively resorb, preferably at a pace that corresponds to the rate of new bone development. However, the resorption rate of compact HAp blocks might be unreasonably slow, lasting for years or even decades (Proussaefs et al. 2002). The most common strategy for overcoming these obstacles is combining HAp with other substances that have comparable qualities and produce synergistic effects (Ghiasi et al. 2019). The superior osteoconductivity and lack of immunological rejection make HAp appropriate for implants in addition to applications in tissue engineering. Additionally, HAp is used as a drug delivery vehicle to carry medications to bones, where they can benefit from their natural osteoconductivity, as well as to other organs and tissues, typically by attaching the appropriate targeting tags to the HAp. Due to the pH-sensitive dissolving characteristics of HA, medications can be released intelligently in acidic environments, such as those near tumors and infection sites (Lelli et al. 2016). The ability to regulate particle size and the binding of functional groups by physisorption or surface phosphate substitution to allow more accurate cell/tissue targeting is another benefit of HAp. The very flexible crystal structure of HAp also makes it possible to include ions with a variety of atomic radii with ease (Uskoković 2020). Doped HAp for bioimaging applications

has therefore been developed as a result of the coprecipitation of HAp with luminous or other photoactive ions (Zeng et al. 2017; Ignjatović et al. 2019). For instance, the presence of lanthanide ions can impart the matrix with a photoluminescence property, turning it into a fluorescent probe. This led to the development of the HAp (Eu^{3+}, Gd^{3+}, Er^{3+}, etc.) system and the suggestion that it might be suitable for use as a stable biological probe in imaging research (Mondal et al. 2020a, b). The ability of HAp to adsorb both hydrophilic and hydrophobic molecules is crucial for its use as a drug carrier, given the variety of chemical and pharmacological compositions that might be found (Kim et al. 2018b; Mondal et al. 2017a, 2019a, b). Due to its resemblance to the inorganic phase of bones, it also stands out as a biomaterial that is frequently employed in bone treatments (Mondal et al. 2016, 2018b, 2020c; Mondal and Pal 2019). Tumor excision in conditions like bone cancer leaves flaws that need to be filled up with grafts or prosthetics (Mondal et al. 2017b, c, 2019c; Park et al. 2022b) (Fig. 4.1).

4.2 Structure of Hydroxyapatite

In the hexagonal and monoclinic systems with the space groups P63/m and P21/b, respectively, HAp can crystallize. While the lattice parameters of HAp's monoclinic structure are $a = b/2 = 9.421$, $c = 6.881$, and $= 120°$, the lattice parameters of HAp in hexagonal systems are $a = b = 9.432$, $c = 6.881$, and $= 120°$. In the hexagonal structure of HAp, neighboring hydroxyl (OH) groups face one another in the opposite direction. In contrast, in the monoclinic structure, all of the OH groups in a given column face the same way (Ikoma et al. 1999). Posner et al. first refined the crystal system of HAp with the hexagonal system, suggesting a distribution of 10 Ca^{2+}, 6 PO_4^{3-}, and 2 OH^- in each unit cell of HAp (Posner et al. 1958).

4.3 Synthesis Routes

HAp NPs with a specific microstructure have so far been prepared using a variety of chemical techniques. All of the synthesis methods can be divided into five categories: (1) dry methods (solid-state and mechanochemical routes), (2) wet methods (chemical precipitation, hydrolysis, sol-gel, hydrothermal, emulsion, and sonochemical routes), (3) high-temperature processes (combustion and pyrolysis methods), (4) methods based on biogenic sources (biogenic wastes), and (5) combination techniques. The aforementioned techniques can be used to create HAp nanostructures of various sizes and shapes, including spheres, rods, needles, flakes, flowers, mesoporous spheres, bowknots, dumbbells, etc. (Mondal et al. 2018a). It should be noted that HAp NPs' shape, crystallinity, and size are some of the most important variables impacting their anticancer activities. The aforementioned characteristics had a significant impact on the anionic and cationic sites of HAp that contained hydroxyl, amino, and carboxyl groups, as well as calcium and phosphorus ions. The interaction of HAp with a biomolecule is greatly influenced

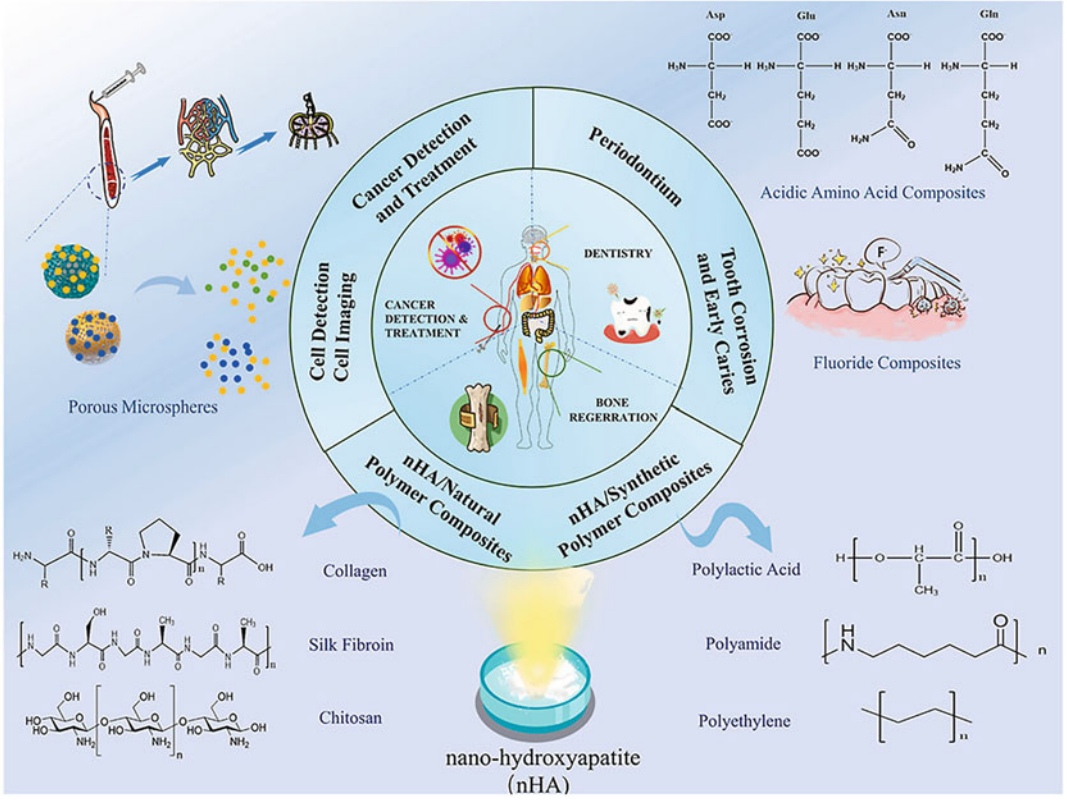

Fig. 4.1 Novel applications of hydroxyapatite in biomedical engineering, such as bone healing, cancer therapy, and dentistry. (Represented with permission from Du et al. 2021)

by the positive and negative surface charges of HAp, which are dependent on its physicochemical characteristics. HAp NPs can be used for cancer cell imaging in addition to structurally modified HAp nanostructures through a variety of well-established methods, such as (1) combining them with organic fluorophores, (2) doping them with different lanthanide ions, and (3) creating composites with other inorganic nanomaterials (such as carbon-quantum and chalcogenide-quantum dots) (Machado et al. 2019).

4.4 HAp in Tissue Engineering and as an Implant

As new technologies are created to develop efficient treatments for degenerative diseases that affect many types of tissues, tissue engineering is expanding. Recently, there has been a discernible increase in the need for bioactive, biodegradable, biocompatible, and multifunctional materials. To consolidate ceramic particles to join together and lessen interparticle gaps, a high-temperature stage (sintering) is often necessary for making HAp products, such as porous or nonporous blocks, coatings, etc. The appealing characteristics of nano-sized HAp, such as topography, geometry, high specific surface area, etc., would be irreparably lost after this heating phase, though. The integration of ceramic NPs within a matrix is a good choice for producing composite biomaterials. Consequently, if employing nano-sized HAp is the goal, scaffolds should be prepared, avoiding the final sintering stage. Mondal et al. reported a composite scaffold of HAp, bioglass, and alumina with enhanced mechanical stability. The study showed enhanced biological activity when cells were seeded on a scaffold surface (Mondal et al. 2018b) (Fig. 4.2).

The inhibition of cancer cell growth and migration by HAp NPs have been shown in several in vitro and in vivo investigations (Han et al. 2014). The shape, size, and crystallinity of Hap NPs are among the physicochemical characteristics that are acknowledged as being important determinants of their anticancer effects (Yuan et al. 2010). The simplest method for incorporating extra anticancer capabilities into a polymer that is otherwise biologically inert is to add HAp NPs to the biocompatible polymer. The first study in this field was published by Pathi et al. (2011), who introduced hydrothermally produced HAp NPs to CO_2-foamed poly(lactide-co-glycolide) (PLGA) scaffolds that were later implanted with metastatic breast cancer cells. The results showed that smaller, less crystalline HAp particles promoted greater adsorption of adhesive serum proteins and enhanced breast tumor cell adhesion and growth, in contrast to larger, more crystalline NPs, which, on the other hand, stimulated a higher expression of the osteolytic factor interleukin-8 (IL-8). Therefore, it was proposed that bone development, which supports improved cell colonization and proliferation, depends critically on modulating the nanoscale characteristics of the bone mineral found in the microenvironment.

Mondal et al. reported 3D printed PLA scaffold modified with HAp nanomaterials with enhanced cell attachment properties (Figs. 4.3 and 4.4) (Mondal et al. 2020c). More recently, a research group from Poland used 3D printed poly(L-lactic acid) (PLLA) scaffolds with HAp NPs doped with europium (III) ions (Eu^{3+})

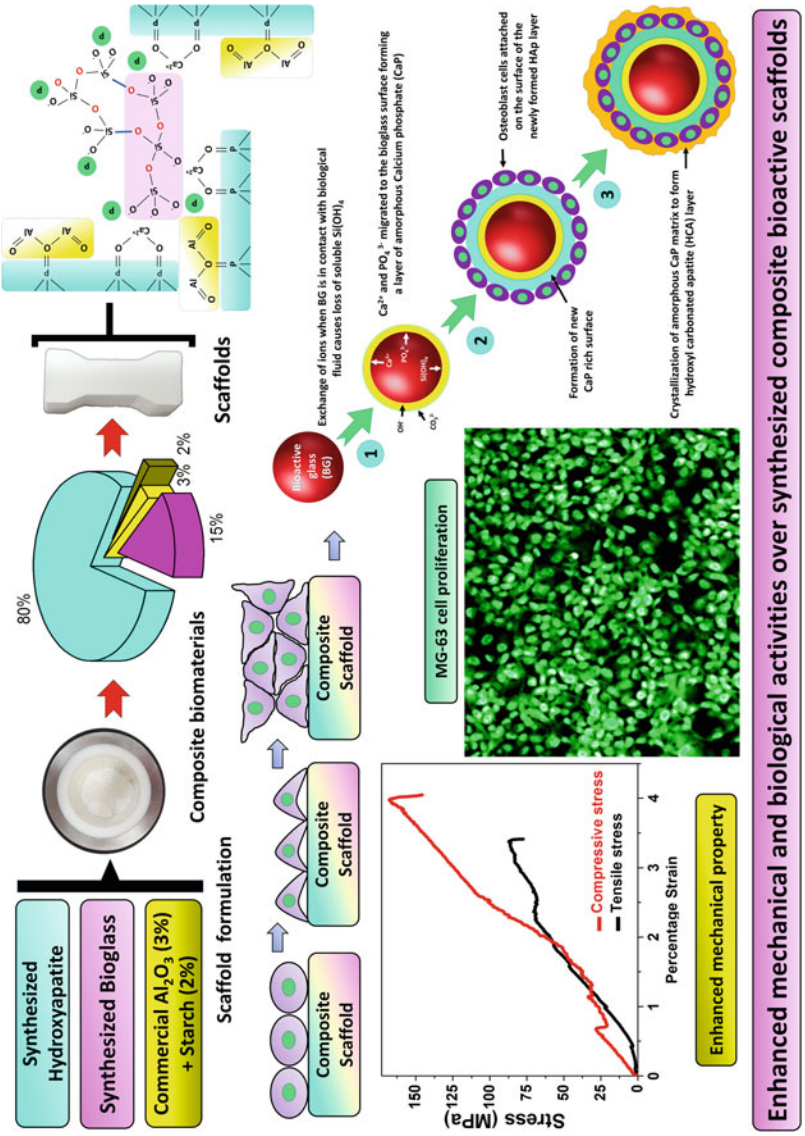

Fig. 4.2 For tissue engineering applications, composite scaffold fabrication with improved mechanical and biological performance. (Represented with permission from Mondal et al. 2018b)

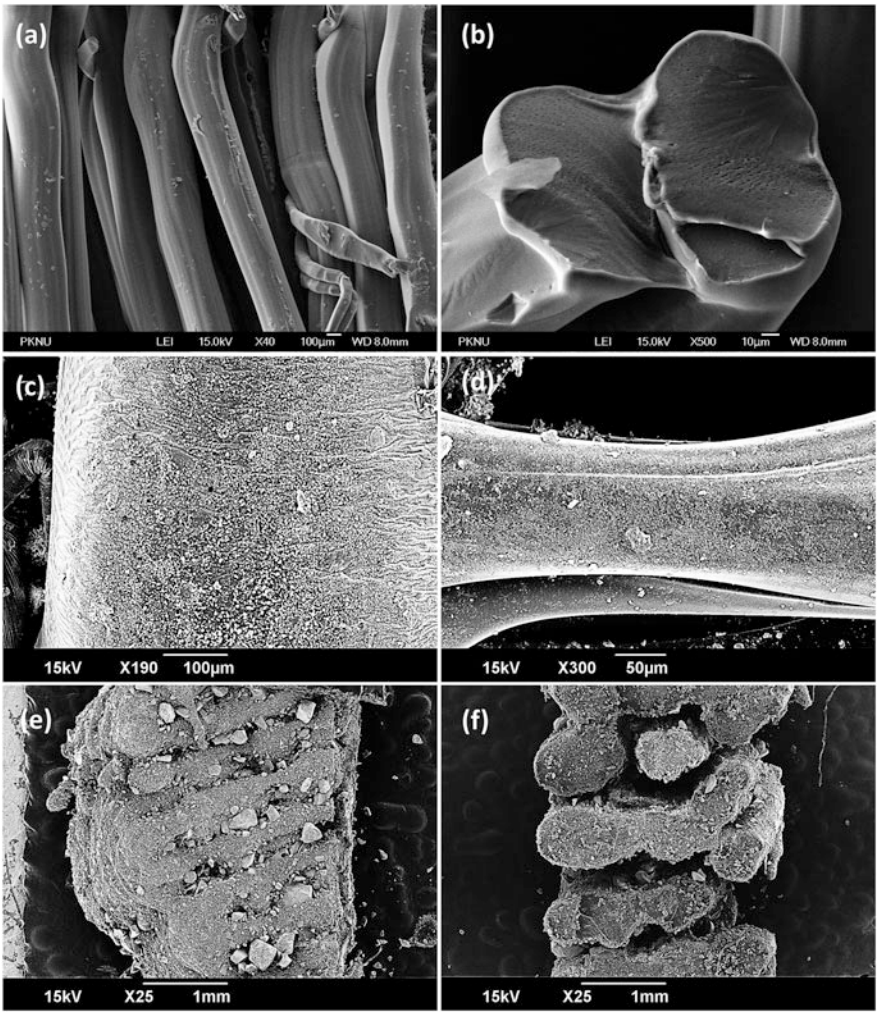

Fig. 4.3 SEM images of PLA scaffold modified with HAp nanoparticles. (Represented with permission from Mondal et al. 2020c)

to conduct several in vitro investigations. In this study, the hydrothermal technique-based microwave stimulation was used to prepare the Eu-doped HAp NPs. According to a study (Sikora et al. 2019), these composite scaffolds led an osteosarcoma cell line to go into apoptosis while not affecting the viability of unaltered adipose-derived human mesenchymal stromal cells. PLLA/HAp NP composite scaffolds boosted the viability as well as the osteogenic and chondrogenic differentiation capacity of adipose-derived human mesenchymal stromal cells, according to a second study from the same group (Marycz et al. 2020). This was correlated to increased protein and mRNA expression of the osteogenic and chondrogenic

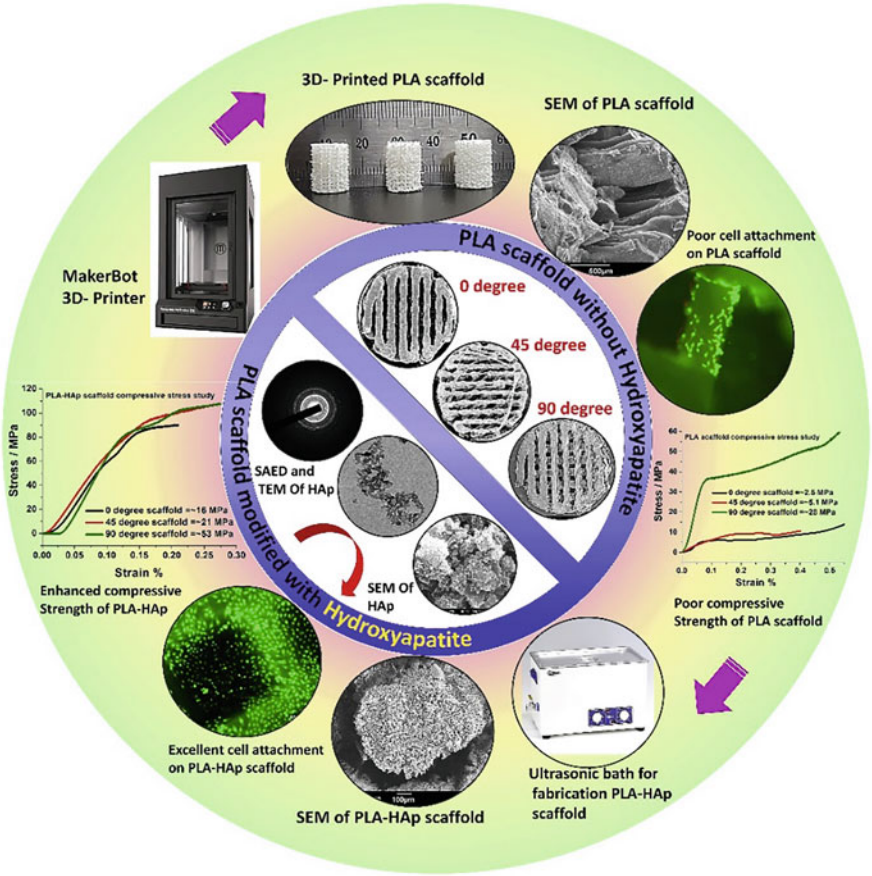

Fig. 4.4 Hydroxyapatite nanoparticle surface modification of 3D printed PLA scaffolds for improved bone tissue engineering applications. (Represented with permission from Mondal et al. 2020c)

markers. The positive impact of these biomaterials on the osteogenic and chondrogenic processes was further confirmed by the increased expression of bone morphogenic protein 2 (BMP-2) and BMP-7, as well as their receptor (i.e., BMP receptor type 1B (BMPR-1B)), suggesting a potential use in those applications where osseous regeneration is required following the removal of bone cancer tumor. Additionally, scaffolds carrying HAp NP were employed to simulate non-osseous tumors like neuroblastoma. To do this, Gallagher et al. employed neuroblastoma cell lines and collagen-based scaffolds supplemented with either HAp NPs or glycosaminoglycans, which are naturally found in bone and bone marrow, the most common metastatic sites for neuroblastoma. In contrast to 2D cultures, these composite scaffolds allowed neuroblastoma cells to attach, proliferate, migrate, and form cell clusters. This resulted in a cell response that was more like

that of the in vivo environment. Additionally, compared to traditional 2D cell culture, this scaffold-based culture technique maintained higher cell densities (Gallagher et al. 2021). It is also important to note that studies using tumor model systems have used polymeric scaffolds that contain HAp NPs. Tornin et al. showed the effects of plasma-based therapies on MG-63 cells in a 3D tissue-engineered osteosarcoma model based on a highly porous HAp NPs/collagen scaffold that allowed cancer cell proliferation and the acquisition of a similar gene expression profile as compared to the original tumors. Cancer cells were less sensitive to treatment with cold plasma-activated Ringer's solution when grown in a 3D scaffold-based model as opposed to 2D cultures because the scaffold's three dimensions induced the expression of several genes that protect against reactive oxygen and nitrogen species in MG-63 cells, promoting cell proliferation and adaptation to oxidative stress (Tornín et al. 2021). According to Nakayama et al., the self-organization of HAp with poly(acrylic acid) (PAA) results in the production of liquid-crystalline hybrid nanorods with desired properties as a drug release platform for photodynamic therapy of cancer (methylene blue was used as a model drug). The spin-coated 2D-oriented scaffolds were also shown to elicit cellular alignment and elongation in the direction of the hybrid nanorods (Nakayama et al. 2019).

In addition to polymer/nano-sized HAp and graphene/nano-sized HAp scaffolds, Zhang et al. also reported the potential of merging metal with nanostructured HAp. They applied a layer of wet-fabricated HAp nanorods on titanium cylindrical scaffolds manufactured by selective laser sintering (porosity 65%, pore size 500 m) (length 46.6 nm, width 13.3 nm). The titanium scaffolds were acid-alkali treated before coating to generate a microporous TiO_2 network on the surface, improving bonding with nano-HAp. The porous metal was next covered three times with a slurry composed of HAp nanorods, methylcellulose, and H_2O_2 before being allowed to dry. The scaffolds were then heated for 1 h at 300 °C. The authors described in vitro and in vivo experiments that demonstrated the nHAp particles' dual action as a bone-regenerating substance and an anticancer agent. In tumor-bearing rabbits treated with HAp nanorods, tumor growth was inhibited, metastases were prevented, and the survival rate was improved. In particular, the nanomaterial induced an anticancer immune response and promoted mitochondrial-dependent tumor death in vivo. Histological studies conducted over a month revealed that the use of HAp nanorods prevented metastasis to the lung effectively but not when micro-sized HAp or nano-sized TiO_2 coatings were used as controls. Abnormalities were not observed in the liver, heart, kidney, and spleen, further demonstrating the biosafety of the nanorods in use. These results confirm and extend the findings of the research by Pathi et al. on the effect of HAp NPs on the growth cycles of cancer cells (Pathi et al. 2011).

4.5 HAp Nanostructures for the Delivery of Anticancer Drugs

In the past, NPs like HAp nanostructures were suggested to concurrently target some of cancer characteristics and transport and release several cytotoxic chemicals safely and effectively (VanDyke et al. 2016). The effectiveness of drug-loaded multimodal HAp NPs as effective nanomaterials for tumor metastasis-resisting therapy (TMRT) and tumor metastasis targeting therapy (TMTT) has been demonstrated in earlier experiments (Xiong et al. 2018). However, there are very few studies in the literature that concentrate on employing nano-sized HAp particles, either in the pristine or in the functionalized and drug-loaded kinds, to target and image the various indicators of cancer. For instance, HAp NPs can reduce the FAK/PI3K/Akt cell signaling pathway both in vitro and in vivo, which suppresses cancer cell proliferation, migration, and invasion (Wang et al. 2020). Through using lysosomal- and mitochondrial-dependent pathways, such as caspase-3, HAp NPs can also induce oxidative stress-induced apoptosis in cancer cells (Jin et al. 2017).

For use as a drug carrier in cancer theranostic applications, nanostructured HAp provides several advantages (Saber-Samandari et al. 2016). These benefits can be summed up as follows:

1. HAp could be formed with substantially similar characteristics to the main components of the targeted tissues, particularly bone, including chemistry, crystalline structure, and size.
2. HAp alone does not expand or change porosity, preventing the burst release of medicines, and is reasonably stable with fluctuations in the solution/environment (e.g., pH, temperature).
3. Both positively and negatively charged compounds can surface-functionalize Hap.
4. By doping HAp with various elements, NPs with desirable electrical, mechanical, magnetic, and optical properties can be prepared (Fig. 4.5).

To treat tumors connected to both hard and soft tissues, a variety of natural and synthetic anticancer drugs have been loaded onto and delivered using HAp NPs (Maia et al. 2018). Mesoporous HAp NPs are a promising class of drug delivery systems that can be used to transport a variety of anticancer cargos, including chemicals, small compounds, and generic medications. Due to their outstanding drug adsorption, storage, and release capabilities, these systems hold promise for cancer therapy methods (Meshkini and Oveisi 2017).

In this study, ribose is used as a highly biocompatible material to cross-link hybrid mineralized composites for the first time. The purpose of this study was to explore the viability of novel, bone-like scaffolds made from type I collagen matrix mineralized with magnesium-doped hydroxyapatite nanophase (MgHA/Coll) through ribose glycation in a pH-driven manner, inspired by biological processes. According to the literature, a significant portion of the experimental research use pH-sensitive nanostructures (Fig. 4.6). A suitable material for improved anticancer medication delivery to cancer cells was also mentioned as being nanostructured

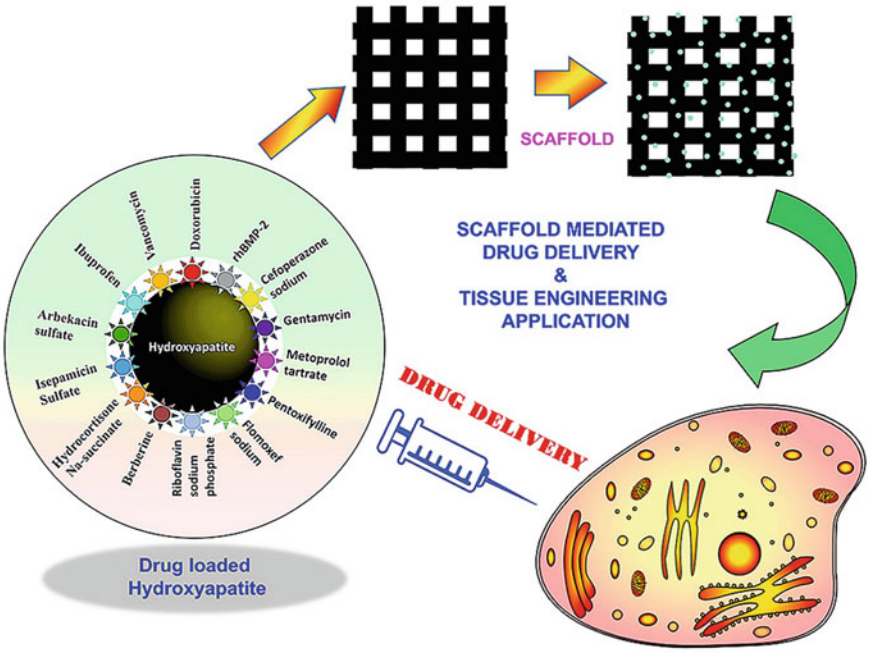

Fig. 4.5 Schematic representation of hydroxyapatite-based scaffold and drug delivery agents. (Represented with permission from Mondal et al. 2017b)

hollow HAp (Mondal et al. 2019b). A lot more focus is now being paid to larger-scale hollow micro-sized HAp structures (like microspheres), even if using nano-sized hollow HAp structures for the delivery of anticancer drugs appears promising in the early stages (Qiao et al. 2017). The outcomes showed that DOX (9.1%) and siRNA (2.0%), as well as the efficient transport of anticancer drugs into drug-resistant breast cancer cells (MCF-7/ADR cells), were loaded appropriately. In addition, after 48 h in cancer cells, the drug-loaded samples started to degrade. A biopolymer coating on HAp can enhance the bioactivity and regulate the release of anticancer medications (Padmanabhan et al. 2020). According to Li et al., the hydrothermal method followed by freeze-drying produced nano-sized HAp (20 wt. %)/GO composite scaffolds that shared the same dual functionality (photothermal anticancer effect and osteogenesis) (Li et al. 2018). Twenty minutes of in vitro exposure to 808 nm NIR radiation on osteosarcoma cells (MG-63) resulted in the death of all but 8% of the cells. Tumor xenografts implanted with the scaffolds in mice reached 60 °C after 4 min of radiation exposure and ceased growing or even shrunk in size following photothermal therapy. In addition, micro-tomographic and histological evaluations supported the notion that nano-sized HAp/GO scaffolds encouraged bone regeneration in rat cranial defects: At 8 weeks, new tissue had grown by over 65% in the cranial defect area for the scaffold-implanted group, whereas only 20% regeneration had been seen for the control (empty defect). The

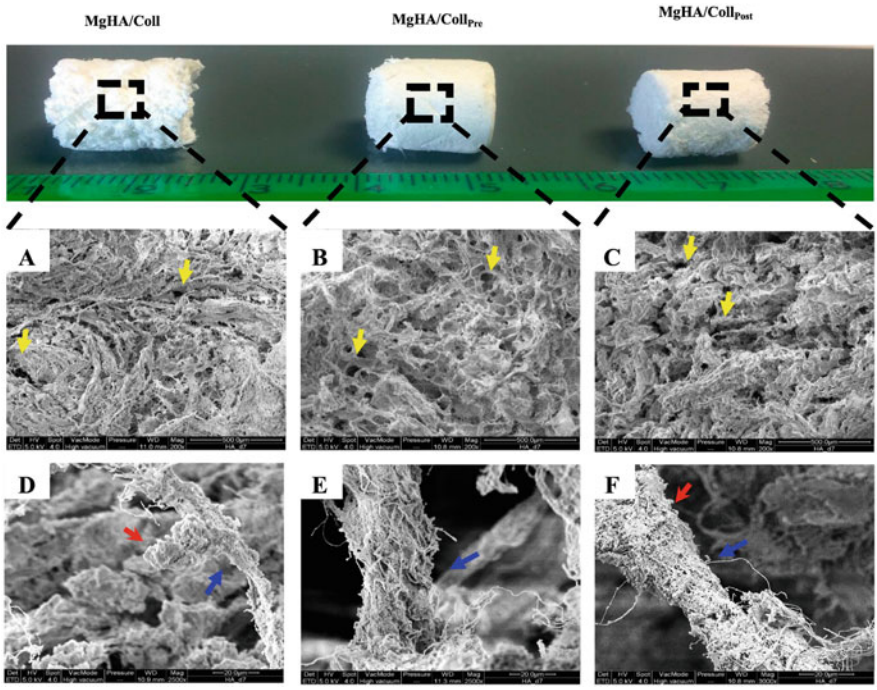

Fig. 4.6 Using the matching magnifications, SEM images of the scaffold are shown in (**a**, **d**) MgHA/Coll, (**b**, **e**) MgHA/CollPre, and (**c**, **f**) MgHA/CollPost. Red arrows denote the binding mineral phase on fibrils, yellow arrows point to open surface pores on the fibrous matrix, and blue arrows denote a small or large bundle of self-assembled collagen fibers with visible mineral deposition. Scale bars: 500 mm for (**a**–**c**) and 20 mm for (**d**–**f**). (Reprinted with permission from Krishnakumar et al. 2017)

scaffold-implanted group's bone mineral density also reached about 285 mg/cm^3, indicating fresh bone mineral deposition, compared to the control at 96 mg/cm^3. The properties of HAp-NPs, which specifically affect the drug/gene/adsorption protein's capacity and solubility in physiological fluids, subsequently affect how HAp interacts with cancer cells. Additionally, it was claimed that HAp NPs encourage p53 production and its downstream genes, which causes apoptosis (programmed cell death) in tumor cells (Sun and Ding 2009). Tang et al. found that HAp reduces cell proliferation and promotes apoptosis in several cancer cells via activating caspase-3 and caspase-9 (but not caspase-8) (gastric cancer cells [MGC80-3], cervical adenocarcinoma epithelial cells [HeLa], and hepatoma cells [HepG2]) (Tang et al. 2014). Other experimental results indicate that HAp NPs are formed by and contribute to the intracellular accumulation of reactive oxygen species (ROS), which damage the DNA of cancer cells (Xu et al. 2012). Due to their high ribosome adsorption ability, HAp NPs can be internalized in large quantities by endocytosis in cancer cells in the endoplasmic reticulum, inhibiting protein synthesis by reducing the binding of

mRNA to the ribosomes in cells and stopping the cell cycle in the G0/G1 phase (Han et al. 2014).

4.6 HAp for Advanced (PTT/PDT/Hyperthermia) Cancer Therapies

Despite numerous treatments, cancer remains the second most significant cause of mortality on Earth. The next generation of anticancer agents will focus on supporting healthy cell proliferation while causing malignant cell death. As a result, HAp NPs doped with a variety of therapeutic ions have been created and used for theranostic applications for the treatment and diagnostics of cancer (Šupová 2015). Targeted magnetic hyperthermia for cancer treatment has attracted significant interest in HAp NPs as well (Abdel-Hamid et al. 2017) (Fig. 4.7). A well-known method for triggering cancer cell death without harming healthy cells is hyperthermia, which relies on the modest rise of temperature to 40–43 °C upon application of an external magnetic field. Hyperthermia also improves the effects of radiation therapy and chemotherapy (Sedighi et al. 2022). Furthermore, by providing an alternating magnetic field to the tumor, cancer-targeting magnetic HAp NPs can gather there. Additionally, the effectiveness of magnetic HAp NPs for synergistic chemo-hyperthermia therapy has been demonstrated in the past. At this point, chemotherapeutic drug-loaded magnetic nanocomposites of cobalt ferrite/HAp were created using the microwave-assisted wet precipitation method (5-fluorouracil, FU) (Sangeetha et al. 2019). With a magnetic saturation value of roughly 2.5–8.2 emu/g, the produced nanocomposites displayed ferromagnetic properties. After being exposed to an alternating magnetic field, they were able to release the encapsulated FU and raise the temperature (producing a hyperthermic effect) quickly (43 °C in 4.5 min). The samples also showed a suitable ability to inhibit the growth of osteosarcoma cells (MG-63), demonstrating their suitability for synergistic chemo-hyperthermia therapy.

One of the most recent techniques for treating tumors using external radiation sources is photodynamic therapy (PDT), which is also known as photothermal therapy (PTT) (Santha Moorthy et al. 2018). The NPs are illuminated with a suitable near-infrared (NIR) wavelength in PTT or methods incorporating NP-mediated hyperthermia (the electromagnetic radiations are NIR with a wavelength within 780–2526 nm) (Mondal et al. 2022). Under the influence of NIR, the treated NPs' conduction band electrons experience synchronized oscillations. It kills cancer cells by destroying cell membranes, tumoral DNA denaturation, and angiogenesis inhibiting processes and converts light into heat (45–50 °C) (Mondal et al. 2022; Doan et al. 2021; Vo et al. 2021; Phan et al. 2019). When a photosensitizer (PS) is activated by specific wavelength irradiation in photodynamic treatment (PDT), reactive oxygen species (ROS) and free radicals are created (620–690 nm). When exposed PS interacts with oxygen ($^3O_2$) and a specific light wavelength to produce lethal singlet oxygen ($^1O_2$ and O_2), the known pathways for cancer cell death in PDT are direct (necrosis and apoptosis) and indirect (microvascular damage and antitumor immune responses) (Pinto and Pocard 2018).

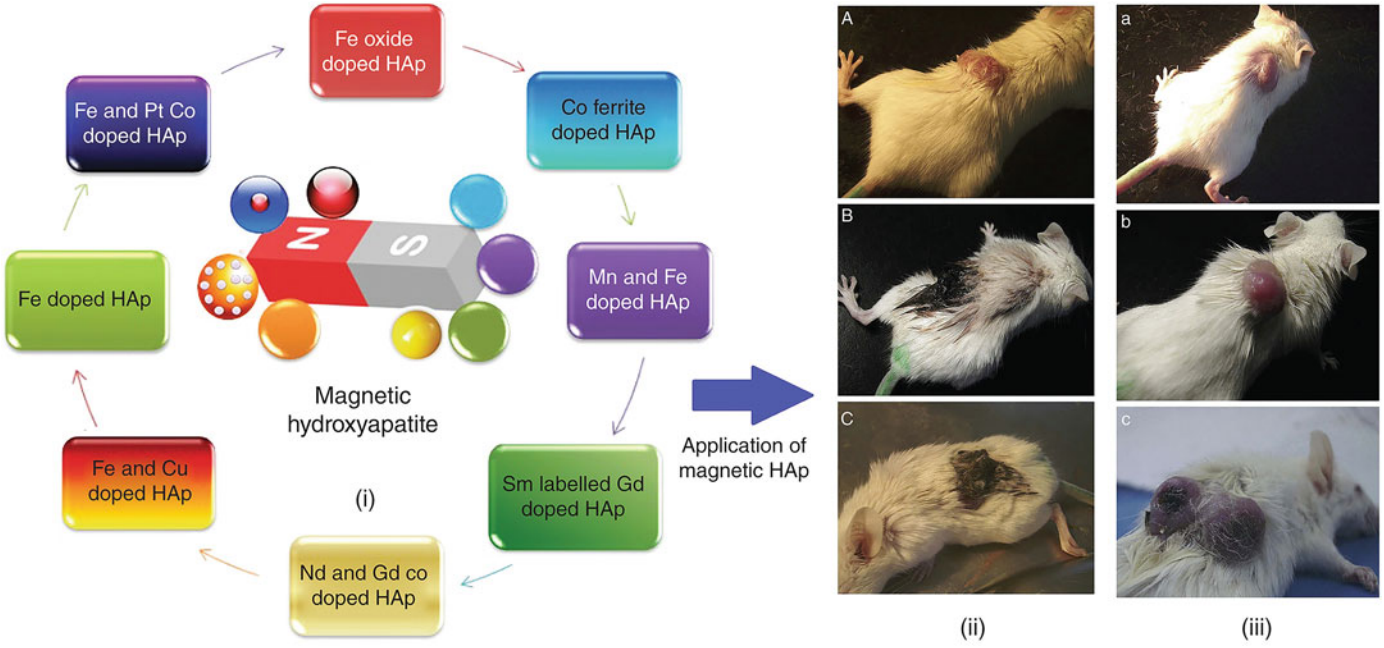

Fig. 4.7 Magnetic hydroxyapatite (mHAp) nanoparticles are based on several dopants. (ii) The tumor's diagnostic photos (mHAp with magnetic field). Tumors on days 1 (A), 5 (B), and 14 (C). The tumor's clinical pictures (iii) (mHAp without magnetic field). The tumor was on days 1 (a), 5, and 14 (b and c). (Reprinted with permission from Mondal et al. 2018a; Hou et al. 2009)

According to Zhang et al., a biocompatible system incorporating HAp and graphene could efficiently convert NIR into heat to hasten bone regeneration following photothermal therapy of malignant bone lesions. Their findings demonstrated that following three cycles of treatment at low photothermal temperatures (40–43 °C), the growth of MC3T3-E1 cells was dramatically boosted. The findings showed that for pure HAp and HAp scaffolds, including 1 wt% graphene, the observed temperature after exposing Hap NPs to NIR was 31.6 and 45.2 °C, respectively. The technique being used appears promising for NP-mediated hyperthermia (PTT) (Zhang and Ma 2021). There are several obstacles that prevent anticancer chemicals from being loaded and desirably delivered to tumor cells, including ineffective targeting and a lack of drug solubility. To overcome these limitations, several novel techniques have been used to create HAp nanostructures as smart theranostic platforms that can target cancer cells without harming healthy cells. One of the most alluring methods for supporting sustained anticancer medication release is the surface functionalization of HAp nanostructures (Verma et al. 2016). To successfully load and distribute curcumin to MCF-7 cells, for instance, HAp NPs functionalized with several carboxylic acids (lactic acid, tartaric acid, and citric acid) were used (Lee et al. 2019). Based on the electrostatic interactions of opposite charges between the medication and the bioceramic particles, carboxylic modifiers may increase the binding affinity between curcumin molecules and the HAp surface. The results showed that, in comparison with unmodified samples, surface-functionalized HAp NPs exhibited stronger antiproliferative and apoptotic actions against cancer cells. For instance, several types of cancer cells overexpress folate receptors (such as FR), making it viable to target tumors with drug delivery systems conjugated with folic acid, a ligand with a high affinity for folate receptors (Cheung et al. 2016).

4.7 Nano-Sized HAp in Imaging

Currently, a variety of biomedical imaging approaches are being used to find cancer in all stages of development. Imaging techniques can be used to identify a variety of features of cancer, such as morphological, structural, metabolic, and functional data. These methods are divided into those that use (1) nonionizing electromagnetic radiation, including magnetic resonance imaging (MRI), electrical impedance spectroscopy, and near-infrared spectroscopy, and (2) ionizing radiation (such as gamma rays, X-rays or UV light, CT scans, and PET scans) (Fass 2008). To visualize tumors using particular imaging modalities, such as MRI, the choice of appropriate contrast agents is essential. Over the past few decades, contrast agents based on nanotechnology have been created and used for cancer imaging. Different kinds of nano-sized HAp have been applied in this way for the molecular imaging of solid tumors. For optical, magnetic resonance (MR), and multimodal imaging of malignancies, luminescent, magnetic, and luminomagnetic HAp NPs exhibit the necessary properties (Kataoka et al. 2019). The effect of the calcination temperature and the amount of Eu^{3+} doping were previously evaluated about the luminescence characteristics and

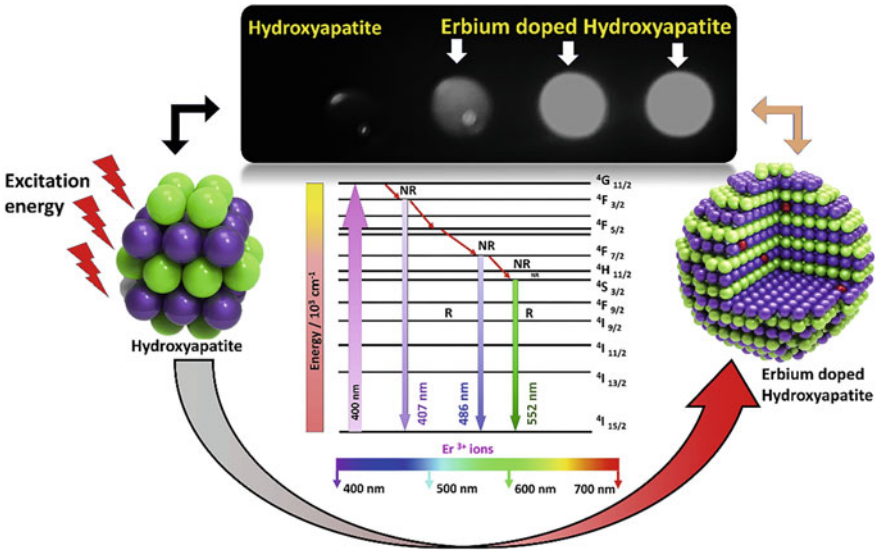

Fig. 4.8 Schematic representation of erbium-doped hydroxyapatite as a bioactive luminescent agent. (Represented with permission from Mondal et al. 2020d)

phase composition, crystal size, and crystallinity of Eu^{3+}-doped HAp NPs (Han et al. 2013). To manufacture nanocrystalline Eu-doped HAp (20–40 nm in diameter) with high luminescence, the thermal treatment (600 °C) and 2% Eu^{3+} doping content were optimized. In a different study, HAp nanocrystals (Er-HAp) were combined with luminescent erbium (Er^{3+}) ions at various concentrations (0.1, 0.25, 0.5, and 1.0 mol %) to create a nontoxic luminescent agent for biomedical imaging applications (Mondal et al. 2020d). The outcomes demonstrated that after being stimulated at 400 nm, 1.0 mol% Er-doped HAp nanocrystals (50 nm size distribution) possessed high-efficiency light emission (Fig. 4.8).

It is usual practice to categorize the contrast materials utilized in MRI scans into (1) positive (T1, Gd-based agents, and brightness contrast) and (2) negative (T2, Fe-based agents, and darkness contrast) categories. The most often utilized substances for MRI to increase diagnostic precision are hydrophilic Gd(III)-based chelates. The long-term safety of these materials for the human body, however, is still a matter of concern (Wahsner et al. 2018). Due to their distinctive characteristics, such as their wide surface area and effective contrasting impact, inorganic NPs have been identified as suitable contrast agents for MRI over the years (Na et al. 2009). Superparamagnetic iron oxide nanoparticles (SPIONs), of them, have garnered a lot of interest as MRI contrast agents. However, the buildup of Fe in soft tissues harms SPIONs as contrast agents. The solution to all of the aforementioned problems was suggested to be the addition of contrast agents to HAp NPs. For instance, Fe-doped HAp NPs have been described as appropriate contrast agents that can produce more contrast for MRI than SPIONs (Adamiano et al. 2018). In addition to MRI, the efficacy of 99mTc-MDP-labeled Fe-doped HAp NPs as a scintigraphy

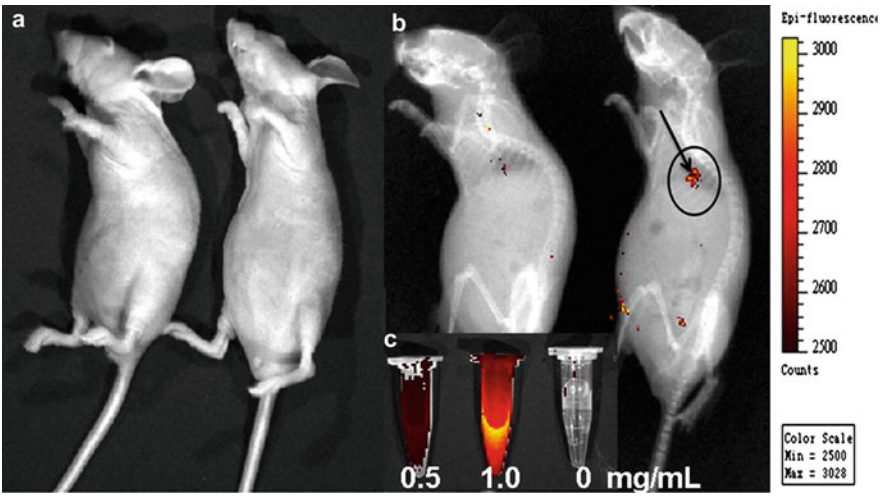

Fig. 4.9 Mice following without (**a**) and with (**b**) Eu^{3+}/Gd^{3+}-HAp (Eu^{3+}:Gd^{3+} = 1:2) nanorods, subcutaneous injection. Imaging using PL in vivo. (**c**) Photographs of the PL emission from Eu^{3+}/Gd^{3+}-HAp nanorods at various concentrations. The excitation wavelength was 430 nm. (Reprinted with permission from Chen et al. 2011)

imaging agent for PET and single-photon emission computed tomography was proven (SPECT). The preparation of paramagnetic HAp NPs for use as PL contrast agents for cancer imaging by substituting other elements (such as Eu^{3+}/Gd^{3+}) was also shown to be beneficial (Fig. 4.9).

For MRI imaging, the luminomagnetic HAp may offer a very promising multimodal imaging probe. In this manner, microwave-assisted synthesis of multifunctional Eu^{3+}/Gd^{3+} dual-doped HAp nanorods was previously achieved (Chen et al. 2011). This system (Eu^{3+} to Gd^{3+} ratio 1:2, Ms = 0.15) demonstrated useful features as a T1 and T2 contrast agent of MRI after being subcutaneously injected into nude mice, as the attenuation value increased from 26 to 96 HU (Fig. 4.9). The magnetization of the samples increased along with more significant concentrations of the Gd^{3+} dopant, and the photoluminescence intensity was dependent on the Eu^{3+}/Gd^{3+} ratio in the HAp nanorods. In particular, it should be noted that bio-nanoplatforms made of doped HAp NPs and other substances, such as carbon dots, have been suggested as suitable tools for cancer cell imaging because they can produce bright blue fluorescence under UV illumination with excellent photostability and colloidal stability (Zhao et al. 2015).

4.8 Limitations of HAp and Future Directions

The biological activity, degradability, and osteoconductivity of HAp are all significant. In recent years, it has seen widespread usage in orthopedic repair, antitumor medication carriers, and dentistry (Fig. 4.10). However, hydroxyapatite has

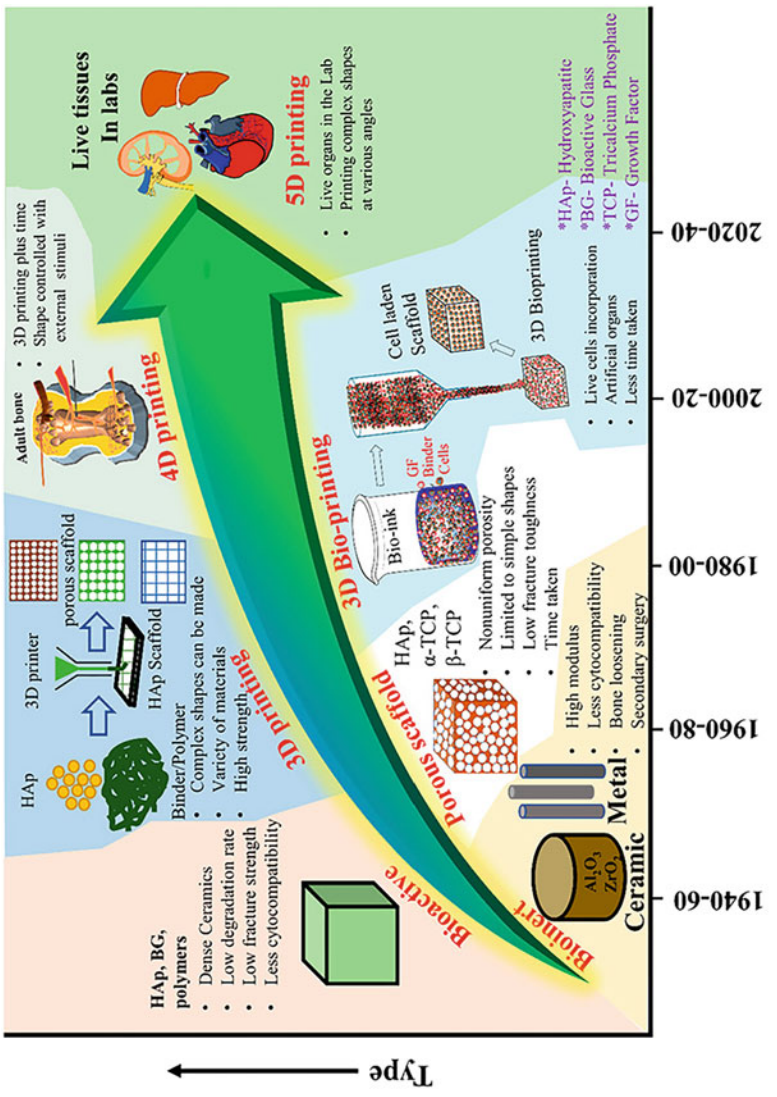

Fig. 4.10 The evolution of HAp-based composites from the early 1940s to the near future is depicted diagrammatically. (Represented with permission from George et al. 2022)

limitations, including brittleness for bone transplantation and weak mechanical characteristics for directly triggering dental enamel remineralization. The difficulties that have been experienced in the preparation, use, and modification of hydroxyapatite in the aforementioned sectors are discussed in this article along with the state of the study. Because of this, the most important contribution of this chapter is to thoroughly integrate and defend the forms and effects of HAp-based biomaterials, which offers a strong foundation for their use and gives readers clear insights into future research. We must overlook the fact that nano theranostic is still a young scientific discipline that has, for the most part, not yet attained the minimal requirements for clinical translation. The intricacy and synergistic mechanisms of the materials employed for such multifunctional applications are the cause of this reality. The more complicated a system is (e.g., when nanostructured HAp is used as a vehicle for the simultaneous release of ions and drugs with anticancer properties), the more variables must be considered, which makes it more challenging to disentangle the therapeutic effects or determine the precise magnitude of synergistic contributions.

4.9 Concluding Remarks

Over the past few years, HAp has significantly broadened the scope of biomedical applications beyond bone restoration, demonstrating considerable promise in cancer theranostics. Due to its polar surface, HAp with nanoscale dimensions is ideally adapted to interact with biomolecules in cells and tissues as well as with medicines. This characteristic offers the possibility for targeted cell- and tissue-specific applications, such as cancer treatment and imaging, in addition to the biocompatibility and biodegradability of HAp upon interaction with bodily fluids (diagnosis). In comparison with metal or composite nanoparticles, multifunctional HAp nanostructures are more adaptable and secure since they may integrate hyperthermia, drug transport, photothermal/photodynamic treatment, imaging, and, generally, superior targeting capabilities.

Further investigation should be done on the combination of HAp with natural anticancer pharmaceuticals and the potential for metallic ion doping and co-doping to reduce the need for conventional chemotherapeutics, which frequently have harmful side effects on the body. By adding functionalization treatments or stimuli-responsive polymeric coatings (serving as molecular gates) on the surface of HAp, it is also possible to carefully control the release of ions and medications. By using additive manufacturing techniques to process HAp, it will be possible to fabricate exact goods and 3D porous scaffolds with excellent control over pore size, shape, and other features. If 3D printing and medical imaging are coupled to recreate the anatomy of patients' flaws left after cancer removal, it will also be feasible to customize and individually design implants.

The experimental work addressed to this purpose is quite complex, requiring the collaboration of biomaterials scientists, biomolecular chemists, biologists, and oncologists in addition to the assessment of full in vitro/in vivo toxicity profiles

along with the relationships to the stated hallmarks. A deeper understanding of the biomolecular impact of HAp-based systems on various types of cancer is more important than ever for the research to advance. This study primarily focuses on the groundbreaking discoveries that foreshadowed the interesting modern drug delivery technologies based on HAp and HAp-based composite nanostructures. A particular focus has been placed on describing the use and efficacy of modified HAp as a drug carrier agent for various ailments, including carriers for antibiotics, anti-inflammatory, and cancer-causing medications, medical imaging, and protein delivery agents. This article examines a wide range of nHAp and HAp-modified inorganic drug carriers, highlighting some of their unique characteristics that should be considered for upcoming drug delivery applications.

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