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Innovative hybrid nanostructures: pioneering advances in modern therapy

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Innovative hybrid nanostructures have revolutionized modern therapy by combining different materials at the nanoscale, offering unique synergistic properties that enhance their functionality. These advancements are pivotal in areas such as targeted drug delivery, photothermal and photodynamic therapy, and gene delivery, where they significantly improve therapeutic outcomes. The article discusses the synthesis methods and characterization techniques of HNSs, providing a comprehensive analysis of their mechanisms of action in various therapeutic applications. Highlighted case studies demonstrate their efficacy in treating conditions such as cancer, neurodegenerative diseases, and cardiovascular disorders, underscoring their potential to bridge existing gaps in medical treatments. The review also emphasizes the need for continued innovation and interdisciplinary collaboration to optimize these nanostructures for clinical applications. Future research should focus on enhancing biocompatibility, targeting capabilities, and integrating advanced imaging techniques and AI-driven applications to further improve the precision and efficacy of HNSs in therapy. These advancements herald a new era in medical treatment, offering transformative solutions for complex diseases.

KEYWORDS

hybrid nanostructures (HNSs), photothermal and photodynamic therapy, multifunctional nanostructures, gene delivery and editing, cancer therapy, cardiovascular diseases, neurodegenerative diseases, autoimmune diseases

1 Introduction

Nanotechnology enables precise interventions at the molecular level, improving targeted drug delivery, reducing side effects, and enhancing therapeutic efficacy (Cheng et al., 2023). Hybrid nanostructures (HNSs) combine different materials at the nanoscale, exhibiting synergistic properties that enhance their functionality for various therapeutic applications (Desouky et al., 2023). For instance, HNSs can integrate the benefits of both organic and inorganic materials, leading to improved stability, biocompatibility, and multifunctionality in treatments ranging from cancer to cardiovascular diseases (Yang et al., 2022). Foundational studies such as the work by Tang et al. (2012) on mesoporous silica nanoparticles have been pivotal in demonstrating the synthesis, biocompatibility, and drug delivery capabilities of these structures. This article provides a comprehensive analysis of HNS synthesis methods and characterization techniques, identifying effective approaches for creating multifunctional nanostructures. It explores mechanisms of action in therapies such as drug delivery, photothermal and photodynamic therapy, and gene delivery through specific case studies. Additionally, the article reviews clinical applications across various

diseases, offering insights into recent advancements and future research directions that can guide clinical practice and further innovation in the field.

2 Fundamentals of HNSs

HNSs are advanced materials that combine two or more distinct components at the nanoscale to exploit their synergistic properties for enhanced functionality. These components can vary widely in nature, including organic and inorganic materials, metals, polymers, or a combination of these. The integration of different materials at the nanoscale allows for the creation of novel structures with unique physical, chemical, and biological properties, making them highly versatile for various applications, especially in modern therapy (Povolotskaya et al., 2015).

2.1 Types of HNSs

Organic-inorganic HNSs, for instance, involve combining organic molecules like polymers with inorganic materials such as metals or semiconductors (Le et al., 2024). These hybrids enhance mechanical strength, electrical conductivity, and biocompatibility, making them ideal for drug delivery systems where stability and targeted delivery are crucial. Metallic-polymeric hybrids integrate metallic nanoparticles with polymers, used in photothermal therapy (PTT) for cancer treatment. The metallic part provides thermal response, while the polymer ensures biocompatibility and controlled therapeutic release (Silva et al., 2019). Inorganic-inorganic hybrids, combining different inorganic materials like metal oxides and nanoparticles, are used for antibacterial coatings (Tanveer et al., 2022). Titanium dioxide with silver nanoparticles, for example, provides photocatalytic activity and antimicrobial properties (Chand et al., 2020; Harun-Ur-Rashid et al., 2024). Organic-organic hybrids combine different organic materials, such as polymer-based nanocarriers with peptides for targeted drug delivery, enhancing targeting and therapeutic efficacy (Ribeiro et al., 2019). Hybrid quantum dot nanostructures involve the integration of quantum dots (QDs) with various materials to enhance their photophysical properties. Graphene quantum dots (GQDs) incorporated into polymer nanocomposites enhance fluorescence for bioimaging applications. The quantum dots provide superior optical properties, while the polymer matrix offers biocompatibility and mechanical support (Mansur et al., 2019).

2.2 Synthetic routes of HNSs

The synthesis of HNSs involves various methods tailored to combine distinct materials at the nanoscale effectively. For organic-inorganic hybrids, the sol-gel method transitions a system from a liquid "sol" to a solid "gel" phase, ensuring uniform nanoparticle dispersion in a polymer matrix, while *in situ* polymerization disperses inorganic nanoparticles in a monomer solution followed by polymerization, creating homogeneous nanocomposites. Metallic-polymeric hybrids are often created using chemical reduction, where metallic nanoparticles form within a polymer matrix via reduction of metal ions, and electrospinning, which produces nanofibers embedded with metallic nanoparticles from a solution containing both polymer and metal precursors. Inorganic-inorganic hybrids can be synthesized through co-precipitation, simultaneously precipitating two or more inorganic materials from a solution, or hydrothermal synthesis, which employs high-pressure and high-temperature conditions to create well-crystallized nanocomposites. Organic-organic hybrids are formed using self-assembly, where organic molecules and polymers organize into structures through non-covalent interactions, or layer-by-layer assembly, which sequentially adsorbs oppositely charged polymers to fabricate multilayered structures. Hybrid quantum dot nanostructures can be synthesized via solution-phase synthesis, forming nanoparticles in a solution followed by their incorporation into polymers, or ligand exchange, replacing quantum dot surface ligands with molecules that facilitate polymer integration. Table 1 providing a classification of different methods to synthesize HNSs for modern therapies, including specific examples.

2.3 Classification and applications of nanostructures in modern therapies

Nanostructures can be classified based on their dimensionality into zero-dimensional (0D), one-dimensional (1D), two-dimensional (2D), and three-dimensional (3D) (Tiwari et al., 2012). Each category possesses unique characteristics that make them suitable for specific therapeutic applications, including PTT, PDT, and gene therapy.

0D nanostructures, such as nanoparticles and quantum dots, have all three spatial dimensions confined to the nanoscale. These structures are extensively utilized in various therapies due to their high surface area and unique optical properties. Gold nanoparticles (AuNPs) are widely used for PTT. Their strong absorption in the near-infrared (NIR) region allows them to convert light into heat efficiently, leading to the localized ablation of cancer cells (Dheyab et al., 2023). Quantum dots (QDs) can act as photosensitizers, generating reactive oxygen species (ROS) upon light activation. This makes them effective in targeting and destroying cancer cells (Uprety and Abrahamse, 2022). Polymeric nanoparticles are designed for gene delivery, protecting genetic material from degradation and facilitating efficient cellular uptake (Khan et al., 2024).

1D nanostructures, including nanorods, nanotubes, and nanowires, have one dimension significantly larger than the other two. Their high aspect ratio provides unique mechanical and electrical properties beneficial for therapeutic applications. Gold nanorods (AuNRs) are preferred for their efficient light-to-heat conversion capabilities, making them ideal for targeted thermal ablation of tumors (Deinavizadeh et al., 2024). Carbon nanotubes (CNTs) can be functionalized with photosensitizers to enhance ROS production upon light activation, improving PDT efficacy (Naief et al., 2023). Nanowires are used as delivery vehicles for nucleic acids, enhancing transfection efficiency and promoting targeted gene editing (Inal et al., 2022).

TABLE 1 A classification of different methods to synthesize HNSs for modern therapies.

Type of HNS	Synthesis methods	Examples	Advantages	Limitations	References
Organic-inorganic	Sol-gel	TiO_2 nanoparticles in a polymer matrix	Uniform dispersion, good control	Potential for phase separation	Di et al. (2007)
	In situ polymerization	Silver nanoparticles in PMMA	Homogeneous nanocomposites	Complex synthesis process	Serrano-Claumarchirant et al. (2022)
Metallic-polymeric	Chemical reduction	Gold nanoparticles in PVP	High thermal/electrical conductivity	Possible nanoparticle aggregation, cost	Hussain et al. (2020)
	Electrospinning	Copper nanofibers in a polymer matrix	Controlled release, good dispersion	Equipment-intensive	Santos et al. (2018)
Inorganic-inorganic	Co-precipitation	Fe_3O_4 and SiO_2 nanoparticles	High thermal stability, enhanced activity	Brittleness, limited flexibility	Munasir et al. (2017)
	Hydrothermal synthesis	ZnO and TiO_2 nanostructures	Well-crystallized, high purity	Requires specialized equipment	Siwińska-Stefańska et al. (2019)
Organic-organic	Self-assembly	Polyethylene glycol and peptide nanostructures	Improved targeting, reduced toxicity	Stability issues, complex synthesis	Castelletto and Hamley, (2009)
	Layer-by-layer assembly	Polyelectrolyte multilayers for drug delivery	Precise control over layer composition	Time-consuming, complex process	Yuan et al. (2020)
Hybrid quantum dot	Solution-phase synthesis	CdSe quantum dots in a polymer matrix	Superior optical properties, biocompatibility	Potential quantum dot leakage, expensive	Cho et al. (2013)
	Ligand exchange	PbS quantum dots with thiol ligands	Enhanced integration, improved stability	Complex ligand exchange process	Teh et al. (2020)

2D nanostructures, such as nanosheets and nanoplates, have a thickness much smaller than their length and width, providing a large surface area for functionalization. Graphene oxide (GO) nanosheets exhibit excellent photothermal conversion efficiency and are used for thermal ablation of tumors (Lim et al., 2018). Molybdenum disulfide (MoS_2) nanosheets can be loaded with photosensitizers to enhance ROS production and improve treatment efficacy (Zhao et al., 2024). Layered double hydroxides (LDHs) are utilized for gene delivery due to their biocompatibility and ability to protect nucleic acids from degradation (Yu et al., 2020).

3D nanostructures encompass bulk materials with nanoscale features in three dimensions, including nanocages, nanoflowers, and nanospheres. These structures offer structural stability and multifunctionality. Gold nanocages are used for their hollow structure, which allows for efficient light absorption and heat generation, making them suitable for cancer treatment (Hu et al., 2021). Porous silicon nanospheres can be loaded with photosensitizers and drugs, providing a combination of PDT and chemotherapy (Kang et al., 2022). 3D DNA nanostructures, such as DNA origami, are used for precise gene delivery and editing, offering high loading capacity and targeted delivery (Tang et al., 2023).

2.4 Recent developments in HNSs

Recent advancements highlight the emergence of nanobubbles as eco-friendly HNSs with promising biomedical applications. Jannesari et al. have developed reduced graphene oxide/copper peroxide (rGO/CuO_2) nanocomposites that deliver *in situ* oxygen nanobubbles (O_2 NBs) to combat bacterial infections (Jannesari et al., 2020). The presence of rGO allows for the decomposition of CuO_2 into O_2 NBs in a controllable and prolonged manner, effectively battling methicillin-resistant *Staphylococcus aureus* (MRSA) and other bacteria by enhancing reactive oxygen species (ROS) generation and inducing mechanical disruptions via near-infrared laser irradiation. Another study by Jannesari et al. introduced oxygen-rich rGO/ZnO_2-Ag nanoframeworks as suppliers of O_2 NBs with dual pH-and-temperature-sensitive behavior (Jannesari et al., 2023b). These nanoframeworks demonstrated significant antibacterial properties against MRSA by facilitating the generation and controlled release of O_2 NBs, thereby enhancing ROS production and utilizing the inherent photothermal properties of rGO to combat bacterial infections more efficiently. These recent developments underscore the potential of nanobubbles in biomedical applications, particularly in hybrid forms, offering a new avenue for eco-friendly and efficient therapeutic strategies.

Modern developments in HNSs reveal the promise of triboelectric nanogenerator (TENG) devices as sustainable HNSs for biomedical applications. These devices are particularly effective in converting waste energy for treatments and minimizing long-term side effects. Jannesari et al. developed a polypyrrole-graphene oxide (PPy-GO) composite TENG with superior electrical outputs and bactericidal activity (Jannesari et al., 2023a). The PPy-GO TENG, fabricated through a facile electrodeposition route, exhibited high electrical outputs with an open-circuit voltage of 413.2 V and a short-circuit current of ~41 μA. This device demonstrated marked bactericidal activity against *S. aureus*, attributed to enhanced ROS generation and cellular membrane rupture. Another study by Jannesari et al. (2024) investigated the antibacterial properties of TENGs by examining the effects of charge

polarity and host material composition. They found that positively charged substrates inhibited bacterial growth through electrostatic interactions, while negatively charged substrates, particularly graphene oxide (GO), exhibited strong antibacterial properties by generating ROS. The study demonstrated that TENGs could harness waste energy to provide self-powered antibacterial treatments, highlighting their potential for advanced wearable healthcare and biomedical applications. This eco-friendly technique offers a promising approach to reducing long-term side effects associated with traditional nanostructures.

2.5 Characterization of HNSs

Characterization of HNSs is vital for understanding their properties and optimizing their performance in therapeutic applications. For organic-inorganic hybrids, Transmission Electron Microscopy (TEM) provides detailed images of internal structures, while Fourier Transform Infrared Spectroscopy (FTIR) identifies chemical bonds and confirms material integration. Metallic-polymeric hybrids are examined using Scanning Electron Microscopy (SEM) for surface morphology and X-ray Diffraction (XRD) for crystalline structure analysis. Inorganic-inorganic hybrids benefit from Energy Dispersive X-ray Spectroscopy (EDS) for elemental composition and Thermogravimetric Analysis (TGA) for thermal stability. Organic-organic hybrids are characterized using Nuclear Magnetic Resonance (NMR) Spectroscopy for molecular structure and Gel Permeation Chromatography (GPC) for molecular weight distribution. Hybrid quantum dot nanostructures are analyzed with Photoluminescence (PL) Spectroscopy for optical properties and Dynamic Light Scattering (DLS) for size distribution and stability.

3 Mechanisms of action in therapy

3.1 Drug delivery systems

HNSs have revolutionized drug delivery systems by providing innovative mechanisms for drug loading and release, as well as precise targeting strategies. The mechanisms of drug loading typically involve encapsulating therapeutic agents within the nanostructure or attaching them to the surface via covalent or non-covalent bonds. This encapsulation ensures the stability and bioavailability of the drugs (Huang et al., 2019; Harun-Ur-Rashid et al., 2023a; Harun-Ur-Rashid et al., 2023b). For drug release, stimuli-responsive strategies are often employed, where the nanostructure responds to specific triggers such as pH, temperature, or light to release the drug in a controlled manner.

Targeting strategies for HNSs are designed to increase the efficacy of drug delivery by directing the therapeutic agents precisely to the diseased cells while minimizing impact on healthy tissues. Active targeting involves modifying the nanostructure surface with ligands, antibodies, or peptides that recognize and bind to specific receptors overexpressed on target cells. This approach enhances cellular uptake and improves therapeutic outcomes. Passive targeting exploits the enhanced permeability and retention (EPR) effect, which allows nanostructures to accumulate in tumor tissues due to their leaky vasculature (Subhan et al., 2021). Both strategies have shown significant efficacy in preclinical and clinical studies, offering promising avenues for cancer therapy and beyond.

3.2 Photothermal and photodynamic therapy

Photothermal therapy (PTT) and photodynamic therapy (PDT) are cutting-edge approaches that utilize light to activate HNSs for therapeutic purposes (Asadian et al., 2023). PTT is a minimally invasive therapeutic approach that utilizes light energy to generate heat for the ablation of cancer cells. The principle behind PTT involves the use of photothermal agents, such as gold nanoparticles, carbon nanotubes, or HNSs, which can absorb near-infrared (NIR) light and convert it into heat. This localized heating effect leads to the destruction of cancer cells through hyperthermia, which disrupts cellular structures and induces apoptosis. Zhang et al. enhanced the bactericidal performance of polymeric nanopillars by integrating PTT (Zhang, et al., 2023). Using a cost-effective anodized aluminum oxide (AAO) template and Layer-by-Layer (LbL) assembly with tannic acid (TA) and iron ion (Fe^{3+}), they fabricated hybrid nanopillars. These HNSs achieved over 99% bactericidal efficacy against Gram-negative *Pseudomonas aeruginosa* and Gram-positive *S. aureus*.

PDT involves the use of photosensitizing agents that, upon activation by specific wavelengths of light, produce reactive oxygen species (ROS) that induce cellular damage and apoptosis. Imanparast et al. designed and fabricated a microfluidic chip to synthesize PpIX-loaded micelles, transforming PpIX into photo-protoporphyrin (PPP) and integrating it with bovine serum albumin (BSA) and hollow gold nanoshells (HGN) (Imanparast et al., 2023). The resulting HGN-BSA-CTAB-PPP HNSs, sized at 120 nm with a strong absorption peak at 670 nm, showed significant cytotoxicity against MDA-MB-231 and 4T1 cancer cells at low radiation doses (<10 J/cm^2). This study highlights the potential of albumin-based HNSs for enhancing PDT efficacy.

The integration of nanotechnology has significantly advanced the efficiency and specificity of both PTT and PDT. Nanomaterials such as HNSs combine the benefits of multiple materials, enhancing their functionality and therapeutic outcomes. For instance, Özkan et al. developed HNSs composed of a red-emitting conjugated oligomer (COL) and gold nanoparticles (Au-NPs) using a one-pot synthetic method (Özkan et al., 2020). The conjugated oligomer served as both a reducing agent and a matrix for the Au-NPs. These HNSs (COL-Au-NPs) demonstrated both photodynamic and photothermal activity against Gram-positive and Gram-negative bacterial strains. They exhibited high photostability and thermal reversibility. The dark cytotoxicity of COL-Au-NPs towards pathogens and mammalian breast cancer cells (MCF-7) was significantly reduced upon complexation with cucurbit [7]uril, while their light-induced cytotoxicity was preserved when irradiated with a 915 nm laser for PTT and white light for PDT.

3.3 Gene delivery and editing

HNSs offer groundbreaking techniques for gene delivery and editing, addressing challenges associated with conventional

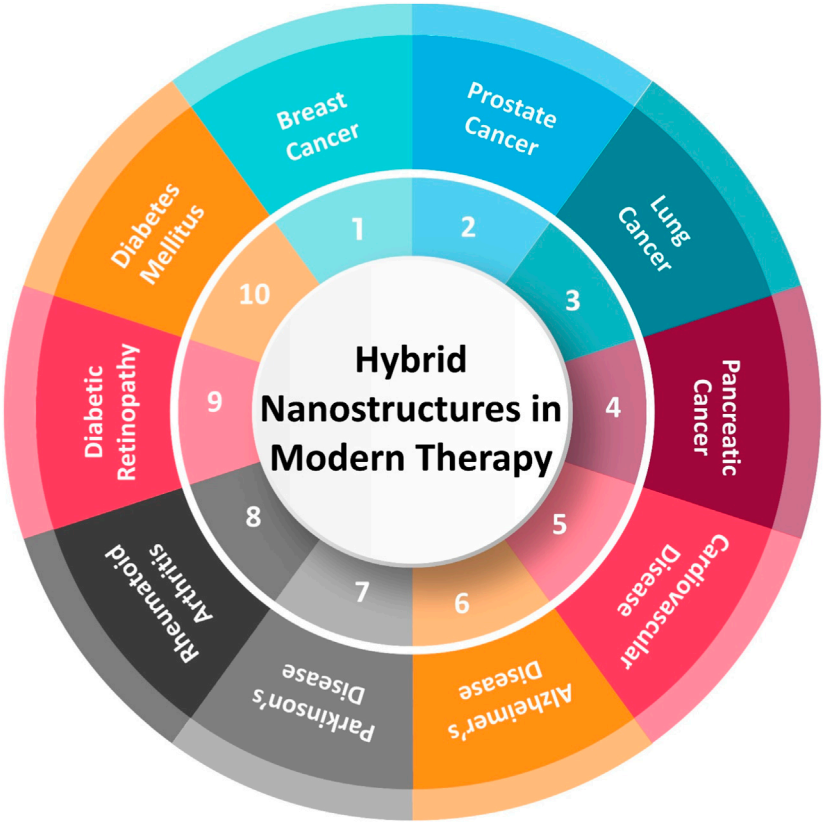

FIGURE 1
Applications of hybrid nanostructures (HNSs) in modern therapy.

methods. These nanostructures protect genetic material from degradation and facilitate efficient cellular uptake (Tang et al., 2023b). Polymeric nanoparticles and lipid-based hybrids are widely used to deliver nucleic acids such as DNA, RNA, and CRISPR-Cas9 components. Success stories in gene delivery include the use of lipid nanoparticles for mRNA vaccines, which have proven highly effective in recent applications like COVID-19 vaccines (Lee et al., 2023). However, challenges remain, including potential immunogenicity and the need for precise control over gene expression. HNSs are being continuously refined to overcome these hurdles, with ongoing research focusing on enhancing delivery efficiency and minimizing side effects.

4 HNSs in modern therapy

HNSs represent a cutting-edge advancement in the field of modern therapy, offering multifaceted approaches to diagnose, treat, and manage various diseases. By combining different materials at the nanoscale, these nanostructures exhibit unique properties that enhance their therapeutic potential. They can target specific cells or tissues, improve drug delivery efficiency, overcome biological barriers, and reduce side effects, making them highly effective in treating complex conditions. HNSs have shown significant promise in treating various diseases, including cancer and cardiovascular disorders. The foundational work by Medintz et al. (2008) on the intracellular delivery of quantum dot-protein cargos mediated by cell-penetrating peptides is a key example of how HNSs can be effectively utilized for targeted therapy. Additionally, the work by Silva et al. (2012) on the cellular transfer of magnetic nanoparticles provides crucial insights into the mechanisms of action and the impact of these nanoparticles on cell tracking by magnetic resonance imaging. Figure 1 visually summarizes the therapeutic applications of hybrid nanostructures across various medical fields, including cancer therapy, cardiovascular diseases, neurodegenerative diseases, autoimmune diseases, diabetic retinopathy, and gestational diabetes mellitus.

4.1 Targeted drug delivery and enhanced efficacy

HNSs have revolutionized the field of targeted drug delivery by combining multiple materials to optimize therapeutic outcomes. These structures can be engineered to possess specific surface modifications, such as ligands, antibodies, or peptides, which allow for precise targeting of diseased cells while sparing healthy tissues. This specificity enhances the efficacy of the drug delivery system, as demonstrated in various clinical applications including cancer therapy. For instance, plasmonic platinum nanoclusters (PtNC) with a protein scaffold have shown superior efficacy in treating breast cancer by enhancing tumor delivery and reducing

TABLE 2 Comprehensive comparison of clinical applications and case studies of HNSs.

Therapeutic area	Type of HNS	Mechanism of action	Application	Efficacy	Safety	Advantages	Limitations	Ref
Cancer therapy	Plasmonic platinum nanocluster (PtNC) with protein scaffold (ABP-HBVC)	Light-to-heat conversion, acoustic wave generation, enhanced tumor delivery	Breast cancer treatment	Superior efficacy in breast cancer xenograft mice	Negligible resistance and side effects, rapid urinary excretion	Precise control, non-invasive, high resolution, effective delivery, low toxicity	Developing a clinically feasible PTT and photoacoustic imaging (PAI) material	Jeong et al. (2024)
	Luminescent-superparamagnetic Ag_2S-Fe_3O_4 (AS-SPION) hybrid nanoparticles	Imaging guided enhanced PDT-PTT combination therapy, drug delivery, ROS generation, apoptosis/necrosis induction	Prostate cancer treatment	Strong emission in the medical imaging window, effective PDT-PTT combination therapy, significant cell death in prostate cancer cells	Non-toxic to L929 cells, approved for use in clinical settings (FDA approved 5-ALA)	Dual-modality imaging, enhanced PTT and PDT, effective drug delivery	Needs further validation in clinical trials, optimization of treatment parameters for *in vivo* applications	Aydindogan et al. (2023)
	DNA and RNA hybrid origami nanostructures	Degrades RNA, releases antisense oligonucleotides (ASON) to exert antitumor effect	KRAS-mutated non-small cell lung cancer (NSCLC) treatment	Inhibited cell proliferation and tumor progression in cellular and *in vivo* studies	High safety, specific targeting, reduced side effects	Universal strategy, potential for targeting various pathogenic genes and diseases, high specificity	Requires further clinical validation, complex synthesis and assembly processes	Ding et al. (2023)
	Gold and Copper ultrasmall-in-nano architectures (AuNAs, CuNAs)	Modulate gene and protein expression of EMT-related factors, reduce tumor growth and metastasis progression	Treatment of pancreatic cancer metastasis	Reduced tumor growth and metastasis progression, altered gene and protein expression of EMT-related factors	Non-toxic metal concentrations, efficient excretion of metals	Dual-metal nanostructures, effective metastasis modulation, biodegradable silica shell	Needs further clinical validation, potential metal persistence if not properly excreted	Zamborlin et al. (2023)
	PTX@ANG/FA-NPs (Paclitaxel-loaded Angiopep-2/Folate-modified PLGA nanoparticles)	Overcomes BBB, tumor targeting, promotes apoptosis, inhibits cell migration	Glioblastoma treatment	Inhibited cell proliferation and tumor progression, improved BBB penetration	Negligible side effects, biocompatible	Dual-targeting, improved pharmacokinetics, efficient BBB permeability, reduced off-target effects	Needs further clinical validation and optimization for human application	Ou et al. (2023)
Cardiovascular diseases	Biomimetic nanomaterials, such as noble metal-based nanozymes and biomimetic nanocarriers	Enzymatic catalytic activity, targeted drug delivery, ROS scavenging, anti-inflammatory	Diagnosis and treatment of cardiovascular diseases, including atherosclerosis and myocardial infarction	Enhanced disease detection and treatment, reduced oxidative stress and inflammation, improved drug delivery	Good biocompatibility, reduced toxicity, effective targeting	Multifunctional, mimic natural biological features, improved pharmacokinetics and targeting	Requires further optimization for biostability, biodistribution, biosafety, and clinical application	Gong et al. (2023)
Neurodegenerative diseases	Lipid-polymer hybrid (LPH) nanoparticles (cationic and anionic)	Enhanced drug loading, amyloid inhibition, improved brain bioavailability, nose-to-brain targeting	Intranasal delivery of rivastigmine hydrogen tartrate (RIV-HT) for Alzheimer's treatment	Improved amyloid inhibition, enhanced brain concentrations, better pharmacokinetics	Safe delivery system, no significant histological damage to nasal mucosa	High brain bioavailability, reduced oral side effects, concentration-dependent amyloid inhibition, improved pharmacokinetics	Requires further validation in clinical trials, optimization for broader applications	Nikita et al. (2023)
	Boron nitride nanotube (BNNT) and boron nitride nanolayer (BNNL)	Inhibition of α-synuclein protein aggregation, destabilization of amyloids	Treatment of Parkinson's disease	Destabilization and weakened aggregation of α-synuclein proteins	Safe, biocompatible	Tunable properties, highly capable of structural conversions in α-synuclein protein, effective amyloid inhibition	Requires further experimental validation, optimization for clinical application	Smida et al. (2023)

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TABLE 2 (*Continued*) Comprehensive comparison of clinical applications and case studies of HNSs.

Therapeutic area	Type of HNS	Mechanism of action	Application	Efficacy	Safety	Advantages	Limitations	Ref
Antimicrobial activity	LBG-s-AgNPs@ g-C_3N_4 NS HNSs	Photocatalytic degradation, antibacterial activity, reduced recombination of electrons and holes	Photodegradation of hazardous dyes, antibacterial activity	~100% RhB degradation and ~99% MB degradation in 160 min, highest kinetic rates for MB and RhB degradation, superior antibacterial activity	Environmentally friendly synthesis, no toxic chemicals used	High photocatalytic performance, effective against Gram-ve/Gram + ve pathogens, efficient dye degradation	Needs to be tested further for long-term stability and effectiveness in various environmental conditions	Pandey et al. (2024)
Autoimmune diseases	TNF-α-targeted aptamer-modified tetrahedral frame nucleic acid (Tapt-tFNAs) carrying methotrexate (MTX)	Inhibition of NF-κB and ERKs signaling pathways, targeting TNF-α, enhanced bioavailability and stability of MTX	Treatment of rheumatoid arthritis (RA)	Promoted M2 macrophage expression, reduced inflammatory factor infiltration, decreased CIA lesions, and bone and cartilage defects	More concentrated in inflammatory joints, reduced systemic toxicity	Targeted delivery, enhanced stability and bioavailability of MTX, reduced side effects	Requires further clinical validation and optimization for broader applications	Zhang et al. (2023)
Diabetic retinopathy (DR)	Chitosan-modified 5-Fluorouracil Nanostructured Lipid Carriers (CS-5-FU-NLCs)	Sustained drug release, deep penetration to the posterior segment of the retina, antiangiogenic effect	Non-invasive treatment of diabetic retinopathy	Higher and sustained drug release, confirmed antiangiogenic effect *in vivo*	Non-irritant nature confirmed by HET-CAM model	Non-invasive, enhanced drug delivery and sustained release, reduced need for expertise	Requires further clinical validation, optimization for broader applications	Sharma et al. (2023)
Gestational diabetes mellitus (GDM)	Nanostructured lipid carriers (NLC) loaded with glibenclamide	Enhanced skin permeation, sustained drug release, improved bioavailability	Transdermal delivery of glibenclamide for GDM treatment	Higher drug release, 2.5-fold higher flux and permeation coefficient, improved bioavailability	Non-toxic as indicated by cell viability studies	Improved skin permeation, sustained drug action, better patient compliance	Requires further clinical validation, optimization for human application	Sudheer et al., (2024)

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side effects. Similarly, luminescent-superparamagnetic hybrid nanoparticles have proven effective in prostate cancer treatment by combining PDT and PTT, resulting in significant cell death with minimal toxicity. These examples highlight the transformative potential of HNSs in improving drug bioavailability, reducing systemic toxicity, and ensuring targeted therapeutic action.

4.2 Multifunctional therapeutic applications

The multifunctionality of HNSs extends their application beyond drug delivery to include diagnostic and therapeutic roles in various diseases. This versatility is particularly evident in the treatment of neurodegenerative diseases and cardiovascular conditions. For example, lipid-polymer hybrid nanoparticles have been developed for the intranasal delivery of rivastigmine, significantly improving amyloid inhibition and brain bioavailability for Alzheimer's treatment. In cardiovascular therapy, biomimetic nanomaterials, such as noble metal-based nanozymes, offer enzymatic catalytic activity and targeted drug delivery, enhancing the diagnosis and treatment of conditions like atherosclerosis and myocardial infarction. Additionally, boron nitride nanotubes (BNNT) have shown promise in destabilizing α-synuclein proteins in Parkinson's disease, highlighting their potential in neurodegenerative disease management. These multifunctional applications underscore the importance of HNSs in providing comprehensive therapeutic solutions that integrate treatment, diagnosis, and monitoring, thereby paving the way for innovative approaches in modern therapy.

Table 2 provides a comprehensive comparison of the clinical applications and case studies of various HNSs, highlighting their mechanisms of action, applications, efficacy, safety, advantages, and limitations. These innovative solutions showcase the transformative impact of nanotechnology in healthcare and underscore the importance of continued research and development in this promising field.

5 Future perspectives and directions

5.1 Emerging trends

The field of HNSs is poised for significant advancements, with several emerging trends shaping its future. One promising trend is the development of multifunctional nanostructures capable of simultaneous diagnosis and therapy, known as theranostics. These nanostructures can target specific disease sites, deliver therapeutic agents, and monitor treatment responses in real-time, providing a comprehensive approach to disease management. For example, polydopamine-based multifunctional HNSs are particularly suitable for treating cancer and neurodegenerative diseases, offering benefits such as improved targeting, biocompatibility, and minimized side effects (Battaglini et al., 2024). Polydopamine-based HNSs have superior biocompatibility and targeting efficiency compared to other multifunctional nanostructures.

Thermal ablation treats hepatocellular carcinoma but often leaves tumor residues that cause recurrence. The biodegradable polymeric nanoparticle@(131I-Hyp) targets and eliminates these residues, offering fluorescence imaging, SPECT imaging, and necrosis-targeted radiotherapy (Bao et al., 2024). This nanoparticle is composed of iodine-131-labeled hypericin (131I-Hyp) as the core and an amphiphilic copolymer shell of poly (ethylene glycol)-block-poly (ε-caprolactone) (PEG–PCL). This material is able to show its multifunctional capabilities, including imaging and targeted radiotherapy, which are not commonly combined in other nanostructures.

Another innovation is the use of biodegradable and biocompatible materials to minimize long-term toxicity and environmental impact. Researchers are also exploring the potential of HNSs in immunotherapy, where they can modulate immune responses to enhance the efficacy of treatments for cancer and autoimmune diseases (Angelopoulou, 2024; Moon et al., 2024; Patra et al., 2024). Additionally, the integration of nanostructures with advanced imaging techniques is enabling more precise and early detection of diseases. For instance, 50-nm gas-filled protein nanostructures enable access to lymphatic cells by ultrasound technologies, providing a novel method for early disease detection and monitoring (Shen et al., 2024). These nanostructures were selected for their innovative approach to enabling access to lymphatic cells by ultrasound technologies.

5.2 Technological advancements

Significant strides in synthesis and characterization technologies are driving the evolution of HNSs. Advanced synthesis methods, such as microfluidic systems and self-assembly techniques, allow for the precise control over size, shape, and composition of nanostructures, enhancing their functionality and effectiveness (Petrova et al., 2024; Du et al., 2024). Characterization technologies, including high-resolution electron microscopy and spectroscopy, provide detailed insights into the structural and functional properties of nanostructures, facilitating their optimization for specific applications (Jagadeesh et al., 2024; Gupta et al., 2024). Furthermore, the integration of HNSs with emerging technologies such as artificial intelligence (AI) and personalized medicine is opening new frontiers in healthcare. AI can analyze large datasets to predict the behavior of nanostructures and personalize treatments based on individual patient profiles, improving outcomes and reducing adverse effects (Chugh et al., 2024).

5.3 Strategic recommendations

For researchers and clinicians, several strategic recommendations can guide the future development and application of HNSs. Researchers should focus on interdisciplinary collaboration, combining expertise from materials science, biology, medicine, and engineering to develop innovative solutions. Clinicians should be involved in the early stages of research to ensure that the developed nanostructures meet clinical needs and can be seamlessly integrated into existing treatment protocols. Additionally, it is crucial to invest in robust preclinical and clinical studies to validate the safety and efficacy of HNSs before their widespread adoption. Policymakers and funding agencies should support collaborative research efforts and create frameworks that facilitate the translation of laboratory findings into clinical practice.

6 Conclusion

HNSs have significant potential in modern therapy, demonstrated by their multifunctionality for diagnosis and therapy, reduced toxicity through biodegradable materials, and enhanced treatment efficacy in immunotherapy. They show promise in treating residual tumors post-thermal ablation and advancing therapies for cancer, neurodegenerative diseases, and cardiovascular conditions. Future research should refine HNSs for better biocompatibility and targeted delivery, explore their use in personalized medicine and AI-driven applications, and validate their safety and efficacy through comprehensive studies. Integrating advanced imaging techniques with HNSs could also improve early disease detection and monitoring. The continuous evolution of this technology, supported by interdisciplinary collaboration and strategic research, can revolutionize healthcare and provide innovative solutions for complex medical challenges.

Author contributions

MH-U-R: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Resources, Software, Supervision, Validation, Visualization, Writing–original draft, Writing–review and editing. IJ: Conceptualization, Data curation, Formal Analysis, Methodology, Validation, Writing–original draft, Writing–review and editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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