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Review Article

A Comprehensive Review: The Role of Organic Modifiers in Engineering Hydroxyapatite Composites for Advanced Biocompatibility and Photothermal Therapy

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Running Title: Organic Modifiers in Engineering Hydroxyapatite Composites

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Abstract

Hydroxyapatite (HA, $Ca_{10}(PO_4)_6(OH)_2$), the main component of bone and dental tissue, has long served as a foundation for bone tissue engineering and orthopedic implants due to its natural osteoconductivity and bioactivity. However, its use as a monolithic material has been limited by subpar mechanical properties, the absence of self-antibacterial and therapeutic features, and difficulties in processing and soft tissue integration. The strategic addition of organic modifiers ranging from simple amino acids and polyelectrolytes to more complex hosts, like cyclodextrins, has become a key approach to address these limitations. This review critically evaluates over 28 different classes of organic modifiers aimed at fundamentally enhancing HA-based composites. It concentrates on two complementary areas: (i) improving biocompatibility, including cell adhesion, proliferation, differentiation, immune modulation, and antibacterial effects; and (ii) designing photothermal properties for non-invasive hyperthermia cancer treatment, biofilm removal, and bone regeneration. Through an in-depth, chemistry-focused discussion of electrostatic, covalent, and supramolecular interactions between modifiers and HA, we clarify the structure-property relationships involved. A notable strength of this review is the inclusion of detailed comparative tables listing the modifiers, their preparation methods, the main properties enhanced, and their applications. Additionally, it offers an integrated overview of recent advances and existing gaps, such as the need for long-term *in vivo* biodistribution studies of photothermal HA composites and exploring artificial intelligence for modifier design. Ultimately, this review aims to serve as a reference for developing the next generation of multifunctional HA-based composites for regenerative medicine and cancer therapy.

Keywords: biocompatibility, composite materials, hydroxyapatite, organic modifiers, photothermal therapy

Introduction

1.1. Hydroxyapatite: From Bioinert to Bioactive

Hydroxyapatite (HA) is a well-established bioceramic that exhibits strong osteoconductivity due to its biochemical similarity to bone mineral[1,2]. However, its natural stoichiometric form is

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largely bioactive, with slow *in vivo* degradation rates that sometimes hinder its replacement by newly formed bone. Moreover, its brittleness, low tensile strength, and lack of inherent biological activity (such as anticancer or antibacterial effects) limit its use in more advanced biomedical applications[1]. It is largely these shortcomings that have driven the development of composite materials, where the inorganic phase of HA is combined with organic materials to create hybrids with customizable and outstanding properties.

1.2. The Need for Organic Modification

However, incorporating organic materials into inorganic HA involves a level of sophistication beyond simple addition, as it mimics the nanocomposite structure of bone, which consists of about 70.0% inorganic HA and approximately 30.0% organic material, mainly Type I collagen[3,4]. Organic modifiers control: (i) formation of HA crystals, influencing their size and shape; (ii) serve as conjugation agents; (iii) facilitate dispersion in polymer matrices and biological fluids; (iv) introduce new properties, such as responsiveness to stimuli and antimicrobial effects; and (v) significantly enhance the bond strength at the interface with host tissue[4,5]. **Figure 1**

1.3. Defining the Scope: Biocompatibility versus Photothermal Properties

This review describes two important, often complementary axes of enhancement.

• **Biocompatibility:** Extending the traditional definition of non-toxicity to include active biological functions. This involves promoting cell adhesion and migration through specific ligand-receptor interactions (e.g., Arg-Gly-Asp (RGD)-integrin binding), guiding osteogenic differentiation, modulating immune responses, and preventing infection via antimicrobial surface properties[5].

• **Photothermal Properties:** The ability to convert absorbed Near-Infrared (NIR) light into localized heat. When integrated into HA composites, this property can be used for Photothermal Therapy (PTT), a minimally invasive method for destroying tumor cells or pathogenic biofilms[1,6,7].

1.4. Review Objectives and Novelty

Although various existing reviews have addressed HA composites or organic-inorganic hybrids in general, none have provided a systematic analysis of the role of organic modifiers in

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achieving biocompatibility alongside photothermal properties. The novelty of this article lies in: **1**. Reviewing over 28 different types of organic modifiers that directly influence the properties of the synthesized composites. **2**. Creating comprehensive comparative tables using a design toolbox approach to establish a correlation between chemical structure and function.

2. Fundamental Interactions: The Chemistry of the HA-Organic Interface

The effectiveness of any organic modifier is based on its particular interaction with the HA surface at the molecular level.

Modes of Interaction

Organic modifiers interact with HA by a variety of forces, the preponderance of which decides their stability as well as functionality. **Table 1**.

3. Organic Modifiers: A Systematic Catalog and Their Primary Roles.

Table 2 presents a systematic overview of over 28 categories, organized by chemical type, primary function, interaction mechanisms, and main property enhancements.

4. Synergy at the Interface: Modifiers Enabling Dual Functionality

The section highlights the organic component's role in the multifunctional system.

The most advanced platforms use modifiers to facilitate combination therapies, as represented in **Figure 2**.

4.1. Case Study 1: Polydopamine-Modified HA Composites

Polydopamine (PDA), a catechol-based polymer, is an example of a single modifying agent used to create a theranostic HA composite. **Figure 2A.**

- **System Architecture and Synthesis:** Immersion of HA particles in an alkaline solution containing dopamine.
- **Multifunctional Role:**
  1. **Adhesive and Biocompatibility Promoter:** The PDA-HA composite is used for adsorbing serum proteins and activating FAK/PI3K/Akt osteogenic signaling.

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2. **Intrinsic Photothermal Absorption (PTA):** The composite has photothermal efficiency, η value of 20.0-45.0%, thus making it applicable for photothermal therapy (PTT).

3. **Drug Loading Platform:** The PDA-HA composite is used for accommodating drugs via π-π stacking (e.g., doxorubicin), covalent conjugation, and/or ion chelation (e.g., Ag^{+} and Sr^{2+}).

• **Advanced Application:** To create a composite for a PDA-HA 3D-printed scaffold with a melting point of 45°C for thermal safety switch applications[27], a PDA-HA composite for PTT was synthesized, effectively eliminating osteosarcoma cells *in vitro* and *in vivo*.

4.2. Case Study 2: Cyclodextrin-Gated HA Nanocarriers for NIR-Triggered Drug Release

This case study discusses the application of the supramolecular organic modifier, cyclodextrin, for the controlled release of drugs, where the cyclodextrin gates open due to the heat generated from the irradiation of drug-containing HA at an appropriate wavelength[11-13].

• **Architecture:** Mesoporous HA core, aminosilane, cyclodextrin gates, drug-containing pores. **Figure 2B**

• **Mechanism:** Localized heat generated by a co-integrated PTA (PDA), reducing the host–guest interaction, allowing spatiotemporally controlled burst release.

• **Advanced Application:** Although none of the studies in the literature has fully replicated the design, the theory underlying it is strongly supported by previous studies. The HA/cyclodextrin composite has been successfully made for drug delivery[11]. Also, cyclodextrins have been successfully used to control mesoporous structures via their guest-host mechanism of dissociation upon heating[12,13]. The suggested new design incorporates the already successfully tested PDA-HA system, which can be used as an activation source for near-infrared radiation.

5. Synthesis and Characterization Methodologies

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In order to attain accurate engineering of organic-modified hydroxyapatite (HA) composites with well-established structure-property relationships, it is vital that a detailed approach is adopted with regard to the synthesis routes as well as characterization methods. The selected method of synthesis has a direct impact on homogeneity, interfacial characteristics, colloidal stability, as well as the biological activity of the final composite product. In this regard, this segment will highlight a detailed review of recent synthesis routes and characterization methodologies.

5.1. Wet Chemical Synthesis with *In-Situ* Modification

The wet chemical method with *in-situ* modification enables nucleation as well as growth of HA with an organic modifier, controlling the morphology of the product crystals[59]. **Figure 3**

5.1.1. Hydrothermal/Solvothermal Synthesis

A closed vessel is used to expose reactants to temperatures higher than the boiling point of water (usually 120-200°C), under autogenous pressure. This enables high crystallinity as the potential development of anisotropic nanowire structures, nanorods, nanotubes, and superstructures[60,61].

The two-step approach begins with the synthesis of pure HA and then surface modification with organic molecules.

5.2. Surface Modification of Pre-Synthesized HA via a Two-Step Approach

5.2.1. Covalent Grafting

- **Grafting-to:** A polymer chain or molecule with a reactive functional end group, already pre-synthesized, is covalently attached to the functional groups present on the surface of HA.

1. **Silane Coupling:** Involves dispersing HA in an anhydrous solvent, e.g., toluene or an ethanol/water mixture, and then reacting it with an organosilane, e.g., APTES[62].

2. **Phosphonate Anchors:** Phosphonic acids, e.g., alendronate and vinyl phosphonic acid, strongly bind to the surface of the HA in a covalent bond with

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binding energy that corresponds to a tridentate P-O-Ca structure that can be used as a primer for subsequent surface modifications[63].

- **Grafting-from:** Initiators are attached to the surface of the HA, and monomers are polymerized from the surface *in situ*, e.g., **Atom Transfer Radical Polymerization (ATRP)** and **Reversible Addition-Fragmentation Chain Transfer (RAFT)** polymerization, which allow for the controlled synthesis of polymer brushes, e.g., PEG, PAA, and poly(N-isopropylacrylamide) (PNIPAM), creating a dense brush structure for surface modification[64].

5.2.2. Non-Covalent Adsorption

- **Electrostatic Layer-by-Layer Assembly:** An efficient technique for the fabrication of nanostructured multifunctional thin layers with nanometer accuracy. A positively charged HA surface is sequentially immersed in oppositely charged polyelectrolytes, e.g., chitosan with a positive charge and alginate/hyaluronic acid with a negative charge. The thickness of each layer is in the range of 1–3 nm[23,24,44,20].
- **Agar diffusion (Diffusion-Controlled Synthesis in Gel Matrices):** Agar Diffusion, also called the Liesegang Rings Method, describes a new strategy for controlling reaction kinetics by separating reactants in space within a passive, porous agar gel, thereby enabling better control over the morphology of hydroxyapatite[2,65-68]. **Figure 3**

5.3. Advanced and Emerging Fabrication Techniques

5.3.1. 3D Printing/Bioprinting: Organic modifiers are critical components in bioink formulations, particularly for creating complex geometries that closely resemble patient-specific geometries, with rheological properties, such as shear thinning, yield stress, and viscoelasticity. **Figure 3.** Examples of bioinks comprising organic modifiers include:

- Alginate-HA, which can be cross-linked using Ca^{2+}
- Gelatin-HA, which is thermoresponsive and can be cross-linked using cold temperatures
- Silk fibroin-HA, which can provide mechanical strength to bioinks
- PDA-HA-PEG-DA, which can provide high resolution using UV light as a cross-linking agent[69,70]

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5.4. Characterization of Modified HA Composites

The structure-property correlations of the organic-functionalized HA-based composite are determined by using a suite of techniques. The X-ray diffraction technique and FTIR provide information on phase purity and the success of the functionalization process. Morphology and coating homogeneity are investigated using electron microscopy (SEM/TEM), and TGA obtains the amount of organic material[14,26,27]. The colloidal stability of the composite particles is analyzed using dynamic light scattering (DLS) and zeta potential[23]. For photothermally responsive composite nanoparticles, the efficiency of photothermal conversion (η) is calculated based on the heating-cooling cycles under NIR illumination[27].

6. New Discoveries and Prevailing Trends

Recent research has shown a shift from proof-of-concept demonstrations of material capabilities to creating intelligent, complex, and multi-modal systems that can address complex problems[63,71,72].

6.1. Embracing Sustainability and Green Synthesis

Biomolecule-Directed Mineralization: Synthesis of HA-based drug delivery systems through the use of self-assembling peptides, proteins such as elastin-like polypeptides, and bacterial and cell culture supernatants at near-physiological conditions is not only eco-friendly but also results in the formation of a composite structure that is closer to the natural structure of HA[73,36].

Waste-to-Value and Natural Modifiers: The use of environmentally friendly calcium sources, such as eggshells and fish bones, in combination with polyphenolic extracts, such as tannic and gallic acids from plants, would enable the development of fully green, multifunctional drug delivery systems with enhanced adhesive, antioxidant, and antimicrobial properties[35,74,75,26,27].

6.2. The Promising Frontier: Computational and Data-Driven Design

Moving beyond empirical approaches and embracing the potential of computational materials science and artificial intelligence.

6.2.1. In Silico Screening and Mechanistic Modeling

- **Density Functional Theory (DFT):** It is used to predict the electronic structure and binding mechanisms at the fundamental level, with DFT being particularly useful for

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understanding covalent grafting or chelating reactions such as phosphonate binding to HA surfaces[76-80].

- **Machine Learning (ML) and Artificial Intelligence (AI):** With sufficient data availability in terms of quantity and quality, ML/AI can be used to **(i)** predict the optimal modifiers or combinations thereof for specific properties, **(ii)** uncover unknown relationships between synthesis conditions and biological activity, and **(iii)** optimize synthesis conditions to achieve maximum yield[81,82].

Recent Efforts: ML techniques such as K-nearest neighbors, CatBoost, XGBoost, and artificial neural networks have been used by [82] to predict HA crystallinity for different dopant ions such as Sr^{2+}, Zn^{2+}, Ag^{+}, F^{-}, Ni^{2+}, Fe^{3+}, Er^{3+}, B^{3+}, Al^{3+}, Ba^{2+}, W^{6+}, sintering temperatures, and times.[82] used ML potentials to predict hydroxyl reorientation in HA**.**

7. Conclusion and Future Perspectives

Future Perspectives

The focus of future work should be on the design and synthesis of scalable, continuous-flow-based organic-modified hydroxyapatite composites using Process Analytical Technology (PAT), ensuring reproducibility and Good Manufacturing Practice-grade composites. Long-term *in vivo* biodistribution, immunogenicity, and efficacy tests will be critical for advancing these potential multifunctional materials from the bench to the clinic[83,84].

Conclusion

The role of organic modifiers in HA composites has evolved from peripheral to central, and they now provide the basis upon which the next generation of precision biomaterials will be developed. The direction this field is set to take in the future is predicated on applying established chemical principles to address clinical challenges in a safe, reproducible, and scalable manner. New avenues of research are expected to combine **synthetic chemistry**, **computational materials science**, and pathophysiology models, thereby realizing the promise of smart biomaterials in regenerative medicine, cancer therapy, and infection control.

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List of abbreviations

PTA – Photothermal Agent

CTAB - Cetyltrimethylammonium Bromide

AuNP – Silver nanoparticles

PCL - Poly(ε-caprolactone)

PPy - Polypyrrole

PEDOT - Poly(3,4-ethylenedioxythiophene)

EDC - 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide

NHS - N-Hydroxysuccinimide

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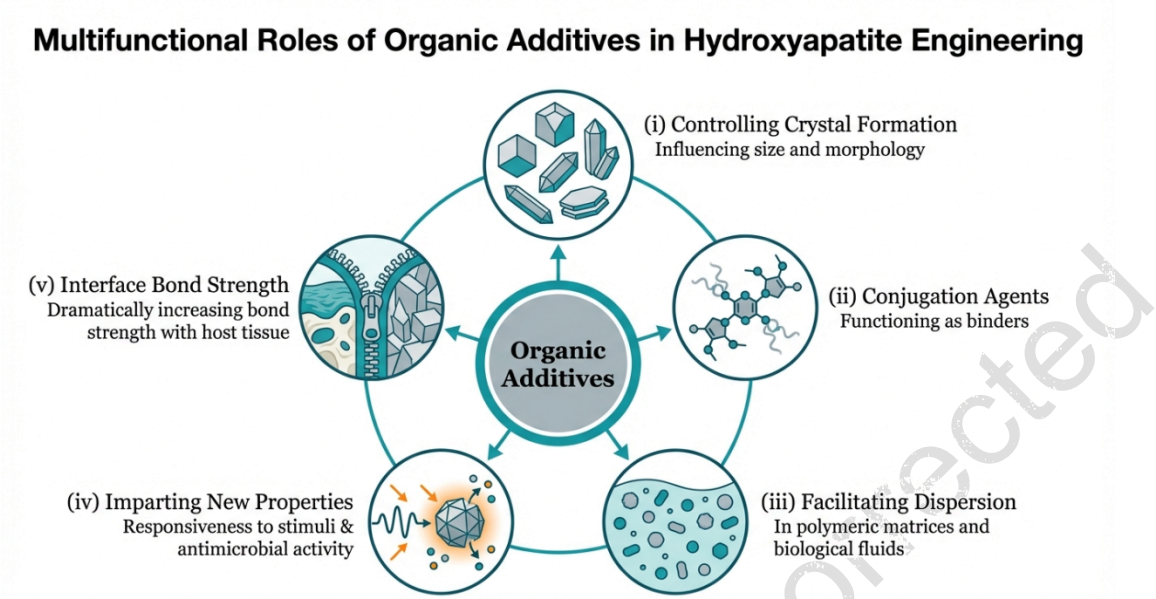


Figure 1. Multifunctional Roles of Organic Additives.

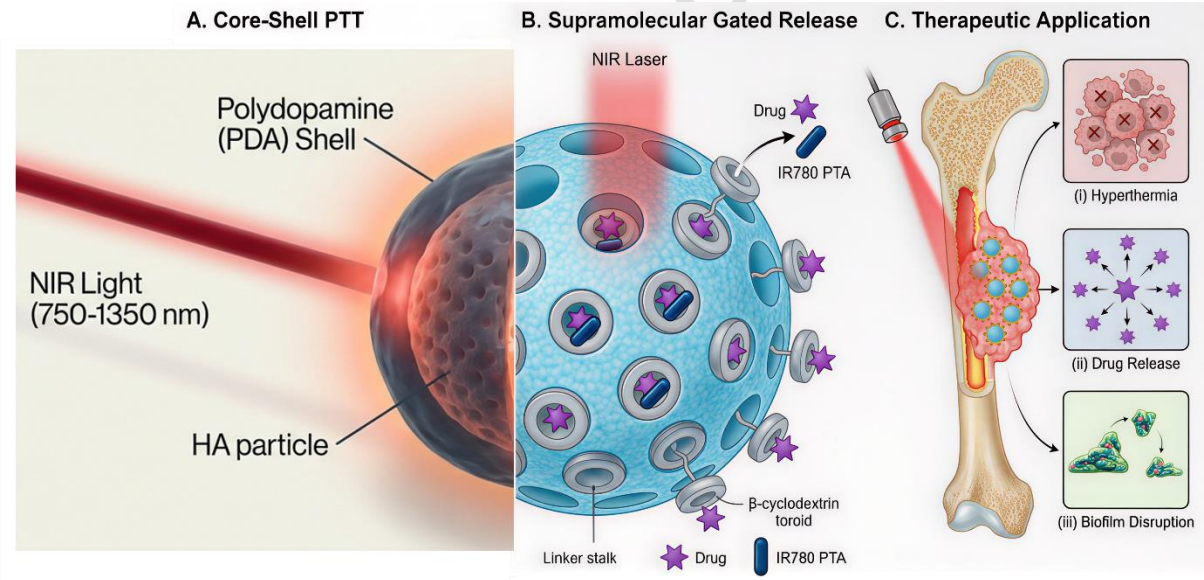


Figure 2. Schematic illustration of the multifunctional role of organic-modified hydroxyapatite in the framework of photothermal therapy and drug delivery. (A) A core-shell structured composite in which polydopamine acts as an adhesive, a photosensitizer, and a drug carrier, represented by PTA. (B) A supramolecular nano-valve drug delivery system in which the gates are made up of a cyclodextrin. (C) Use in the treatment of a bone tumor/microbial invasion.

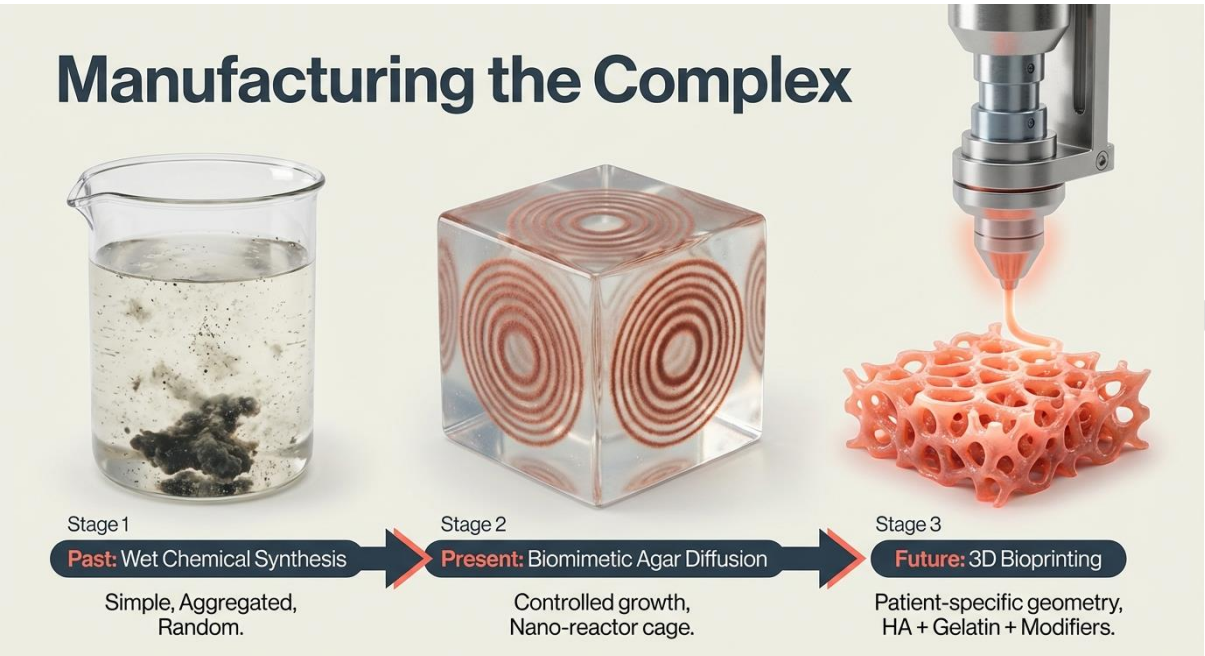


Figure 3. Manufacturing the Complex.

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Table 1. Modes of Interaction

Interaction Type	Mechanism & Examples	References
Electrostatic	Most prevalent and controllable. Anionic polymers like polyacrylic acid and alginate bind with Ca^{2+} ions. Cationic polymers such as chitosan and polyethylenimine bind with phosphate groups. This is regulated by the Debye length and ionic strength.	[8]
Coordination/Complexation	Stable chelating compounds attach to surface Ca^{2+} ions. These compounds are usually multidentate and have a high affinity for Ca^{2+}. They are generally not reversible. Examples include citrates, bisphosphonates (like alendronate), and acidic amino acids.	[8]
Covalent Grafting	Provides permanent and stable bonding. Examples include silane coupling agents such as 3-aminopropyltriethoxysilane (APTES) and the formation of Si-O-P/Ca bonds; phosphonic acids and the creation of P-O-Ca bonds.	[9,10]
Supramolecular	Non-covalent, specific interactions. Examples include: Cyclodextrins (used in drug delivery systems); π-π stacking (e.g., polydopamine with aromatic drugs).	[11,12,13]

Note. At physiological pH (~7.4), HA is expected to have a slightly negative surface charge due to its high HPO_4^{2-} ion content compared to Ca^{2+}, although its local environment is heterogeneous at the nanoscale.

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Table 2. Comprehensive Catalog of Organic Modifiers for HA Composites

Modifier Class & Examples	Functional Category	Primary Interaction with HA	Photothermal Conversion Efficiency (η %)	Activation Wavelength (nm)	Key Property Enhancements	Representative Applications	Biocompatibility/ Toxicity Status & Validation	References
1. SIMPLE AMINO ACIDS • Arg • Gly • Lys • Asp • Glu	Osteogenic/Structural Support	Electrostatic, Coordination via -COOH, H-bonding.	N/A	N/A	Control crystal morphology (nanorods, plates). Introduce charges: Arg/Lys/Gly (+) for antibacterial properties; Asp/Glu (-) for mineralization control. Enhance protein adsorption capabilities.	Bone filler additives, colloidal stabilizers for injectable pastes, and a precursor for peptide conjugation	Biocompatible (*in vitro* & *in vivo*)	5,14,15
2. CELL-ADHESIVE PEPTIDES • RGD (Arg-Gly-Asp) • KRSR (Lys-Arg-Ser-Arg) • Bone Morphogenetic	Osteogenic/Structural Support	Covalent grafting via linker groups (silanes, polyethylene glycol (PEG), **Polydopamine** (PDA).	N/A	N/A	Enhance cell adhesion, spreading, and osteogenic differentiation via integrin/heparan	Surface coating of orthopedic/dental implants and functionalization of 3D	Biocompatible (*in vitro* & *in vivo*)	16,17

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Protein (BMP-2) mimetic peptides					sulfate/BMP receptor binding.	printed scaffolds.		
3. CATIONIC POLYSACCHARIDES • **Chitosan (CS)** • Quaternary Ammonium Chitosan (QACS) • Chitosan-graft-PCL	Osteogenic/Structural Support	Strong electrostatic (NH_3^+/PO_4^{3-}), H-bonding	N/A	N/A	Inherent antibacterial properties through membrane disruption, osteoconductive properties, mucoadhesive properties, and immunomodulatory properties through M2 macrophage promotion.	Antibacterial bone cement and coatings, and wound dressings.	Biocompatible (*in vitro* & *in vivo*)	[18,19]
4. ANIONIC POLYSACCHARIDES • **Alginate (Alg)** • **Hyaluronic Acid (HA)** • **Heparin** • Carboxymethyl Cellulose (CMC)	Osteogenic/Structural Support	Electrostatic, H-bonding.	N/A	N/A	Alg/CMC: Injectable gelling with calcium ion crosslinking. HA/Heparin: Lubricity, CD44 targeting, anti-inflammatory, sequestering growth factor (BMP/ Vascular Endothelial Growth Factor	Injectable *in situ* gelling composites, coatings for targeted delivery and promotion of angiogenesis.	Biocompatible (*in vitro* & *in vivo*)	[20-24]

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					(VEGF)).			
5. SYNTHETIC POLYELECTROLYTES **• Poly(acrylic acid) (PAA)** • Poly(methacrylic acid) (PMAA) **• Poly(ethylene imine) (PEI)** **•Polydiallyldimethylammonium chloride (PDADMAC)**	Osteogenic/Structural Support	PDADMAC/PAA/PMAA: strong chelation/electrostatic interaction (COO^{-}/PO_4^{3-}). PEI: electrostatic interaction (NH_3^{+}/PO_4^{3-}).	N/A	N/A	PDADMAC: Positive charge for burst reduction, drug loading, and release. PAA: Dispersant properties, crystallization control, pH responsive. PEI: high positive charge density for gene/drug loading.	Dispersants for nanocomposites, building blocks for Electrostatic Layer-by-Layer (LbL) films, drugs, and non-viral gene delivery vectors.	Biocompatible (primarily *in vitro*)	25,23,24,2
6. MACROCYCLIC HOSTS **• α-, β-, γ-Cyclodextrin (CD)** • Hydroxypropyl-β-CD	Dual-Function	Grafted via linker groups (PAA, silanes, PDA).	N/A	N/A	Host-guest complexation for hydrophobic drug solubilization and release. Can act as "gatekeepers" on mesoporous HA.	Drug delivery systems for anti-inflammatory (dexamethasone) and anticancer (doxorubicin) agents.	Biocompatible (*in vitro* & *in vivo*)	12,13
7. CONJUGATED POLYMERS (as Photothermal agents (PTAs))	PTA	**PDA: U**niversal adherent via catechol-Ca^{2+}-coordination and	20.0–45.0% (PDA)	NIR (typically 808 nm)	NIR absorption properties for PTT, excellent adhesive	Photothermal bone tumor ablation, conductive	Biocompatible (*in vitro* & *in vivo*)	26,27,28

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• **PDA** • **Polypyrrole (PPy)** • Poly(3,4-ethylenedioxythiophene) (PEDOT)		H-bonding. **PPy/PEDOT:** often polymerized *in situ* or doped with anionic HA**.**			properties through PDA.	scaffolds for neural and cardiac tissue engineering, and antibacterial coatings.		
8. SMALL MOLECULE PTAs • **Indocyanine Green (ICG)** • **IR-780 iodide** • Methylene Blue	PTA	Physically adsorbed or encapsulated within a polymer/HA matrix. Weak direct interaction.	High (ICG ~ high efficiency)	NIR	Strong photothermal conversion efficiency, fluorescence imaging properties through ICG. Tends to cause photobleaching and lacks stability without a carrier system.	Imaging-guided PTT and antimicrobial PTT for disruption of biofilms.	Generally biocompatible when encapsulated (*in vitro*/*in vivo*)	[26,27]
9. PHOSPHONATE COUPLERS • **Alendronate** • Pamidronate • (Vinyl/Amino)phosphonic acids	Osteogenic/Structural Support	**Strong covalent-like P-O-Ca interaction.**	N/A	N/A	High affinity anchoring layer. Bisphosphonates (e.g., alendronate) also have anti-osteoporotic drug properties.	Robust priming agents for subsequent grafting of polymers and biomolecules.	Biocompatible (*in vitro* & *in vivo*)	[29]
10. SILANE COUPLING AGENTS • **APTES** (aminoisilane	Osteogenic/Structural Support	Covalent Si-O-P or Si-O-Ca bonds. H-bonding and	N/A	N/A	Introduce specific functional	Surface passivation of HA	Biocompatible (*in vitro* & *in vivo*)	[16,17,12,13]

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) • GPTMS (epoxysilane) • MPTS (mercaptosilane)		weak electrostatic interaction			groups (-NH_2, -Epoxy, -SH) for click chemistry or biomolecule conjugation. Universal method for surface functionalizatio n.	nanoparticles for systemic delivery in photothermal oncology.		
11. POLYETHERS (Stealth Agents) • **Poly(ethylene glycol)** • Pluronics (PEO-PPO-PEO)	Shield/Stealth	H-bonding and weak electrostatic interaction	N/A	N/A	"Stealth" effect reduces protein fouling and macrophage uptake, improves blood circulation time. Enhances hydrophilicity and dispersion.	Surface passivation of HA nanoparticles for systemic delivery in photothermal oncology.	Biocompatible (*in vitro* & *in vivo*)	[30]
12. STRUCTURAL PROTEINS • **Collagen Type I** • **Gelatin** • Silk Fibroin	Osteogenic/Str uctural Support	Electrostatic interaction, H-bonding, often involves carboxyl groups of amino acids.	N/A	N/A	Achieves full biological recognition, excellent cell adhesion, and biodegradability . Collagen is the natural partner of HA in bone.	Gold standard in biomimetic composites (collagen/HA) , coatings, and drug delivery systems	Biocompatible (gold standard, *in vivo*)	[31,32,33]

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13. POLYESTERS (Mechanical Matrix) • Poly(L-lactic acid) (PLLA) • Poly(ε-caprolactone) (PCL) • Poly(lactic-co-glycolic acid) (PLGA)	Osteogenic/Structural Support	Physical blending/interpenetration often requires compatibilizing agents (e.g., grafted polymers).	N/A	N/A	Delivers mechanical toughness, flexibility, and biodegradability. Allows for 3D scaffold fabrication, fibers, and films.	Load-bearing scaffolds and electrospun membranes for guided bone regeneration.	Biocompatible (*in vitro* & *in vivo*)	[34]
14. POLYPHENOLS • **Tannic Acid (TA)** • Gallic Acid • Epigallocatechin Gallate (EGCG)	Dual-Function	Multidentate coordination via pyrogallol/catechol groups to Ca^{2+}. H-bonding.	Variable (platform)	NIR (when forming PTA)	Strong adhesion properties like PDA, antioxidant, and antibacterial. Can reduce metal ions to form nanoparticles *in situ.*	Green multifunctional coatings, antioxidative implants, and platforms for *in situ* synthesis of PTA.	Biocompatible (*in vitro* & *in vivo*)	[35,36]
15. LIPIDS & SURFACTANTS • Phospholipids (e.g., DPPC) • Fatty Acids (e.g., Oleic Acid) • Cetyltrimethylammonium Bromide (**CTAB**)	Osteogenic/Structural Support	Hydrophobic interaction: electrostatic interaction (for charged headgroups).	N/A	N/A	Enhances dispersion in organic solvents and creates bilayer films for "stealth" effect. CTAB can be used as a template for mesoporous film synthesis.	Processing aids in polymer/HA composite systems and templates for mesoporous HA.	CTAB: Potential cytotoxicity (*in vitro*); limited *in vivo* use; others biocompatible	[34]

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16. NUCLEIC ACID APTAMERS • AS1411 (targets nucleolin) • Bone-targeting aptamers	Osteogenic/Structural Support	Grafted via terminal -SH or -NH_2 groups to a primed HA surface (e.g., via silane).	N/A	N/A	Achieves high-affinity, specific targeting of cancer cells or bone tissue. It can also be used for controlled assembly.	Active targeting of HA nanoparticles to osteosarcoma and bone surfaces.	Biocompatible (*in vitro* & *in vivo*)	[37,38]
17. IONIC LIQUIDS • Choline-based ILs • Imidazolium-based ILs	Osteogenic/Structural Support	Electrostatic, ion exchange, H-bonding (depending on the nature of the anion/cation).	N/A	N/A	Potent dispersant and shape-controlling agents can also impart antimicrobial properties. Used as a green synthesis medium.	Green synthesis of HA nanostructures and antimicrobial coatings.	Biocompatible (green, *in vitro*)	[39]
18. VITAMINS & COFACTORS • **Vitamin E (α-Tocopherol)** • **Vitamin C (Ascorbic Acid)** • Vitamin D3	Osteogenic/Structural Support	Hydrophobic encapsulation or covalent grafting.	N/A	N/A	Antioxidant activity (Vit E, Vit C), pro-osteogenic activity (Vit D3) can increase the rate of collagen synthesis and reduce oxidative stress at the site of the implant.	Green synthesis of HA nanostructures and antimicrobial coatings. Functional additives in composite scaffolds for healing in	Biocompatible (*in vitro* & *in vivo*)	[40,41]

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						compromised environments (aged and diabetic).		
19. ANTIBIOTICS & DRUGS • **Tetracycline** • **Vancomycin** • **Doxorubicin (DOX)** • **Dexamethasone**	Dual-Function	Physical adsorption, encapsulation, or covalent conjugation through modified functional groups.	N/A	N/A	Direct therapeutic action: Antibacterial, chemotherapeutic, anti-inflammatory. Modifier: drug itself.	Localized drug delivery from HA carriers for osteomyelitis, bone cancer, and inflammation.	Biocompatible when delivered via HA (*in vitro*/*in vivo*)	42,22
20. GROWTH FACTORS • **BMP-2** • **VEGF** • Fibroblast Growth Factor 2 (FGF-2)	Osteogenic/Structural Support	Often through an intermediary (heparin, collagen) or encapsulation	N/A	N/A	Strong osteoinductive and angiogenic signals. Direct biological instruction for tissue regeneration.	Biofunctionalization of scaffolds to induce bone formation and vascularization in critical-sized defects.	Biocompatible (*in vivo* critical-size defects)	43-46

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Modifier Class & Examples	Functional Category	Primary Interaction with HA	Photothermal Conversion Efficiency (η %)	Activation Wavelength (nm)	Key Property Enhancements	Representative Applications	Biocompatibility/Toxicity Status & Validation	References
21. ELASTIN-LIKE POLYPEPTIDES (ELPs) **• $(VPGXG)_n$ sequences (X = guest residue)**	Osteogenic/Structural Support	Electrostatic, H-bonding; often engineered to include acidic functional groups to facilitate Ca^{2+} interaction.	N/A	N/A	**Thermally responsive (inverse phase change),** biocompatibility, genetic controllability, and presentation of biofunctional groups.	Injectable, thermally gelling bone fillers; templates for biomimetic mineralization; temperature-triggered drug delivery.	Biocompatible (*in vitro* & *in vivo*)	[47]
22. METAL-ORGANIC FRAMEWORKS (MOFs) **• Zeolitic Imidazolate Frameworks (ZIF-8)** **• MIL-series (e.g., MIL-100(Fe))**	Dual-Function	Physical encapsulation/coating; potential interaction via linker groups.	Variable (some PTT)	NIR (platform)	**High porosity and surface area** for drug/gas loading, and native catalytic or antibacterial activity (e.g., Zn^{2+}, Ag^{+} ions).	Drug delivery systems with high drug-carrying capacity; platforms for combination therapy (PTT, Chemodynamic therapy, chemotherapy); antibacterial coatings	Biocompatible (*in vitro* & *in vivo*)	[48]
23. CARBON NANOMATERIALS **• Graphene**	PTA / Mechanical	π-π stacking, electrostatic (GO is anionic), H-	High (NIR-II)	NIR-II	**GO/CNTs:** Excellent mechanical reinforcement, electrical	Mechanical reinforcement; conductive composites for	Generally biocompatible (*in vitro* & *in vivo*)	[49]

Modifier Class & Examples	Functional Category	Primary Interaction with HA	Photothermal Conversion Efficiency (η %)	Activation Wavelength (nm)	Key Property Enhancements	Representative Applications	Biocompatibility/Toxicity Status & Validation	References
Oxide (GO) • Carbon Nanotubes (CNTs) • Carbon Dots (CDs)		bonding, and covalent grafting.			conductivity, photothermal properties (NIR-II). **CDs:** Photoluminescence, low toxicity, ROS generation.	electroactive tissues; photothermal/photoacoustic agents; bio-imaging probes.		
24. SILICONES & PDMS • Polydimethylsiloxane (PDMS) • Silicone resins	Osteogenic/Structural Support	Physical blending requires the use of compatibilizers/surface-modified HA.	N/A	N/A	Flexibility, hydrophobicity, oxygen permeability, and long-term biostability. Can reduce the hardness of brittle HA ceramics.	Craniofacial devices (interface with soft tissues); otologic devices; composite coatings on flexible substrates.	Biocompatible (long-term *in vivo*)	[50,6]
25. DENDRIMERS & HYPERBRANCHED POLYMERS • PAMAM dendrimers • Boltorn® hyperbranched polyesters	Osteogenic/Structural Support	Multivalent electrostatic and/or covalent attachment via peripheral $–NH_2$ and/or –COOH	N/A	N/A	**Multivalency,** controlled structure for high-density functionalization, and nanoscale drug/PTA containers.	Multifunctional nanoparticles for targeted co-delivery of drugs, genes, and/or imaging agents; crosslinkers for composite materials.	Biocompatible (*in vitro* & *in vivo*)	[28,30]

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Modifier Class & Examples	Functional Category	Primary Interaction with HA	Photothermal Conversion Efficiency (η %)	Activation Wavelength (nm)	Key Property Enhancements	Representative Applications	Biocompatibility/Toxicity Status & Validation	References
26. BIOMIMETIC MINERALIZATION PEPTIDES • Dentin Matrix Protein-1 (DMP-1) peptides • Amelogenin-derived peptides • PolyAspartic acid (pAsp)	Osteogenic/Structural Support	Electrostatic and chelation interaction with Ca^{2+}mimics natural protein templates.	N/A	N/A	Direct and control HA nucleation under physiological conditions, forming nanostructures mimicking the structure of the tooth enamel and dentin.	Remineralization of dental caries; fabrication of ultra-strong nanocomposites through bottom-up approaches; bioactive coatings.	Biocompatible (*in vitro* & *in vivo*)	[51-53]
27. STIMULI-RESPONSIVE SMART POLYMERS • Poly(N-isopropylacrylamide) (PNIPAM) • pH-sensitive polymers (e.g., poly(histidine)) • Redox-sensitive (disulfide-linked) polymers	Dual-Function	Grafting-to or grafting-from methods; physical entrapment.	N/A	N/A	Temperature, pH, or redox-sensitive swelling/collapse, allowing for on-demand drug release or surface property change	"Smart" drug delivery systems responsive to tumor microenvironment (pH, temp); injectable thermally gelling bone pastes.	Biocompatible (*in vitro* & *in vivo*)	[50,6,54,55]

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Modifier Class & Examples	Functional Category	Primary Interaction with HA	Photothermal Conversion Efficiency (η %)	Activation Wavelength (nm)	Key Property Enhancements	Representative Applications	Biocompatibility/Toxicity Status & Validation	References
28. ENZYME-RESPONSIVE PEPTIDES/POLYMERS • Matrix metalloproteinase-9 (MMP)-cleavable peptides (e.g., GPLGVRG) • Alkaline phosphatase (ALP)-sensitive motifs	Dual-Function	Covalent attachment as a linker between HA and the drug.	N/A	N/A	Site-specific drug release is triggered by enzymes specifically overexpressed at the site of the disease. (e.g., MMPs in tumors, ALP in bone).	Targeted therapy of bone metastasis and osteosarcoma; activation of prodrug in bone tissue.	Biocompatible (*in vitro* & *in vivo*)	56-58,1

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