Publishing Excellence
Inspiring Progress
ARISTON PUBLICATIONS

BioMed and BioSci Advances

ISSN: 0000-0000 www.aristonpubs.com/biomed-and-biosci-advances https://doi.org/10.69626/bba.2024.0003

REVIEW ARTICLE

Nanoparticles for Advanced Drug Delivery Systems: Innovations, Applications, and Future Perspectives in Nanomedicine

Sadik Tyagi [1], Mohd Aarim[1], Salman Khan [2], Bushra Ahmad [1], Muzammil Liyakat Mir [3], Faiqua Haque[3], Suhaima Safdar [3], Amreen Fatima [3], Nuzhat Parveen [4], G.G.H.A. Shadab [3,*]

ABSTRACT: Nanotechnology, first conceptualized by Richard Feynman in 1959, has revolutionized science and medicine by enabling precise manipulation at the nanoscale. Nanoparticles (NPs), defined as structures with at least one dimension below 100 nm, exhibit unique physicochemical properties that make them indispensable in biomedical applications, particularly in diagnostics and drug delivery. Their high surface-area-to-volume ratio, tunable surface chemistry, and ability to encapsulate therapeutic agents allow for enhanced pharmacokinetics, targeted tissue delivery, and reduced systemic toxicity. In oncology, RNA-conjugated nanoparticles enable selective drug release at tumor sites, minimizing off-target effects. Polymeric nanoparticles—such as liposomes, dendrimers, and silica-based carriers—improve drug solubility, stability, and bioavailability, optimizing therapeutic outcomes. Green nanotechnology further advances sustainability by employing plant-based synthesis methods, reducing environmental impact while maintaining efficacy. DNA nanotechnology represents another frontier, where programmable nanostructures facilitate precision medicine through gene correction and personalized therapies. Despite these advancements, challenges persist in regulatory compliance, safety, and ethical considerations. Ensuring nanoparticle biocompatibility, long-term toxicity profiles, and scalable manufacturing remains critical for clinical translation. Regulatory frameworks must evolve to address these concerns while fostering innovation. This review comprehensively examines nanoparticle synthesis, characterization techniques, and functional applications in drug delivery. It highlights breakthroughs in nanobiotechnology, including gene therapy and stimuli-responsive systems, while addressing barriers to commercialization. By integrating interdisciplinary research, nanotechnology continues to redefine medical paradigms, offering transformative solutions for cancer, neurodegenerative disorders, and infectious diseases. The future of nanomedicine lies in harmonizing innovation with sustainability, ensuring safe and equitable healthcare advancements.

Keywords: Nanotechnology, Nanoparticle Drug Delivery, Liposomes and Dendrimers, Green Nanomedicine, DNA Nanotechnology, Targeted Cancer Therapy.

Received: 13 August 2024; Revised: 10 October 2024; Accepted: 07 November 2024; Published Online: 24 November 2024

[1] Department of Biochemistry, Aligarh Muslim University, Aligarh-202002, India.
[2] Department of Chemistry, Aligarh Muslim University, Aligarh-202002, India.
[3] Cytogenetic and Molecular Toxicology Laboratory, Section of Genetics Department of Zoology, Aligarh Muslim University, Aligarh-202002, India.
[4] Zoology Section, Women's College, Aligarh Muslim University, Aligarh-202002, India.

* Author to whom correspondence should be addressed: gghas.amu@gmail.com (G. G. H. A. Shadab)

1. INTRODUCTION

Nanotechnology, a transformative scientific discipline that involves the manipulation of matter at the atomic and molecular scale, has revolutionized modern medicine, materials science, and engineering since its conceptual foundation was laid by physicist Richard Feynman in his seminal 1959 lecture, *"There's Plenty of Room at the Bottom"* [1]. This visionary discourse proposed that materials could be engineered at the nanoscale to exhibit novel

properties, a prediction that has since materialized through groundbreaking advancements in nanoparticle (NP) research. Defined as particulate structures with at least one dimension between 1 and 100 nanometers (nm), NPs exhibit unique physicochemical properties—such as quantum confinement effects, enhanced surface reactivity, and tunable optical characteristics—that distinguish them from their bulk counterparts [2]. These attributes have positioned NPs at the forefront of biomedical innovation, particularly in drug delivery, diagnostics, and regenerative medicine.

The structural complexity of NPs is a key factor in their functionality. A typical NP consists of three distinct layers: (a) a surface layer, often modified with polymers, surfactants, or biomolecules to enhance stability and targeting; (b) a shell layer, which may differ in composition from the core; and (c) the core, which defines the NP's primary therapeutic or diagnostic function [3]. This layered architecture enables precise control over drug encapsulation, release kinetics, and interactions with biological systems. For instance, liposomes—spherical vesicles composed of phospholipid bilayers—can encapsulate hydrophilic drugs within their aqueous core and hydrophobic agents within the lipid membrane, thereby improving solubility and bioavailability [4]. Similarly, dendrimers, with their highly branched, three-dimensional structures, offer a high density of functional groups for drug conjugation and targeted delivery [5].

One of the most compelling applications of NPs lies in oncology, where they address critical limitations of conventional chemotherapy, including systemic toxicity, poor biodistribution, and multidrug resistance. Polymeric nanoparticles, such as those made from poly(lactic-co-glycolic acid) (PLGA), degrade controllably in physiological environments, releasing chemotherapeutic agents in a sustained manner at tumor sites via the enhanced permeability and retention (EPR) effect [6]. Gold nanoparticles (AuNPs), when functionalized with tumor-specific ligands (e.g., antibodies or peptides), enable active targeting, ensuring selective accumulation in cancer cells while sparing healthy tissues [7]. Furthermore, AuNPs can be engineered for photothermal therapy, where near-infrared (NIR) irradiation induces localized hyperthermia, selectively destroying malignant cells [8]. Another paradigm-shifting application is RNA interference (RNAi) therapy, where small interfering RNA (siRNA) molecules are conjugated to NPs to silence oncogenes with high specificity, offering a potent strategy for precision medicine [9].

Beyond therapeutics, NPs have revolutionized diagnostics and medical imaging. Quantum dots (QDs), semiconductor NPs with superior fluorescence properties, provide high-resolution imaging for early cancer detection [10]. Magnetic nanoparticles (MNPs), such as iron oxide NPs, enhance contrast in magnetic resonance imaging (MRI), enabling non-invasive tracking of disease progression [11]. The bio-barcode assay, an ultrasensitive diagnostic technique, leverages gold NPs and DNA amplifiers to detect disease biomarkers at femtomolar concentrations—far surpassing the sensitivity of conventional assays [12]. Such innovations underscore the potential of NPs to bridge the gap between diagnostics and therapy, giving rise to theranostics—an integrated approach that combines treatment and real-time monitoring of therapeutic response [13].

Despite these advancements, the clinical translation of NPs faces significant challenges. Regulatory hurdles arise from the inherent heterogeneity of NPs in terms of size, shape, surface charge, and degradation profiles, necessitating rigorous standardization for reproducibility and safety [14]. Toxicity concerns, particularly with metal-based NPs (e.g., silver or cadmium-based QDs), include oxidative stress, inflammatory responses, and long-term accumulation in vital organs [15]. For example, while gold NPs are generally considered biocompatible, their surface coatings and aggregation tendencies can influence cytotoxicity and immune recognition [16]. Similarly, polymeric NPs must undergo extensive biodegradability testing to ensure they do not elicit adverse immune reactions or accumulate in tissues [17].

Green nanotechnology has emerged as a sustainable alternative, emphasizing eco-friendly synthesis methods to mitigate environmental and health risks. Plant-mediated NP synthesis, utilizing phytochemicals as reducing and stabilizing agents, offers a cost-effective and scalable approach while minimizing toxic byproducts [18]. Microorganism-assisted synthesis, employing bacteria or fungi, further enhances the biocompatibility of NPs for medical applications [19]. Another promising frontier is DNA nanotechnology, where programmable DNA origami structures enable the design of nanocarriers with atomic precision, facilitating targeted drug delivery and controlled release [20].

Ethical and societal considerations also play a pivotal role in the adoption of nanomedicine. The potential for gene-editing NPs to permanently alter human DNA raises questions about long-term consequences and equitable access to advanced therapies [21]. Additionally, the patenting and commercialization of nanotechnologies may create disparities in healthcare accessibility, particularly in low-resource settings [22]. Policymakers and researchers must collaborate to establish global regulatory frameworks that ensure safety without stifling innovation.

Looking ahead, interdisciplinary research will be crucial in overcoming existing barriers. Advances in computational modeling can optimize NP design, predicting interactions with biological systems before in vivo testing [23]. Stimuli-responsive NPs, engineered to release drugs in response to pH, temperature, or enzymatic triggers, represent the next generation of smart therapeutics [24]. Furthermore, 3D bioprinting combined with NPs may enable the fabrication of personalized tissue scaffolds for regenerative medicine [25].

This review provides a comprehensive analysis of NP synthesis, characterization techniques, and biomedical applications, with a focus on drug delivery systems. It highlights recent breakthroughs in cancer nanomedicine, gene therapy, and green nanotechnology, while addressing unresolved challenges in toxicity, scalability, and regulation. By integrating cutting-edge

research from materials science, biology, and engineering, nanotechnology is poised to redefine healthcare paradigms, offering transformative solutions for some of the most pressing medical challenges of the 21st century.

2. THE NANOSCALE REALM OF BIOLOGICAL SYSTEMS

Biological processes predominantly occur at the nanoscale, where nature has perfected molecular interactions over millions of years of evolution. This intricate world operates with remarkable precision, with essential biomolecules such as hemoglobin—the oxygen-carrying protein in red blood cells—measuring just 5.5 nanometers in diameter. Similarly, the DNA double helix, which encodes genetic information, has a width of approximately 2 nanometers, demonstrating how life's fundamental processes unfold at dimensions invisible to the naked eye [19].

The convergence of nanotechnology and biology has opened new frontiers in medicine by enabling researchers to develop tools and therapies that operate at this same scale. Unlike conventional medical treatments, which often affect both healthy and diseased tissues, nanoscale interventions can be engineered for precision targeting, minimizing side effects while maximizing therapeutic efficacy. A prime example is the bio-barcode assay, a revolutionary diagnostic technique that leverages gold nanoparticles functionalized with antibodies and DNA barcodes to detect disease biomarkers at ultra-low concentrations [20]. Originally developed for prostate cancer detection, this method has demonstrated sensitivity far surpassing traditional diagnostic assays, capable of identifying biomarkers at concentrations as low as attomolar levels. Its adaptability allows for the detection of various disease markers, making it a versatile tool for early diagnosis and personalized medicine [20].

A key advantage of nanoscale materials is their exceptionally high surface-area-to-volume ratio, which dramatically enhances their chemical reactivity compared to bulk materials (Figure 1). This property is particularly valuable in biomedical applications, where nanoparticle surfaces can be modified with targeting ligands, drugs, or imaging agents to improve their functionality. For instance, in drug delivery, nanoparticles with large surface areas can carry higher payloads of therapeutic agents while maintaining stability in biological environments. Similarly, in diagnostics, the increased surface reactivity of nanoparticles allows for more efficient binding to biomarkers, improving detection sensitivity [19].

The implications of nanoscale biology extend beyond diagnostics and therapeutics. Researchers are exploring nanoscale biosensors capable of real-time monitoring of physiological processes, enabling early detection of diseases such as cancer, diabetes, and neurodegenerative disorders. Additionally, advancements in nanoscale imaging techniques, including super-resolution microscopy and quantum dot-based fluorescence, provide unprecedented insights into cellular and molecular dynamics, further bridging the gap between nanotechnology and biology [20].

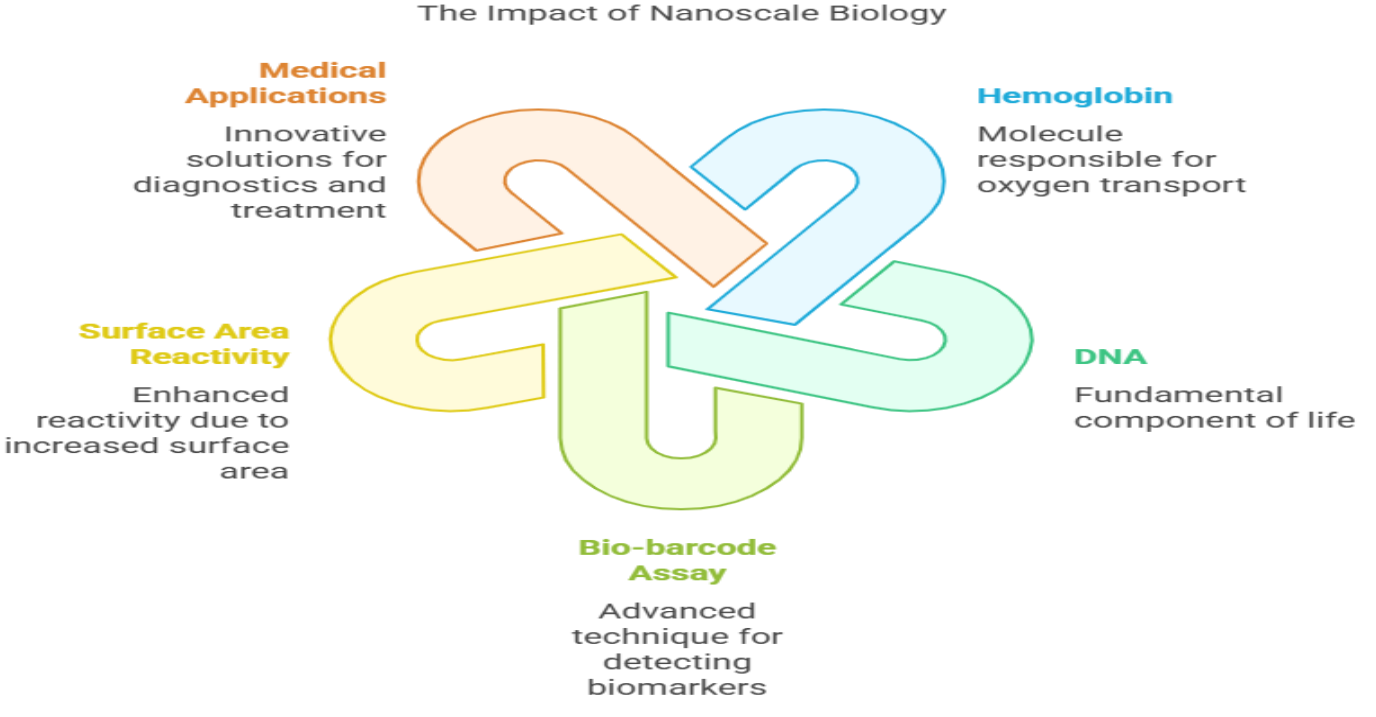

Fig. 1. The Impact of Nanoscale Biology: Exploring Surface Reactivity, Medical Applications, and Biomolecular Functions.

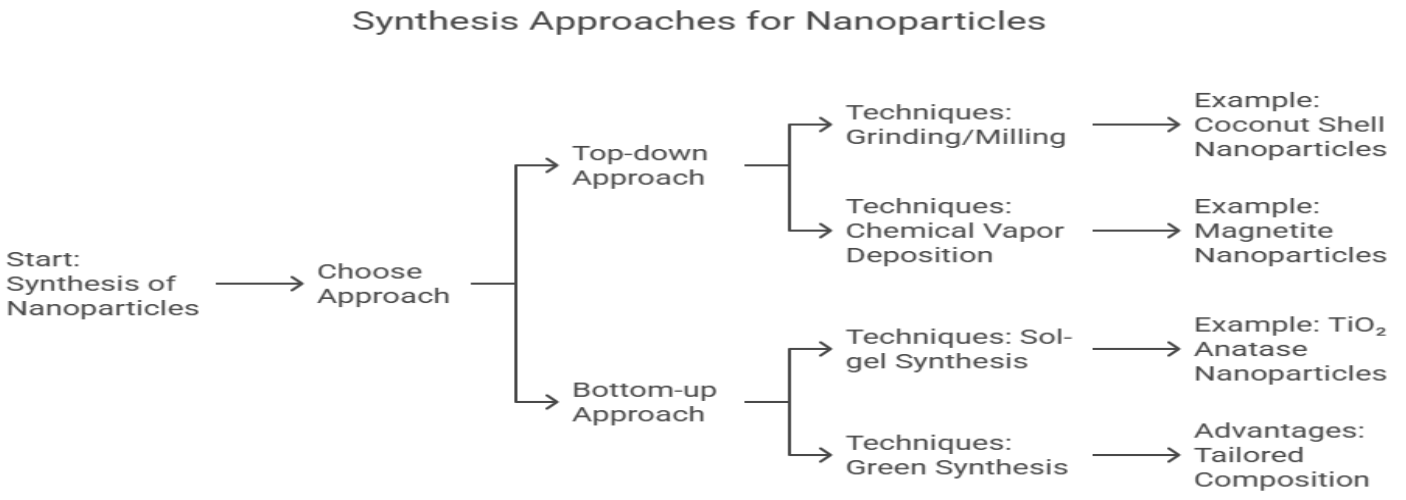

Fig. 2. Schematic representation of nanoparticle synthesis approaches: Top-down methods involve size reduction of bulk materials through mechanical or chemical processes, while bottom-up approaches utilize molecular assembly from atomic or molecular precursors. The diagram highlights key techniques and their applications in nanomaterial fabrication.

As nanotechnology continues to evolve, its integration with biological systems promises to revolutionize medicine by offering solutions that are not only more effective but also minimally invasive. By harnessing the unique properties of nanoscale materials, scientists are developing next-generation therapies and diagnostic tools that align with the body's natural processes, paving the way for a new era of precision medicine [19].

3. SYNTHESIS OF NANOPARTICLES: APPROACHES AND METHODOLOGIES

The synthesis of nanoparticles (NPs) represents a fundamental aspect of nanotechnology, with various chemical processes employed to create nanostructures with precise control over size, shape, and composition. These processes are broadly classified into two primary approaches based on their formation mechanism: the top-down approach and the bottom-up approach (Figure 2). The selection between these methods depends on several factors including reaction conditions, synthesis protocols, and the intended application of the nanoparticles [21]. Each approach offers unique advantages and limitations, making them suitable for different types of nanomaterials and functional requirements.

3.1. Top-Down Synthesis Approaches

The top-down approach involves the physical or chemical breakdown of bulk materials into nanoscale particles through mechanical or energy-based processes. This method is characterized by its destructive nature, where larger structures are fragmented into smaller nanoparticles using techniques such as grinding, milling, chemical vapor deposition (CVD), and physical vapor deposition (PVD) [21]. These methods are particularly useful for producing nanoparticles from hard or brittle materials that can withstand mechanical stress without significant degradation of their properties.

A notable example of top-down synthesis is the production of coconut shell (CS) nanoparticles through high-energy ball milling. In this process, raw CS powders are subjected to prolonged milling using ceramic balls in a planetary mill. Studies have shown that increasing the milling duration leads to a progressive reduction in crystallite size, as confirmed by X-ray diffraction (XRD) analysis using the Scherrer equation. Visual observations, such as the gradual fading of the brownish color of the nanoparticles, further corroborate the reduction in particle size. Scanning electron microscopy (SEM) imaging has provided additional validation, demonstrating a consistent decrease in particle dimensions with extended milling time [22]. This method highlights the effectiveness of mechanical forces in achieving nanoscale particle sizes from bulk precursors.

Another application of the top-down approach is seen in the synthesis of magnetite (Fe_3O_4) nanoparticles from natural iron oxide (Fe_2O_3) ore. By employing size reduction techniques in the presence of organic stabilizing agents like oleic acid, researchers have successfully produced spherical magnetite nanoparticles with controlled sizes ranging between 20 to 50 nm [23]. The oleic acid acts as a surfactant, preventing particle aggregation and ensuring uniform dispersion. Similarly, colloidal carbon spherical nanoparticles have been synthesized using a top-down method that relies on the adsorption of polyoxometalates (POM) onto carbon surfaces. This process breaks down carbon black aggregates into smaller, well-dispersed particles with narrow size distributions. The role of

sonication time in this process has been particularly significant, with longer sonication periods resulting in smaller particle sizes, as evidenced by micrographic analysis [23]. These examples underscore the versatility of top-down methods in producing nanoparticles from diverse starting materials.

3.2. Bottom-Up Synthesis Approaches

In contrast to top-down methods, the bottom-up approach builds nanoparticles atom-by-atom or molecule-by-molecule, starting from simpler precursors such as ions or molecular clusters. This constructive approach is widely used in techniques like sol-gel synthesis, green synthesis, biochemical synthesis, and various reduction processes [21]. Bottom-up methods are particularly advantageous for creating nanoparticles with precise control over composition, crystallinity, and surface properties, making them ideal for applications requiring high purity and tailored functionalities.

A representative example of bottom-up synthesis is the fabrication of titanium dioxide (TiO_2) anatase nanoparticles incorporated with graphene domains. In this process, alizarin and titanium isopropoxide serve as precursors, forming a photoactive composite capable of degrading methylene blue under light exposure. Alizarin was specifically chosen due to its strong binding affinity with TiO_2 through hydroxyl groups, which facilitates the formation of a stable nanocomposite. XRD analysis confirmed the anatase phase of the synthesized nanoparticles, while SEM imaging revealed that higher reaction temperatures led to increased particle sizes [24]. This temperature-dependent growth illustrates the fine control achievable with bottom-up methods, where reaction parameters can be adjusted to tailor nanoparticle properties.

Another significant application of bottom-up synthesis is in green nanotechnology, where biological agents such as plant extracts, fungi, or bacteria are used to reduce metal ions into nanoparticles. This eco-friendly approach avoids toxic chemicals and harsh conditions, making it suitable for biomedical applications. For instance, silver nanoparticles synthesized using plant-derived reducing agents exhibit excellent antimicrobial properties while maintaining biocompatibility [21]. The bottom-up approach also enables the production of complex nanostructures, such as core-shell nanoparticles and quantum dots, which are challenging to achieve through top-down methods. By carefully controlling nucleation and growth conditions, researchers can engineer nanoparticles with specific optical, magnetic, or catalytic properties.

Both top-down and bottom-up approaches offer distinct advantages depending on the desired nanoparticle characteristics. Top-down methods excel in producing nanoparticles from bulk materials with relatively simple equipment, making them cost-effective for large-scale production. However, they may introduce defects or impurities during the size reduction process, which can affect nanoparticle performance. In contrast, bottom-up methods provide superior control over particle composition and morphology, enabling the synthesis of high-purity, defect-free nanoparticles. Nevertheless, these methods often require precise control over reaction conditions and may involve complex purification steps.

The choice between these approaches ultimately depends on the specific application requirements. For instance, top-down methods are well-suited for producing metallic or ceramic nanoparticles used in catalysis or composite materials, while bottom-up methods are preferred for biomedical applications where purity and surface functionalization are critical. Future advancements in nanoparticle synthesis are likely to focus on hybrid approaches that combine the scalability of top-down methods with the precision of bottom-up techniques. Additionally, the integration of artificial intelligence and machine learning in synthesis protocols could optimize reaction parameters in real-time, leading to more efficient and reproducible nanoparticle production [21].

The synthesis of nanoparticles through top-down and bottom-up approaches represents a cornerstone of nanotechnology, enabling the creation of materials with tailored properties for diverse applications. As research progresses, the development of innovative synthesis strategies will continue to expand the frontiers of nanomaterial science, driving advancements in medicine, energy, electronics, and environmental remediation.

4. CLASSIFICATION OF NANOPARTICLES

Nanoparticles represent a diverse class of materials with wide-ranging applications in medicine, electronics, and materials science. Their classification is primarily based on composition, structure, and synthesis methods, with each type exhibiting unique properties that make them suitable for specific applications (Figure 3). The major categories include liposomes, dendrimers, ceramic nanoparticles, silica nanoparticles, polymeric nanoparticles, and green synthesized nanoparticles, each offering distinct advantages in drug delivery, diagnostics, and therapeutic interventions.

4.1. Liposomes: Versatile Drug Delivery Vehicles

Liposomes are spherical vesicles ranging from 50 to 1000 nm in diameter that have revolutionized drug delivery systems. These nanostructures consist of one or more phospholipid bilayers surrounding an aqueous core, mimicking the natural structure of cell membranes. Rumiana et al. published a comprehensive review on lipid nanoparticles (LNPs), tracing their evolution from liposomes to mRNA vaccine delivery systems (Figure 4) [25]. The article highlights LNPs' pharmaceutical significance, particularly their crucial role in COVID-19 mRNA vaccines by protecting and delivering genetic material. While liposomes remain versatile, newer LNPs like solid lipid and nanostructured carriers provide superior stability and complex architectures.

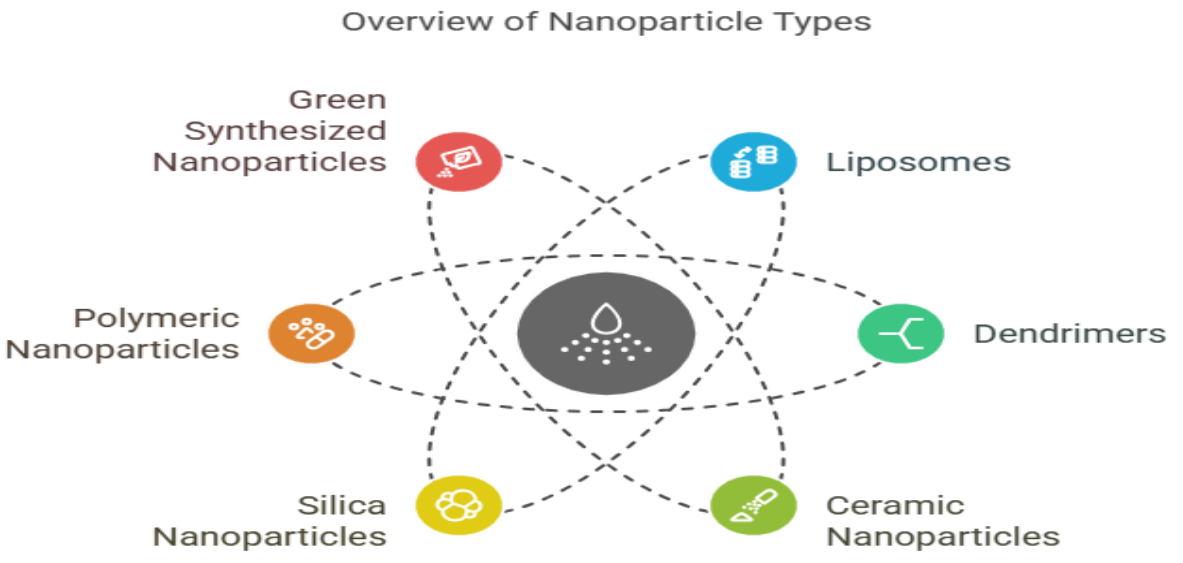

Fig. 3. Classification of major nanoparticle types for biomedical applications, highlighting their structural characteristics and functional advantages. The illustration compares liposomal bilayers, dendritic architectures, ceramic matrices, mesoporous silica frameworks, polymeric networks, and plant-mediated green synthesis approaches, emphasizing their respective roles in drug delivery, diagnostics, and therapeutic interventions.

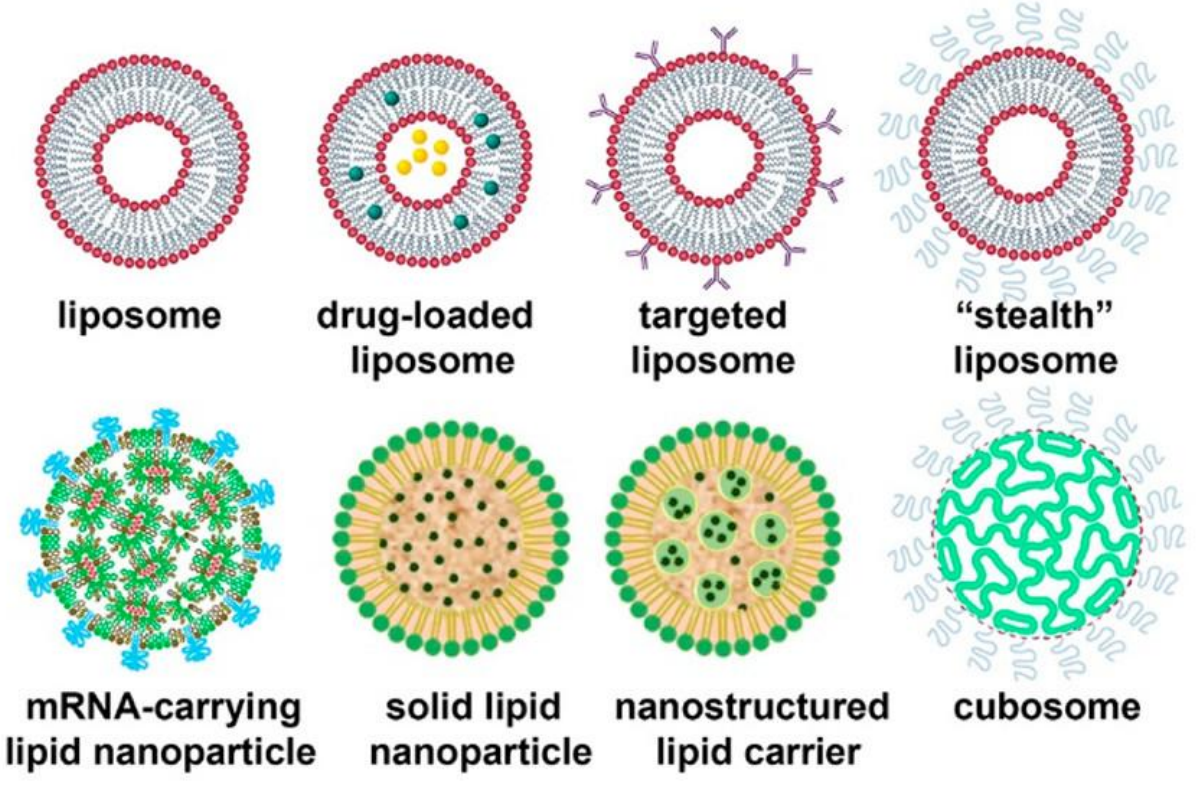

Fig. 4. Evolution and diversity of lipid nanoparticle (LNP) platforms for therapeutic delivery. The illustration highlights key LNP variants, including conventional liposomes (drug-loaded, targeted, and PEGylated "stealth" versions), mRNA-carrying LNPs for vaccine delivery, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), and cubosomes. These systems demonstrate progressive advancements in lipid-based nanocarrier design for optimized drug encapsulation, stability, and targeted release. [Reprinted with permission from ref. [25], Tenchov, R., Bird, R., Curtze, A.E. and Zhou, Q., 2021. Lipid nanoparticles─ from liposomes to mRNA vaccine delivery, a landscape of research diversity and advancement. *ACS Nano*, *15*(11), pp.16982-17015.Copyright © American Chemical Society].

The review analyzes scientific publications and patents from the CAS Content Collection, identifying emerging trends in LNP applications. Key advancements include their use in cancer treatment, nucleic acid delivery, and vaccine development, with growing potential in medical imaging, cosmetics, and agriculture.

The authors provide a valuable resource for researchers by examining both current applications and future opportunities in LNP technology, while addressing existing challenges across various fields. The analysis underscores LNPs' transformative potential as targeted drug delivery systems capable of precise therapeutic release. The amphipathic nature of phospholipids, with their hydrophilic heads and hydrophobic tails, enables spontaneous self-assembly into bilayers when hydrated [26]. This unique architecture allows liposomes to encapsulate both hydrophilic drugs within their aqueous core and hydrophobic compounds within the lipid bilayer, making them exceptionally versatile carriers [27]. In cancer therapy, liposomes have demonstrated remarkable success by protecting chemotherapeutic agents from degradation, enhancing their accumulation in tumor tissues through the enhanced permeability and retention (EPR) effect, and significantly reducing systemic toxicity [26]. Recent advancements have focused on modifying liposome surfaces with targeting ligands such as antibodies or peptides to further improve specificity, while stimuli-responsive liposomes that release their payload in response to specific triggers like pH or temperature are opening new possibilities for precision medicine [27].

4.2. Dendrimers: Precision Nanostructures for Targeted Delivery

Dendrimers represent a unique class of synthetic macromolecules characterized by their highly branched, three-dimensional architecture radiating from a central core [28]. These nanostructures are synthesized through either divergent (outward-growing) or convergent (inward-growing) approaches, allowing precise control over their size, shape, and surface functionality [29]. Polyamidoamine (PAMAM) dendrimers, among the most extensively studied, feature tertiary amines and amide linkages that provide numerous sites for drug conjugation or host-guest interactions. Their well-defined structure and monodisperse nature make dendrimers ideal for drug delivery, with the ability to carry therapeutic agents either encapsulated within their void spaces or attached to their surface functional groups. The nanoscale dimensions of dendrimers (typically 1-10 nm) closely match those of essential biological molecules like proteins and DNA, ensuring good biocompatibility and cellular uptake. Current research explores their applications in gene therapy, where cationic dendrimers effectively complex with nucleic acids, and in targeted cancer therapy, where surface-modified dendrimers can deliver drugs specifically to tumor cells while minimizing off-target effects. Pawan Kedar et al. reviewed the transformative potential of dendrimers and dendronized nanoparticles in cancer theranostics (Figure 5) [15]. These highly branched, 3D nanostructures enable precise tumor targeting through surface functionalization (e.g., PEGylation, folic acid/RGD peptides), minimizing systemic toxicity while enhancing drug delivery and imaging. Their adaptable architecture supports encapsulation of metal nanoparticles (e.g., gold) for improved tumor imaging via MRI, PET, or CT scans. Dendrimers also facilitate liquid biopsies and targeted therapy across diverse cancers (ovarian, brain, pancreatic, etc.), with clinical trials underway. The review highlights their role in advancing precision oncology through biocompatible, multifunctional designs that integrate diagnostics and treatment.

4.3. Ceramic Nanoparticles: Robust Platforms for Biomedical Applications

Ceramic nanoparticles, including hydroxyapatite (HA), zirconia (ZrO_2), silica (SiO_2), titanium oxide (TiO_2), alumina (Al_2O_3), and magnetic nanoparticles have emerged as important materials for biomedical applications due to their exceptional stability and tunable properties [30, 31]. These inorganic nanoparticles are particularly valued for their high mechanical strength, thermal stability, and resistance to microbial degradation. In drug delivery, ceramic nanoparticles offer several advantages including high loading capacity, protection of encapsulated drugs from degradation, and the ability to functionalize their surfaces for targeted delivery [31]. Mesoporous silica nanoparticles, for instance, have been extensively studied for their ability to provide controlled drug release, with pore size and surface chemistry precisely tuned to regulate release kinetics. However, challenges remain regarding their potential to elicit immune responses and long-term biodistribution, prompting ongoing research into surface modification strategies to improve biocompatibility. Recent innovations focus on developing "smart" ceramic nanoparticles that respond to specific physiological stimuli such as pH, temperature, or enzymatic activity to trigger drug release at desired sites [31]. Pedro M. Martins et al. reviewed the versatile biomedical applications of magnetic nanoparticles (MNPs), highlighting their tailored physicochemical properties for theragnostics, drug delivery, and tissue engineering (Figure 6) [30]. MNPs enable innovative therapies like photothermal/magnetic hyperthermia and photodynamic therapy, while serving as contrast agents for MRI. Their multifunctionality extends to chemotherapy enhancement, bacterial inhibition, and SARS-CoV-2 detection. The article emphasizes recent advances in MNP synthesis, geometry control, and biofunctionalization, addressing current trends and limitations. MNPs' unique magnetic responsiveness and adaptability position them as transformative tools in precision medicine.

4.4. Silica Nanoparticles: Precision Tools for Diagnostics and Therapy

Silica nanoparticles represent a particularly promising subclass of ceramic nanoparticles, with mesoporous silica nanoparticles (MSNs) standing out for their ordered pore structures and large surface areas [31]. These nanoparticles have been engineered to address the limitations of conventional tumor markers in cancer diagnostics, with 7 nm multimodal silica nanoparticles demonstrating exceptional specificity in preclinical studies [32].

These advanced nanoparticles incorporate targeting ligands like arginine-glycine-aspartic acid (RGD) peptides and imaging agents such as radioiodine, enabling both precise tumor targeting and diagnostic imaging capabilities. The successful translation of these nanoparticles into clinical trials marks a significant milestone in nanomedicine [32]. Surface modifications with polyethylene glycol (PEG) have further improved their pharmacokinetics by reducing opsonization and extending circulation time, while optimization of size and surface charge has enhanced tumor accumulation and enabled renal clearance to prevent long-term accumulation [32]. Current research explores their potential in combination therapies, where silica nanoparticles simultaneously deliver therapeutic agents and enable treatment monitoring through incorporated imaging modalities. Shivani Daksh developed pH-responsive manganese-impregnated mesoporous silica nanoparticles (MnOx-MSN-FA-pa) for dual SPECT/MRI imaging of tumors (Figure 7) [32]. The nanoparticles, functionalized with folic acid for folate receptor targeting, demonstrated excellent biocompatibility (>90% cell viability at 200 µg/mL) and specific uptake in MDA-MB-231 cancer cells. The 99mTc-labeled nanoprobe achieved 99.6% radiolabeling efficiency and pH-triggered Mn^{2+} release, enhancing MRI relaxivity ($r_1 = 11.37\ mM^{-1}\ s^{-1}$). In vivo studies showed high tumor-to-muscle ratio (6.01 at 2 h) in xenografts, with optimal T_1 contrast in MRI. This multifunctional platform combines SPECT's sensitivity with MRI's spatial resolution for precise tumor diagnostics.

4.5. Polymeric Nanoparticles: Versatile Carriers for Therapeutic Agents

Polymeric nanoparticles have emerged as one of the most versatile drug delivery platforms due to their tunable physicochemical properties and biocompatibility [33]. These nanoparticles can be fabricated from natural polymers like chitosan and alginate or synthetic polymers such as poly(lactic-co-glycolic acid) (PLGA), with their properties carefully tailored through selection of polymer composition and fabrication methods.

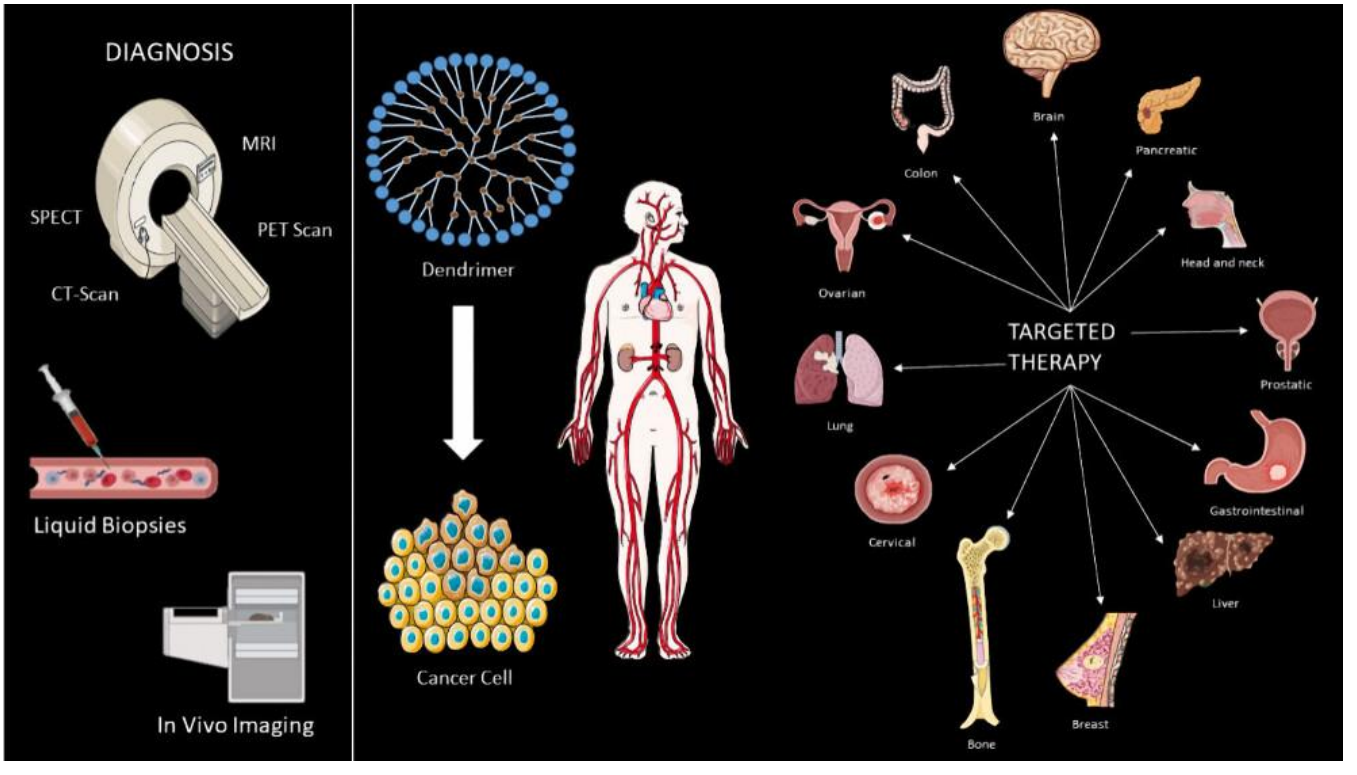

Fig. 5. Dendrimer-based theranostic platforms for precision oncology. The schematic illustrates applications in cancer diagnostics (MRI, PET, CT) and targeted therapy across multiple tumor types (breast, lung, prostate, etc.), emphasizing surface-functionalized dendrimers for imaging enhancement and tumor-specific drug delivery. [Reprinted with permission from ref. [15], Kedar, P., Saraf, A., Maheshwari, R. and Sharma, M., 2024. Advances in Dendritic Systems and Dendronized Nanoparticles: Paradigm Shifts in Cancer Targeted Therapy and Diagnostics. *Molecular Pharmaceutics*, *22*(1), pp.28-57. Copyright © American Chemical Society].

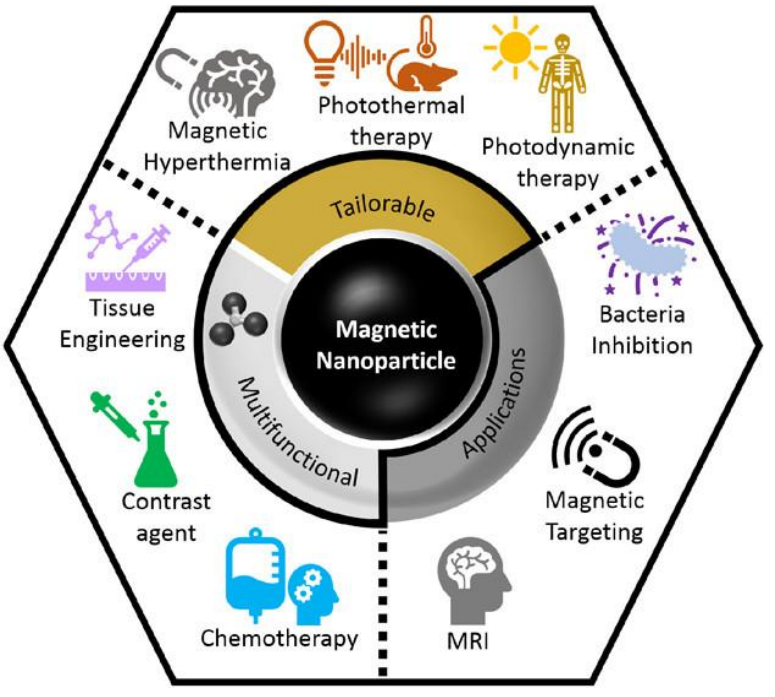

Fig. 6. Multifunctional applications of magnetic nanoparticles (MNPs) in biomedicine. The diagram showcases MNP uses in photothermal/photodynamic therapy, magnetic hyperthermia, tissue engineering, MRI contrast enhancement, chemotherapy, and antimicrobial strategies, illustrating their tailorable properties for diverse therapeutic and diagnostic purposes. [Reprinted with permission from ref. [30] Martins, P.M., Lima, A.C., Ribeiro, S., Lanceros-Mendez, S. and Martins, P., 2021. Magnetic nanoparticles for biomedical applications: from the soul of the earth to the deep history of ourselves. *ACS Applied Bio Materials*, *4*(8), pp.5839-5870. Copyright © American Chemical Society].

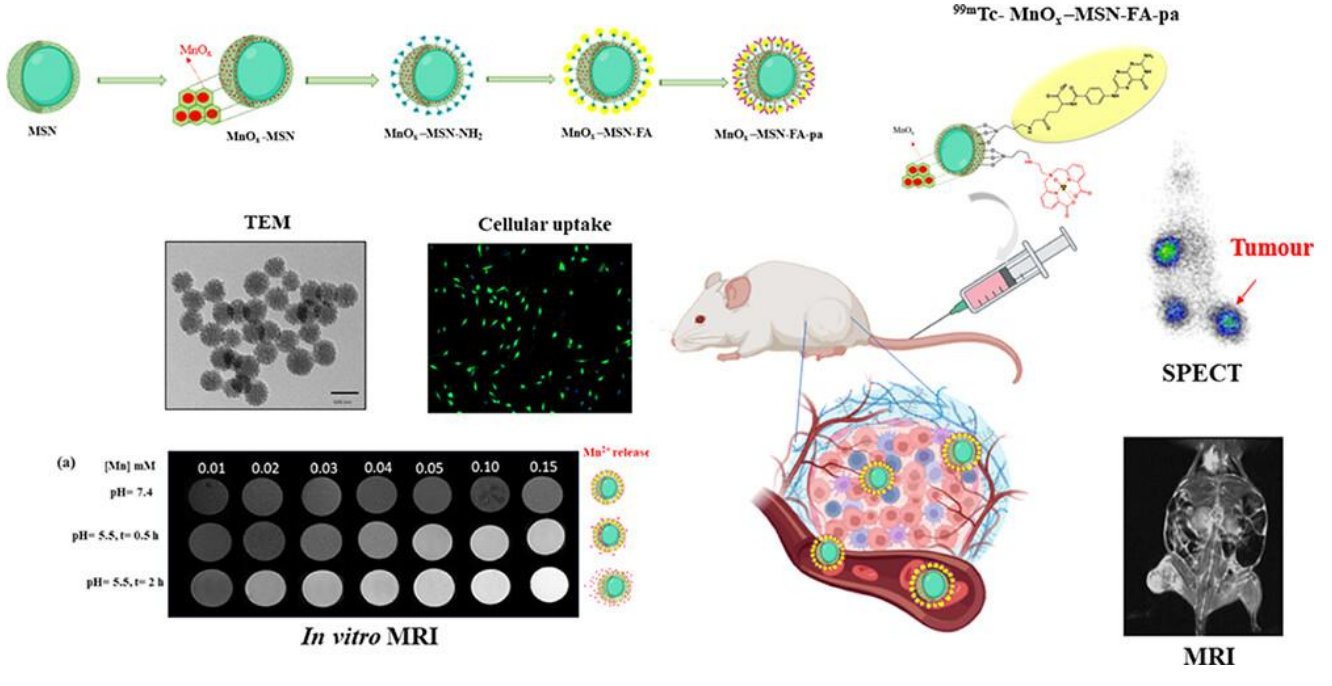

Fig. 7. Design and performance of MnOx-MSN-FA-pa nanoparticles for pH-responsive dual-modality imaging. Schematic of folic acid (FA)-conjugated, manganese-loaded mesoporous silica nanoparticles (MSNs) for SPECT/MRI; TEM images; pH-dependent Mn^{2+} release profiles; Cellular uptake studies in folate receptor-positive cells; and In vivo SPECT/MRI showing tumor-specific accumulation. [Reprinted with permission from ref. [32] Daksh, S., Bose, P., Kumar, S., Kumar, N., Kumaran, S.S., Verma, Y.K., Deep, S. and Datta, A., 2024. Tuned Manganese-Impregnated Mesoporous Silica Nanoparticles as a pH-Responsive Dual Imaging Probe. *ACS Applied Bio Materials*, *7*(12), pp.8503-8516. Copyright © American Chemical Society].

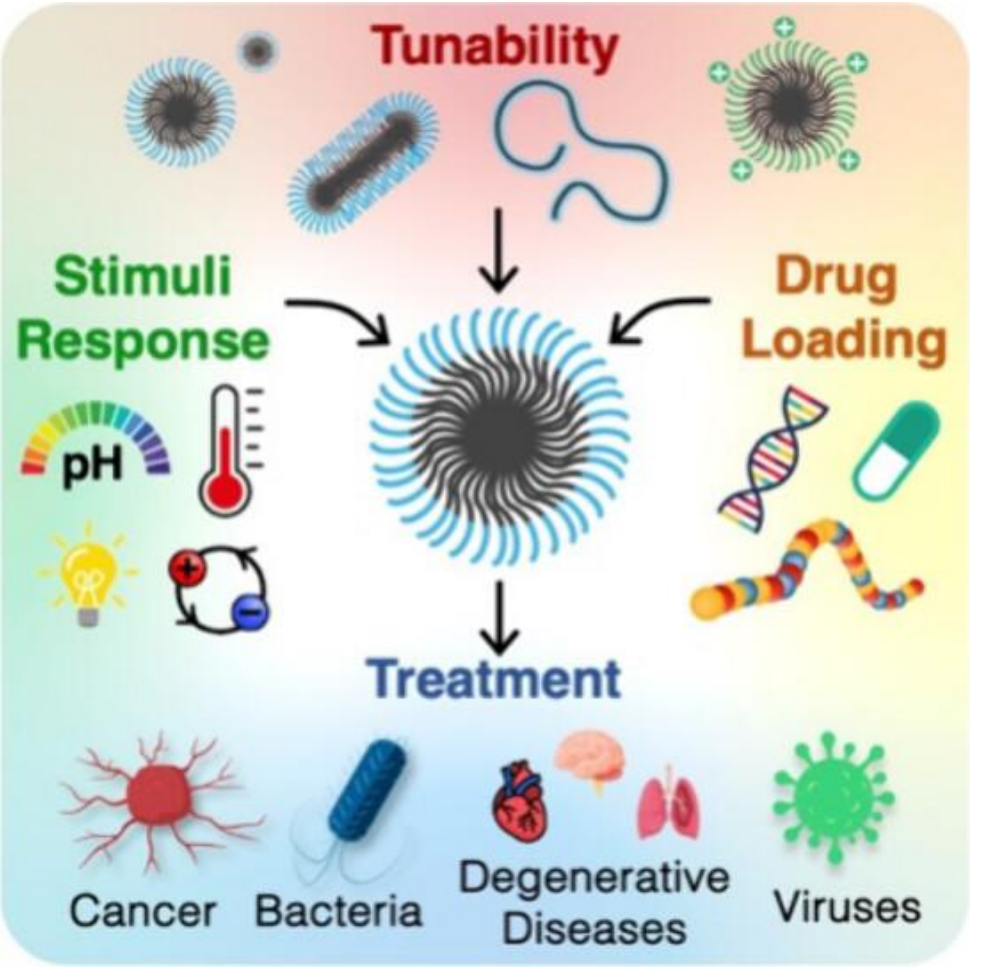

Fig. 8. Key attributes of polymeric nanoparticles for drug delivery. The diagram highlights tunable properties (stimuli-responsiveness, pH-triggered release, drug loading capacity) and therapeutic applications (cancer, bacterial/viral infections, degenerative diseases), illustrating their versatility as next-generation nanocarriers. [Reprinted with permission from ref. [34], Beach, M.A., Nayanathara, U., Gao, Y., Zhang, C., Xiong, Y., Wang, Y. and Such, G.K., 2024. Polymeric nanoparticles for drug delivery. *Chemical Reviews*, *124*(9), pp.5505-5616. Copyright © American Chemical Society].

The advantages of polymeric nanoparticles include protection of encapsulated drugs from degradation, controlled release kinetics, and the ability to modify their surfaces for targeted delivery. In regenerative medicine, polymeric nanoparticles have shown particular promise for delivering growth factors or genetic material to promote tissue repair [33].

Their ability to cross the blood-brain barrier has also made them valuable tools for treating neurodegenerative disorders, where they can deliver therapeutic agents directly to affected neural tissues. Current challenges focus on optimizing production methods to ensure batch-to-batch consistency and developing sophisticated surface modification strategies to enhance targeting specificity while minimizing immune recognition. Maximilian A. Beach's review highlights polymeric nanoparticles as transformative drug delivery vehicles, emphasizing their tunable properties (size, charge, stimuli-responsiveness) for precise therapeutic targeting (Figure 8) [34]. These nanoparticles overcome biological barriers, enabling controlled release of diverse cargo (anticancer drugs, antivirals, antibiotics) in response to pH or other stimuli. While demonstrating promise in treating cancer, infections, and degenerative diseases, their clinical adoption remains limited due to scalability and regulatory challenges. The review systematically analyzes design strategies, polymer selection, and disease-specific applications, underscoring their potential to redefine therapeutics pending resolution of manufacturing and safety hurdles.

4.6. Green Synthesized Nanoparticles: Sustainable Nanotechnology

The growing emphasis on sustainable practices has spurred development of green synthesis methods for nanoparticle production [35]. These approaches utilize natural reducing and stabilizing agents from plant extracts, such as the

Ayurvedic medicinal plant Shankhapushpi, or microbial systems to synthesize metal nanoparticles without hazardous chemicals. The polyphenols and other phytochemicals present in these biological materials not only mediate nanoparticle formation but also confer additional biological activities, such as the antioxidant properties observed in iron oxide nanoparticles synthesized using Shankhapushpi extracts [35]. Green synthesized nanoparticles from sources like Ginkgo biloba, pomegranate seed oil, thymoquinone, and quercetin have demonstrated various therapeutic benefits while addressing concerns about environmental impact and toxicity associated with conventional synthesis methods [35]. However, challenges remain in standardizing these biologically mediated synthesis processes and fully understanding the molecular mechanisms underlying nanoparticle formation and stabilization in these systems. Ongoing research aims to optimize production protocols and characterize the biological activities imparted by the capping agents derived from natural sources. Pratibha Acharya demonstrated that green-synthesized nanoparticles (AgNPs, AuNPs) and nanoemulsions (turmeric, citrus) significantly enhance onion seed germination, growth, and yield (Figure 9) [36]. Using onion extract as a reducing agent, the team created well-characterized nanoparticles (confirmed by UV-vis, TEM, XRD) and low-energy nanoemulsions. Seed priming with these nanomaterials improved emergence rates (63.2% for AuNPs vs. 37.4% control) and boosted yields by 23.9%. Instrumental analysis confirmed nanoparticle internalization in seeds, while field trials validated their efficacy without adverse effects. This study pioneers a sustainable nano-agriculture approach using agro-industrial byproducts, offering a safe, efficient alternative to conventional priming methods.

The diverse array of nanoparticle systems continues to expand the frontiers of nanomedicine, with each class offering unique advantages for specific applications. Liposomes and polymeric nanoparticles remain workhorses for drug delivery due to their biocompatibility and versatility, while dendrimers provide unparalleled precision in molecular design. Ceramic and silica nanoparticles offer exceptional stability for demanding applications, and green synthesized nanoparticles address growing concerns about environmental sustainability. As research progresses, the integration of these different nanoparticle types into hybrid systems and their combination with emerging technologies like artificial intelligence for design optimization promise to unlock new possibilities in targeted therapy, personalized medicine, and diagnostic imaging. The ongoing challenge lies in translating these advanced nanoplatforms from laboratory research to clinical applications, addressing concerns about scalability, reproducibility, and long-term safety while meeting stringent regulatory requirements.

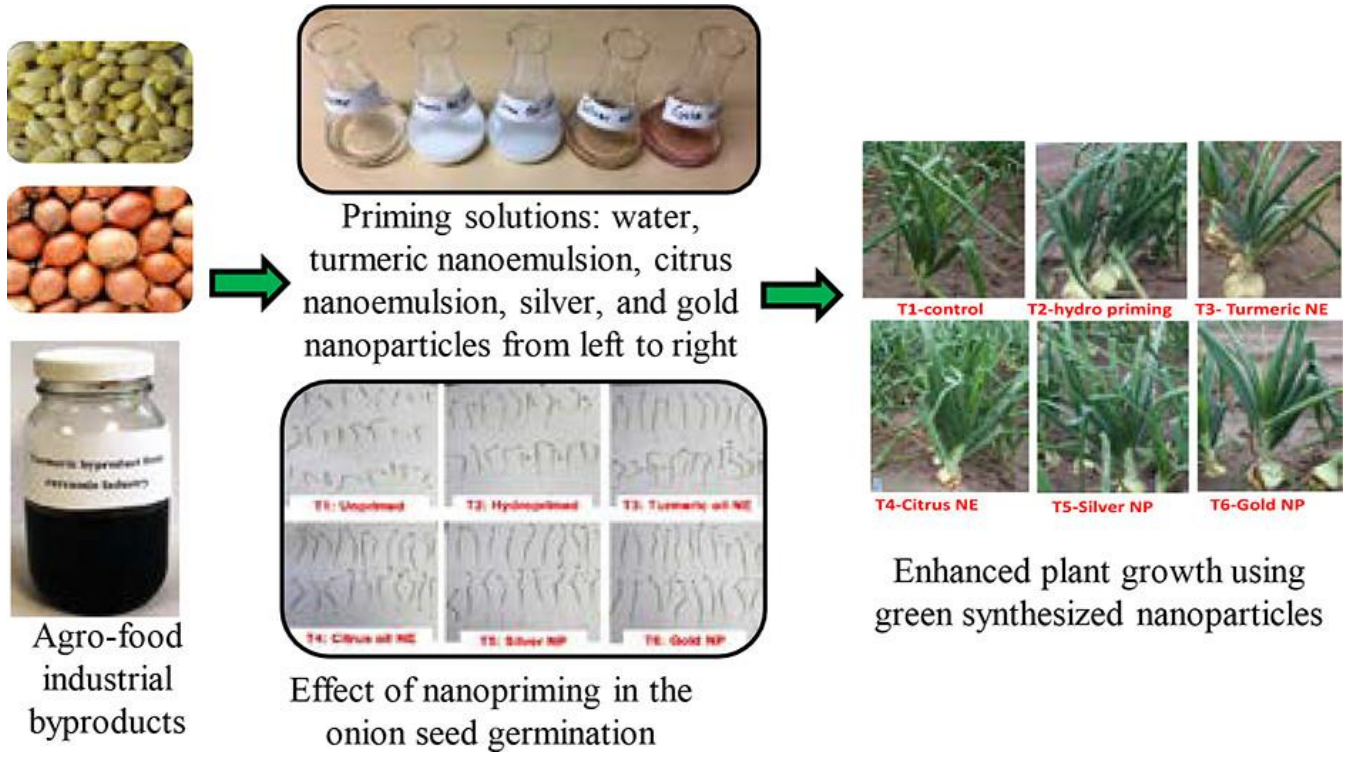

Fig. 9. Green nanotechnology for agricultural enhancement. (Top) Priming solutions: water control, turmeric/citrus nanoemulsions, and biosynthesized silver/gold nanoparticles. (Bottom) Results showing improved onion seed germination and growth with nano-priming compared to controls, demonstrating the potential of eco-friendly nanomaterials in precision agriculture. [Reprinted with permission from ref. [36]. Acharya, P., Jayaprakasha, G.K., Crosby, K.M., Jifon, J.L. and Patil, B.S., 2019. Green-synthesized nanoparticles enhanced seedling growth, yield, and quality of onion (Allium cepa L.). *ACS Sustainable Chemistry & Engineering*, *7*(17), pp.14580-14590. Copyright © American Chemical Society].

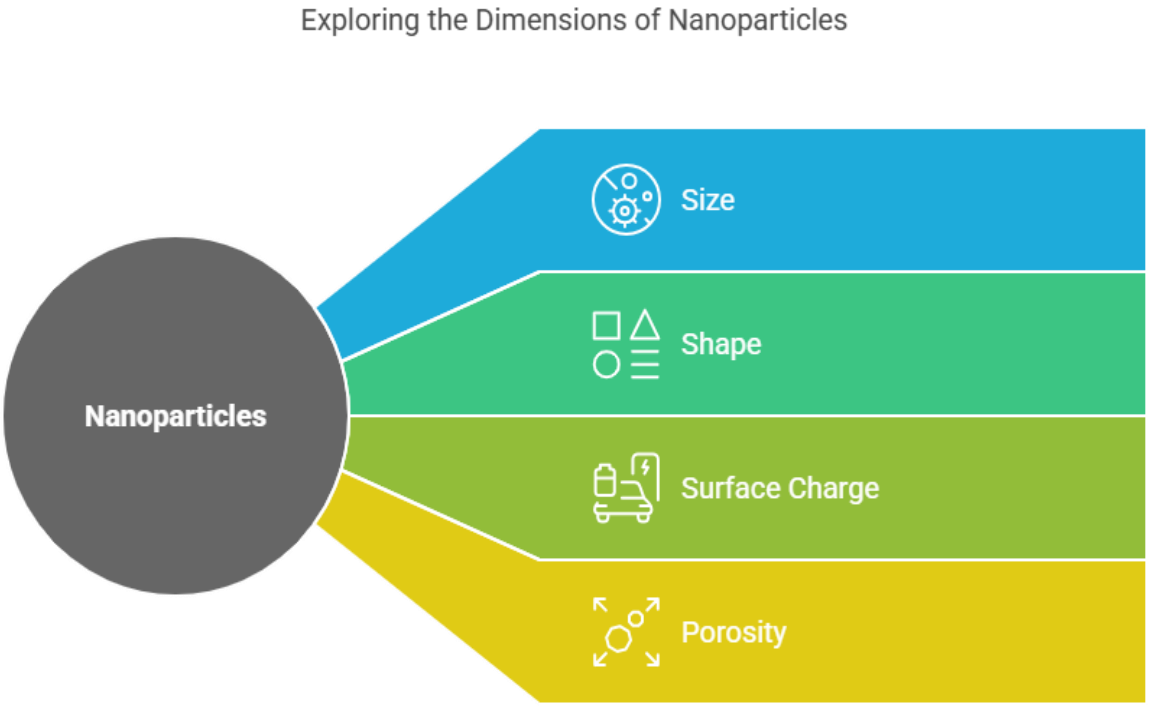

Fig. 10. Characterization and Functional Aspects of Nanoparticles: Exploring Size, Shape, Surface Charge, and Porosity.

5. CHARACTERIZATION AND FUNCTIONAL ASPECTS OF NANOPARTICLES

Nanoparticles represent a diverse class of materials with applications spanning medicine, electronics, and materials science. Their unique properties emerge from their nanoscale dimensions, typically ranging from 1 to 100 nanometers, which confer distinct physicochemical characteristics compared to bulk materials. Comprehensive characterization of nanoparticles is essential for understanding their behavior and optimizing their performance in various applications. This characterization encompasses multiple parameters including size, shape, surface charge, and porosity, each playing a critical role in determining nanoparticle functionality (Figure 10).

The chemical composition of nanoparticles varies widely, encompassing metallic nanoparticles, metal oxides, polymeric structures, and lipid-based systems. Each type exhibits unique chemical properties that can be probed using advanced analytical techniques. Optical spectroscopy methods, including UV-visible absorption and fluorescence spectroscopy, provide information about electronic transitions and surface plasmon resonance in metallic nanoparticles [37]. X-ray fluorescence and absorption spectroscopy offer elemental composition data and oxidation state information, while Raman spectroscopy reveals molecular vibrations and crystal structure details. Solid-state nuclear magnetic resonance (NMR) spectroscopy is particularly valuable for characterizing the molecular environment and dynamics in polymeric and organic nanoparticles [37]. These techniques collectively provide a comprehensive picture of nanoparticle composition and surface chemistry.

A defining feature of nanoparticles is their ability to exist as discrete, individual entities with specific size, shape, and surface characteristics. This distinguishes them from other nanomaterials such as nanostructured films or nanotubes that may have larger overall dimensions [37-39]. The small size of nanoparticles results in an exceptionally high surface area to volume ratio, which dramatically enhances their reactivity and interaction potential with biological systems or other materials [40]. This property is particularly advantageous for applications requiring high catalytic activity or efficient drug loading. Furthermore, the development of porous nanoparticles has expanded these capabilities even further by providing additional internal surface area and void spaces that can be exploited for molecule storage and controlled release [44-48].

5.1. Size and Shape Characterization

Precise determination of nanoparticle size and morphology is fundamental to understanding and predicting their behavior. High-resolution microscopy techniques, particularly transmission electron microscopy (TEM) and scanning electron microscopy (SEM), provide direct visualization of nanoparticles with sub-nanometer resolution [49]. These methods rely on interactions between electron beams and the nanoparticle's atomic structure to generate detailed images of particle morphology. Atomic force microscopy (AFM), a

scanning probe technique, complements electron microscopy by providing three-dimensional topographical information under ambient or liquid conditions [49].

While spherical nanoparticles are commonly discussed in literature, real-world nanoparticles exhibit a diverse range of shapes including rods, cubes, tetrahedrons, and more complex anisotropic structures [50]. These shape variations can significantly influence nanoparticle properties and performance. For instance, rod-shaped gold nanoparticles display different plasmonic responses compared to their spherical counterparts, while sharp-edged nanoparticles may demonstrate enhanced cellular uptake [50-54]. Such shape-dependent behaviors underscore the importance of thorough morphological characterization.

A significant limitation of conventional electron microscopy is its provision of two-dimensional projections of three-dimensional objects. This can lead to misinterpretations, particularly for anisotropic or irregularly shaped particles. Advanced three-dimensional reconstruction techniques such as electron tomography have emerged to address this challenge [55, 56]. By acquiring multiple images from different angles and computationally reconstructing the three-dimensional structure, these methods provide more accurate representations of nanoparticle morphology. However, these high-resolution techniques typically have low throughput and require specialized sample preparation, often involving drying or staining procedures that may alter nanoparticle characteristics [49].

For routine analysis of nanoparticle suspensions, ensemble techniques such as dynamic light scattering (DLS) and nanoparticle tracking analysis (NTA) are widely employed. These methods measure particle Brownian motion to determine hydrodynamic size distributions [49]. While convenient and applicable to native suspension conditions, these approaches provide only equivalent spherical diameters and require complementary shape information for accurate interpretation. Centrifugal and sedimentation methods offer alternative size analysis approaches, particularly for dense nanoparticles, but similarly yield size information based on spherical approximations [49].

5.2. Surface Charge and Colloidal Stability

The interface between nanoparticles and their surrounding medium is a dynamic region that critically influences nanoparticle behavior. Surface charge development occurs through various mechanisms including ionization of surface groups, adsorption of charged species, or lattice defects in crystalline materials [57]. This surface charge creates an electrical double layer around each nanoparticle, comprising a tightly bound Stern layer and a more diffuse Gouy-Chapman layer. The potential at the boundary between these layers, known as the zeta potential (ζ), serves as a key indicator of colloidal stability [58].

Zeta potential measurements are typically performed using electrophoretic light scattering techniques, which analyze particle motion in an applied electric field. Nanoparticles with high absolute zeta potential values (generally > ±30 mV) exhibit strong electrostatic repulsion that prevents aggregation, while lower values indicate poorer stability [58]. The relationship between zeta potential and stability is complex, depending also on solution ionic strength and the presence of stabilizing agents. In physiological environments, the high ionic strength can compress the electrical double layer, reducing electrostatic stabilization and potentially leading to nanoparticle aggregation [57].

Surface charge also plays a crucial role in biological interactions. Positively charged nanoparticles typically exhibit stronger interactions with negatively charged cell membranes, often resulting in enhanced cellular uptake. However, excessive positive charge may also increase cytotoxicity and nonspecific protein adsorption [42, 43]. These considerations are particularly important for drug delivery applications where controlled biodistribution is desired. Surface charge characterization therefore forms an essential part of nanoparticle development and optimization.

5.3. Porous Nanoparticles: Design and Characterization

The development of porous nanoparticles has opened new possibilities in drug delivery, catalysis, and sensing applications. These materials combine the benefits of nanoscale dimensions with the added functionality of internal void spaces and high surface areas [57,59]. Mesoporous silica nanoparticles, for example, can exhibit surface areas exceeding 1000 m^2/g, with pore volumes allowing for substantial drug payloads [60-62]. Metal-organic frameworks (MOFs) represent another important class of porous nanomaterials with exceptionally high surface areas and tunable pore sizes [63].

Characterization of porous nanoparticles requires a multi-faceted approach addressing several key parameters. Pore size distribution is typically analyzed using gas adsorption techniques such as nitrogen physisorption, which provides information about pore diameters through analysis of adsorption-desorption isotherms [64]. Mercury porosimetry may be employed for larger macropores, while small-angle X-ray scattering (SAXS) offers complementary information about pore ordering and connectivity [65]. These techniques collectively provide insights into the hierarchical pore structure that determines nanoparticle loading capacity and release kinetics.

The surface chemistry of porous nanoparticles requires particular attention, as both internal and external surfaces may need separate functionalization for optimal performance [66]. Internal pore surfaces are often modified to control host-guest interactions, while external surfaces may be tailored for specific targeting or stealth properties. This dual functionalization presents analytical challenges, as techniques must distinguish between interior and exterior modifications. Selective probe molecules and controlled access experiments have been developed to address this need [66].

In drug delivery applications, porous nanoparticles must be carefully characterized for their loading efficiency, release kinetics, and stability under physiological conditions. The sealing of pores with stimuli-responsive gatekeepers adds another layer of complexity to these systems [60-62]. These gatekeepers, which may be molecular complexes or polymer coatings, must remain stable during circulation but respond appropriately to specific triggers at the target site. Characterization of these dynamic systems requires techniques capable of monitoring changes in real-time under relevant conditions.

5.4. Emerging Characterization Technologies

Recent advances in characterization technologies are addressing many of the limitations of traditional methods. Liquid-cell TEM allows for direct observation of nanoparticles in their native hydrated state, providing insights into dynamic processes such as growth, dissolution, and interaction with biological components [55]. Super-resolution microscopy techniques, including stochastic optical reconstruction microscopy (STORM) and photo-activated localization microscopy (PALM), are breaking the diffraction limit of light microscopy to provide nanoscale resolution of labeled nanoparticles in complex environments [49].

Advanced spectroscopic techniques are also enhancing nanoparticle characterization. Correlative microscopy approaches that combine multiple techniques on the same particles are providing more comprehensive understanding of structure-property relationships. For example, combining atomic force microscopy with infrared spectroscopy (AFM-IR) allows for chemical mapping with nanoscale spatial resolution [66]. Similarly, the integration of mass spectrometry with microscopy techniques enables simultaneous structural and compositional analysis.

5.5. Standardization Challenges and Future Directions

Despite these technological advances, challenges remain in standardizing nanoparticle characterization protocols. The lack of universally accepted procedures for many measurements complicates comparison between studies and hinders regulatory approval processes [66]. Variations in sample preparation, measurement conditions, and data analysis approaches can lead to significantly different results for the same material. International efforts are underway to develop standardized protocols and reference materials, but much work remains to be done.

Future developments in nanoparticle characterization will likely focus on several key areas. First, the integration of artificial intelligence and machine learning approaches promises to enhance data analysis and interpretation, particularly for complex multi-parameter datasets. Second, the development of more sophisticated in situ and operando characterization techniques will provide better understanding of nanoparticle behavior under realistic application conditions. Finally, the creation of comprehensive characterization workflows that combine multiple complementary techniques will be essential for thorough nanoparticle evaluation.

The thorough characterization of nanoparticles across multiple parameters is essential for their successful development and application. As nanotechnology continues to advance, so too must the analytical methods used to understand and control these materials. The integration of established techniques with emerging technologies will provide increasingly sophisticated tools for nanoparticle analysis, enabling the rational design of next-generation nanomaterials with precisely tailored properties. This comprehensive approach to characterization will be critical for translating laboratory discoveries into real-world applications that meet stringent performance and safety requirements.

6. ADVANCEMENTS AND APPLICATIONS OF NANOMEDICINE

Nanomedicine represents one of the most transformative applications of nanotechnology in healthcare, leveraging the unique properties of materials at the nanoscale (1-100 nm) to develop innovative solutions for disease diagnosis, treatment, and prevention [67]. At this scale, materials exhibit fundamentally different physical, chemical, and biological behaviors compared to their bulk counterparts, enabling unprecedented control over therapeutic interventions. The field has grown exponentially since its inception, with nanoparticle-based therapies now playing crucial roles in oncology, neurology, cardiology, and infectious disease management [68]. These advancements stem from the ability to engineer materials with precise control over size, surface chemistry, and functionality, allowing for targeted interactions with biological systems at the molecular level (Figure 11).

The clinical translation of nanomedicine has been particularly impactful in cancer treatment, where conventional chemotherapy often suffers from poor specificity and severe side effects. Nanoparticle-based drug delivery systems address these limitations through enhanced permeability and retention (EPR) effects in tumor tissues and active targeting using surface-bound ligands [69]. For instance, liposomal doxorubicin (Doxil) and albumin-bound paclitaxel (Abraxane) were among the first FDA-approved nanomedicines that demonstrated improved therapeutic indices over their conventional counterparts [70]. Beyond oncology, nanomedicine approaches are being developed for neurological disorders, with nanoparticles engineered to cross the blood-brain barrier for targeted delivery of therapeutics in Alzheimer's and Parkinson's diseases [71]. The field continues to expand with innovations in diagnostic imaging, where nanoparticle-based contrast agents provide enhanced resolution for early disease detection, and in

regenerative medicine, where nanostructured scaffolds guide tissue repair and regeneration [72].

6.1. Targeted Drug Delivery Systems

The application of nanotechnology in drug delivery has revolutionized pharmaceutical sciences by overcoming numerous biological barriers that limit conventional therapies [73]. Nanoparticle carriers can protect drugs from premature degradation, control their release kinetics, and direct them to specific tissues or cells. This targeting is achieved through both passive mechanisms, such as the EPR effect in tumors, and active strategies using surface-bound targeting moieties like antibodies, peptides, or aptamers [74]. Recent innovations include stimuli-responsive nanoparticles that release their payload in response to pathological cues such as acidic pH, elevated enzymes, or redox conditions in diseased tissues [75]. For example, pH-sensitive polymeric nanoparticles have been developed to selectively release chemotherapeutic agents in the acidic tumor microenvironment while remaining stable in normal tissues [76].

RNA interference (RNAi) therapy has particularly benefited from nanodelivery systems, as demonstrated by the FDA approval of patisiran, a lipid nanoparticle-formulated siRNA therapeutic for hereditary transthyretin-mediated amyloidosis [77]. The success of mRNA vaccines against COVID-19 further highlighted the potential of lipid nanoparticles to deliver nucleic acid therapeutics [78]. Current research focuses on expanding these platforms to deliver other biomacromolecules, including CRISPR-Cas9 gene-editing components, with several candidates already in clinical trials [79]. The ability to co-deliver multiple therapeutic agents in a single nanoparticle further enables combination therapies that can address drug resistance and enhance treatment efficacy [80].

6.2. DNA Nanotechnology in Medicine

DNA nanotechnology has emerged as a powerful tool for constructing precise nanostructures with programmable features [81]. Unlike conventional nanoparticles, DNA-based structures can be designed with atomic-level precision through Watson-Crick base pairing rules, creating customized shapes and functionalities. These structures include DNA origami, where a long single-stranded DNA scaffold is folded into predetermined shapes using short staple strands, and dynamic DNA devices that can undergo conformational changes in response to molecular triggers [82]. In drug delivery, DNA nanostructures offer several advantages: inherent biocompatibility, precise control over drug loading positions, and the ability to incorporate multiple functional elements such as targeting ligands and stimuli-responsive gates [83].

Recent applications include DNA tetrahedrons for targeted delivery of anticancer drugs, where the structure's rigidity and well-defined geometry improve pharmacokinetics and tumor accumulation [84]. DNA walkers, another innovative construct, can perform mechanical movements on cell surfaces to enhance drug internalization or perform computations for diagnostic applications [85]. The field is rapidly advancing toward clinical translation, with ongoing efforts to address challenges related to scale-up production, nuclease stability, and immune recognition [86]. Computational tools now enable in silico design and optimization of DNA nanostructures, accelerating their development for specific medical applications [87].

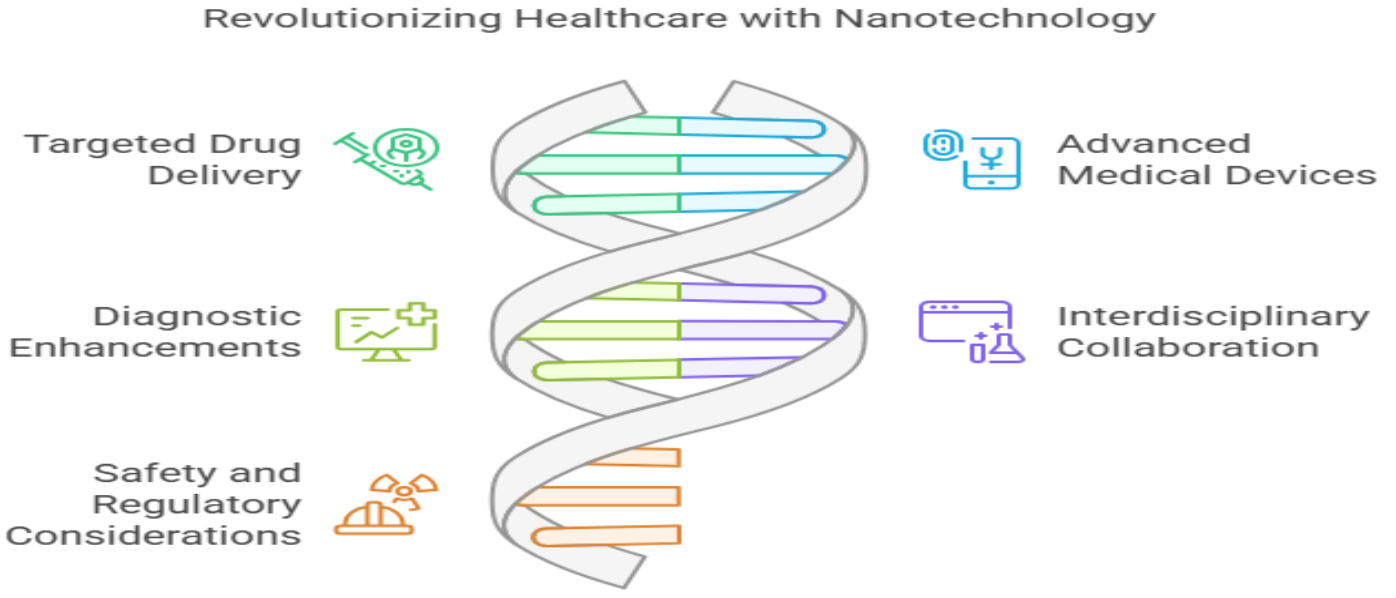

Fig. 11. Revolutionizing Healthcare with Nanotechnology: Advancements in Drug Delivery, Diagnostics, and Medical Devices.

6.3. Nanobiotechnology and Gene Therapy

The convergence of nanotechnology and gene therapy has created new possibilities for treating genetic disorders and other diseases at their molecular roots [88]. Viral vectors, while effective, face limitations including immunogenicity and insertional mutagenesis risks. Non-viral nanocarriers, including lipid-based, polymeric, and inorganic nanoparticles, offer safer alternatives with greater payload capacity and easier manufacturing [89]. These systems protect nucleic acids from degradation, facilitate cellular uptake through endocytosis, and often include endosomolytic components to promote endosomal escape [90].

Recent breakthroughs include lipid nanoparticles delivering mRNA for protein replacement therapy and CRISPR-Cas9 components for gene editing [91]. In cancer immunotherapy, nanoparticle-delivered DNA vaccines have shown enhanced antigen presentation and immune activation compared to conventional formulations [92]. The field is also exploring exosome-based nanocarriers, which leverage natural intercellular communication mechanisms for improved delivery efficiency and biocompatibility [93]. Challenges remain in achieving tissue-specific targeting and minimizing off-target effects, particularly for systemic gene editing applications [93].

6.4. Green Nanotechnology for Sustainable Medicine

The growing emphasis on environmental sustainability has spurred the development of green nanotechnology approaches in medicine [94]. These methods utilize biological resources such as plant extracts, microorganisms, or biomimetic processes to synthesize and assemble nanoparticles with reduced environmental impact [95]. Green-synthesized metal nanoparticles, for instance, employ phytochemicals as both reducing and stabilizing agents, avoiding toxic chemicals used in conventional synthesis [96]. These nanoparticles often exhibit enhanced biocompatibility and additional therapeutic properties derived from their biological capping agents [97].

Applications range from antimicrobial wound dressings incorporating plant-derived silver nanoparticles to antioxidant formulations using green-synthesized selenium nanoparticles [98]. The field also explores sustainable manufacturing processes, including energy-efficient synthesis methods and biodegradable nanoparticle materials [99]. While green nanomedicine shows great promise, challenges remain in standardizing production methods and fully characterizing the complex biomolecule-nanoparticle interfaces that determine their biological behavior [100, 101].

6.5. Clinical Translation and Regulatory Considerations

The path from laboratory discovery to clinical application in nanomedicine involves unique regulatory challenges [102]. Nanoparticle therapeutics are assessed as combination products, requiring evaluation of both the carrier and active pharmaceutical ingredient [103]. Key considerations include characterization of nanoparticle physicochemical properties, stability, and batch-to-batch consistency, as well as comprehensive toxicology studies addressing potential nanoparticle-specific effects [104]. The FDA and EMA have issued guidance documents for nanomedicine development, emphasizing the need for thorough characterization of size distribution, surface properties, and drug release kinetics [105].

Current clinical pipelines feature nanoparticles for targeted cancer therapy, antimicrobial applications, and vaccine delivery, with increasing emphasis on personalized approaches [106]. The lessons learned from COVID-19 mRNA vaccines are accelerating development of nucleic acid nanotherapeutics, while advances in manufacturing technologies address scale-up challenges [107]. Future directions include multifunctional theranostic nanoparticles combining treatment and monitoring capabilities, and AI-driven design of nanoparticle systems optimized for specific patient populations [108].

The continued evolution of nanomedicine requires addressing several critical challenges. Long-term safety assessments are needed to understand nanoparticle fate in biological systems, particularly for non-biodegradable materials [109]. Scalable manufacturing methods must maintain precise control over nanoparticle properties, while cost considerations remain important for global accessibility [110]. Interdisciplinary collaboration will be essential to overcome these hurdles and realize the full potential of nanotechnology in medicine, from basic research to clinical implementation [111]. As the field matures, the integration of nanomedicine with digital health technologies and personalized medicine approaches promises to revolutionize healthcare delivery in the coming decades [112].

7. FUTURE PROSPECTS OF NANOMEDICINE AND NANOPARTICLE-BASED DRUG DELIVERY SYSTEMS

The future of nanomedicine is poised for transformative growth, driven by rapid advancements in nanotechnology, biomaterials science, and precision medicine. As researchers continue to unravel the complexities of nanoparticle (NP)-based therapeutics, several key directions are emerging that promise to redefine drug delivery, diagnostics, and personalized treatment strategies.

One of the most promising areas is adaptive and stimuli-responsive nanocarriers, which are engineered to release drugs in response to specific biological triggers such as pH, temperature, enzymes, or redox conditions. For example, tumors often exhibit an acidic microenvironment, and pH-sensitive NPs can be designed to degrade selectively in these regions, ensuring targeted drug release while minimizing systemic toxicity. Similarly, light- and ultrasound-activated NPs enable spatiotemporal control over drug delivery,

allowing clinicians to administer therapies with unprecedented precision. These smart nanosystems are expected to play a pivotal role in treating complex diseases such as cancer, neurological disorders, and chronic inflammatory conditions, where conventional therapies often fall short due to poor biodistribution and off-target effects.

Another frontier is the integration of artificial intelligence (AI) and machine learning (ML) in NP design and optimization. Computational models can predict NP behavior in biological systems, accelerating the development of high-efficacy formulations while reducing reliance on trial-and-error experimentation. AI-driven platforms can analyze vast datasets on NP-drug interactions, toxicity profiles, and pharmacokinetics to identify optimal nanocarrier compositions for specific diseases. This approach not only shortens the drug development timeline but also enhances the success rate of clinical translations. Furthermore, AI-powered diagnostics using NP-based sensors could revolutionize early disease detection by identifying biomarkers at ultra-low concentrations, enabling interventions before symptomatic onset.

Gene-editing nanotechnology represents another groundbreaking avenue, particularly with the advent of CRISPR-Cas9 and other gene-modulating tools. Lipid-based and polymeric NPs are being engineered to deliver gene-editing machinery directly to target cells, offering potential cures for genetic disorders such as sickle cell anemia, cystic fibrosis, and muscular dystrophy. Recent studies have demonstrated the feasibility of NP-mediated delivery of mRNA vaccines, as evidenced by the success of COVID-19 mRNA vaccines, which utilized lipid NPs to protect and transport genetic material into cells. Future research will likely focus on improving the stability, targeting efficiency, and safety of these systems to expand their applications beyond infectious diseases to cancer immunotherapy and regenerative medicine.

The rise of green nanotechnology is also shaping the future of nanomedicine by addressing environmental and toxicity concerns associated with traditional NP synthesis. Plant-derived NPs, synthesized using biocompatible reducing agents like polyphenols and flavonoids, offer a sustainable alternative to chemically synthesized counterparts. These eco-friendly NPs exhibit reduced cytotoxicity and improved biodegradability, making them ideal for clinical use. Additionally, microbial synthesis—employing bacteria, fungi, or algae—provides a scalable and low-cost method for producing metallic NPs with controlled sizes and morphologies. As regulatory agencies emphasize greener manufacturing practices, the adoption of these methods is expected to grow, ensuring that nanomedicine aligns with global sustainability goals.

Personalized nanomedicine is another transformative prospect, where NPs are tailored to individual patient profiles based on genetic, proteomic, and metabolic data. Advances in microfluidics and 3D printing technologies enable the fabrication of patient-specific nanocarriers loaded with customized drug combinations. For instance, NPs functionalized with biomarkers unique to a patient's tumor could facilitate precision oncology, maximizing therapeutic efficacy while minimizing adverse effects. Similarly, wearable NP-based sensors could provide real-time monitoring of drug levels and disease progression, allowing for dynamic treatment adjustments.

Despite these exciting developments, several challenges must be addressed to fully realize the potential of nanomedicine. Regulatory standardization remains a critical hurdle, as the current lack of uniform guidelines for NP characterization and safety assessment complicates clinical approval processes. Collaborative efforts between academia, industry, and regulatory bodies are needed to establish robust frameworks that ensure reproducibility, scalability, and patient safety. Additionally, long-term toxicity and biodistribution studies are essential to evaluate the potential accumulation of NPs in vital organs and their effects on immune responses. Innovations in biodegradable nanomaterials, such as silica and polymeric NPs, are being explored to mitigate these risks.Ethical considerations also warrant attention, particularly concerning equitable access to advanced nanotherapies. The high cost of NP manufacturing and intellectual property restrictions could limit availability in low-resource settings, exacerbating global health disparities. Policymakers must prioritize inclusive innovation strategies, such as open-source nanotechnology platforms and public-private partnerships, to ensure that breakthroughs benefit all populations. Looking ahead, interdisciplinary collaboration will be paramount in driving nanomedicine forward. Converging fields such as nanorobotics, synthetic biology, and bioelectronics could unlock unprecedented capabilities, such as nanoscale surgical bots for targeted tumor removal or biohybrid NPs that integrate living cells for enhanced therapeutic delivery. The integration of nanotechnology with quantum computing may further revolutionize drug discovery by simulating molecular interactions at an atomic level, enabling the design of ultra-precise nanocarriers. The future of nanomedicine is bright, with innovations in stimuli-responsive systems, AI-driven design, gene editing, and personalized therapies set to transform healthcare. By addressing current challenges in regulation, toxicity, and accessibility, nanotechnology will cement its role as a cornerstone of 21st-century medicine, offering solutions to some of the most persistent and complex medical challenges.

8. CONCLUSION

Nanotechnology has emerged as a cornerstone of modern medicine, offering unprecedented precision in diagnostics and therapeutics. This review underscores the transformative potential of nanoparticles (NPs) in drug delivery, where engineered systems like liposomes, dendrimers, and polymeric NPs enhance drug stability, bioavailability, and targeted release. By minimizing off-target effects, these innovations address critical limitations of conventional therapies, particularly in oncology and neurology. The

integration of DNA nanotechnology and nanobiotechnology has further expanded horizons, enabling gene-editing tools and personalized medicine. For instance, RNA-conjugated NPs and CRISPR-based nanocarriers exemplify how nanotechnology can correct genetic defects or silence disease-causing mutations with minimal invasiveness. Green nanotechnology also contributes to sustainable practices, leveraging eco-friendly synthesis methods to reduce environmental toxicity. However, clinical adoption faces hurdles, including regulatory complexities, long-term biosafety concerns, and scalable production challenges. Nanoparticle heterogeneity, potential immunogenicity, and unpredictable in vivo behavior necessitate rigorous characterization via advanced techniques such as electron microscopy, dynamic light scattering, and zeta potential analysis. Regulatory agencies must establish standardized protocols to evaluate nanomedicine safety, ensuring compliance with global health standards. Future directions should prioritize interdisciplinary collaboration to optimize NP design for multifunctional applications, such as theranostics (combined therapy and diagnostics) and stimuli-responsive drug release. Investments in public-private partnerships can accelerate translational research, bridging the gap between laboratory discoveries and clinical implementation. Additionally, ethical frameworks must guide equitable access to nanomedicine, preventing disparities in healthcare delivery.

DECLARATIONS

Ethical Approval

We affirm that this manuscript is an original work, has not been previously published, and is not currently under consideration for publication in any other journal or conference proceedings. All authors have reviewed and approved the manuscript, and the order of authorship has been mutually agreed upon.

Funding

Not applicable

Availability of data and material

All of the data obtained or analyzed during this study is included in the report that was submitted.

Conflicts of Interest

The authors declare that they have no financial or personal interests that could have influenced the research and findings presented in this paper. The authors alone are responsible for the content and writing of this article.

Authors' contributions

All authors contributed equally in the preparation of this manuscript.

REFERENCES

[1] Feynman, R., **2018.** There's plenty of room at the bottom. In *Feynman and computation* (pp. 63-76). CRC Press.

[2] Laurent, S., Forge, D., Port, M., Roch, A., Robic, C., Vander Elst, L. and Muller, R.N., **2008.** Magnetic iron oxide nanoparticles: synthesis, stabilization, vectorization, physicochemical characterizations, and biological applications. *Chemical Reviews*, *108*(6), pp.2064-2110.

[3] Shin, W.K., Cho, J., Kannan, A.G., Lee, Y.S. and Kim, D.W., **2016.** Cross-linked composite gel polymer electrolyte using mesoporous methacrylate-functionalized SiO_2 nanoparticles for lithium-ion polymer batteries. *Scientific Reports*, *6*(1), p.26332.

[4] Khan, I., Saeed, K. and Khan, I., **2019.** Nanoparticles: Properties, applications and toxicities. *Arabian Journal of Chemistry*, *12*(7), pp.908-931.

[5] Ghosh Chaudhuri, R. and Paria, S., **2012.** Core/shell nanoparticles: classes, properties, synthesis mechanisms, characterization, and applications. *Chemical Reviews*, *112*(4), pp.2373-2433.

[6] Lue, J.T., **2007.** Physical properties of nanomaterials. *Encyclopedia of Nanoscience and Nanotechnology*, *10*(1), pp.1-46.

[7] Cheng, X., Xie, Q. and Sun, Y., **2023.** Advances in nanomaterial-based targeted drug delivery systems. *Frontiers in Bioengineering and Biotechnology*, *11*, p.1177151.

[8] Alavi, S.V. and Dehpour, A.A., **2009,** April. Evaluation of the nanosilver colloidal solution in comparison with the registered fungicide to control greenhouse cucumber downy mildew disease in the north of Iran. In *VI International Postharvest Symposium 877* (pp. 1643-1646).

[9] Singh, M., Sharma, V., Shrivastav, A., Singh, P. and Verma, N., **2023.** Nanotechnology for Novel Drug Delivery: A Systematic Review of Classification, Preparation, Characterization, and Applications of

Nanoparticles in Drug Delivery. *Biosciences Biotechnology Research Asia*, *20*(4), pp.1147-1165.

[10] Shabani, L., Abbasi, M., Azarnew, Z., Amani, A.M. and Vaez, A., **2023.** Neuro-nanotechnology: diagnostic and therapeutic nano-based strategies in applied neuroscience. *Biomedical engineering online*, *22*(1), p.1.

[11] Modi, S., Prajapati, R., Inwati, G.K., Deepa, N., Tirth, V., Yadav, V.K., Yadav, K.K., Islam, S., Gupta, P., Kim, D.H. and Jeon, B.H., **2021.** Recent trends in fascinating applications of nanotechnology in allied health sciences. *Crystals*, *12*(1), p.39.

[12] Avula, L.R. and Grodzinski, P., **2022.** Nanotechnology-aided advancement in the combating of cancer metastasis. *Cancer and Metastasis Reviews*, *41*(2), pp.383-404.

[13] Erkoc, P. and Ulucan-Karnak, F., **2021.** Nanotechnology-based antimicrobial and antiviral surface coating strategies. *Prosthesis*, *3*(1), pp.25-52.

[14] Hulla, J.E., Sahu, S.C. and Hayes, A.W., **2015.** Nanotechnology: History and future. Human & experimental toxicology, 34(12), pp.1318-1321.

[15] Kedar, P., Saraf, A., Maheshwari, R. and Sharma, M., **2024.** Advances in Dendritic Systems and Dendronized Nanoparticles: Paradigm Shifts in Cancer Targeted Therapy and Diagnostics. *Molecular Pharmaceutics*, *22*(1), pp.28-57.

[16] Pramanik, P.K.D., Solanki, A., Debnath, A., Nayyar, A., El-Sappagh, S. and Kwak, K.S., **2020.** Advancing modern healthcare with nanotechnology, nanobiosensors, and internet of nano things: Taxonomies, applications, architecture, and challenges. *IEEE Access*, *8*, pp.65230-65266.

[17] Vaishampayan, V., Kapoor, A. and Gumfekar, S.P., **2023.** Enhancement in the limit of detection of lab-on-chip microfluidic devices using functional nanomaterials. *The Canadian Journal of Chemical Engineering*, *101*(9), pp.5208-5221.

[18] Malik, S., Muhammad, K. and Waheed, Y., **2023.** Emerging applications of nanotechnology in healthcare and medicine. Molecules, 28(18), p.6624.

[19] McNeil, S.E., **2005.** Nanotechnology for the biologist. *Journal of leukocyte biology*, *78*(3), pp.585-594.

[20] Thaxton, C.S., Elghanian, R., Thomas, A.D., Stoeva, S.I., Lee, J.S., Smith, N.D., Schaeffer, A.J., Klocker, H., Horninger, W., Bartsch, G. and Mirkin, C.A., **2009.** Nanoparticle-based bio-barcode assay redefines "undetectable" PSA and biochemical recurrence after radical prostatectomy. *Proceedings of the National Academy of Sciences*, *106*(44), pp.18437-18442.

[21] Iravani, S., **2011.** Green synthesis of metal nanoparticles using plants. *Green chemistry*, *13*(10), pp.2638-2650.

[22] Bello, S.A., Agunsoye, J.O. and Hassan, S.B., **2015.** Synthesis of coconut shell nanoparticles via a top-down approach: Assessment of milling duration on the particle sizes and morphologies of coconut shell nanoparticles. *Materials Letters*, *159*, pp.514-519.

[23] Priyadarshana, G., Kottegoda, N., Senaratne, A., de Alwis, A. and Karunaratne, V., **2015.** Synthesis of magnetite nanoparticles by top-down approach from a high purity ore. *Journal of Nanomaterials*, *2015*(1), p.317312.

[24] Mogilevsky, G., Hartman, O., Emmons, E.D., Balboa, A., DeCoste, J.B., Schindler, B.J., Iordanov, I. and Karwacki, C.J., **2014.** Bottom-up synthesis of anatase nanoparticles with graphene domains. *ACS applied materials & interfaces*, *6*(13), pp.10638-10648.

[25] Tenchov, R., Bird, R., Curtze, A.E. and Zhou, Q., **2021.** Lipid nanoparticles─ from liposomes to mRNA vaccine delivery, a landscape of research diversity and advancement. *ACS Nano*, *15*(11), pp.16982-17015.

[26] Torchilin, V.P., **2007.** Targeted pharmaceutical nanocarriers for cancer therapy and imaging. *The AAPS journal*, *9*, pp. E128-E147.

[27] Jain, A. and Jain, S.K., **2018.** Stimuli-responsive smart liposomes in cancer targeting. Current drug targets, 19(3), pp.259-270.

[28] Tomalia, D.A., Baker, H., Dewald, J., Hall, M., Kallos, G., Martin, S., Roeck, J., Ryder, J. and Smith, P., **1985.** A new class of polymers: starburst-dendritic macromolecules. *Polymer journal*, *17*(1), pp.117-132.

[29] Gillies, E.R. and Frechet, J.M., **2005.** Dendrimers and dendritic polymers in drug delivery. *Drug discovery today*, *10*(1), pp.35-43.

[30] Martins, P.M., Lima, A.C., Ribeiro, S., Lanceros-Mendez, S. and Martins, P., **2021.** Magnetic nanoparticles for biomedical applications: from the soul of the earth to the deep history of ourselves. *ACS Applied Bio Materials*, *4*(8), pp.5839-5870.

[31] Fadeel, B. and Garcia-Bennett, A.E., **2010.** Better safe than sorry: Understanding the toxicological properties of inorganic nanoparticles manufactured for biomedical applications. *Advanced drug delivery reviews*, *62*(3), pp.362-374.

[32] Daksh, S., Bose, P., Kumar, S., Kumar, N., Kumaran, S.S., Verma, Y.K., Deep, S. and Datta, A., **2024.**

Tuned Manganese-Impregnated Mesoporous Silica Nanoparticles as a pH-Responsive Dual Imaging Probe. *ACS Applied Bio Materials*, *7*(12), pp.8503-8516.

[33] Ahl, P.L., Bhatia, S.K., Meers, P., Roberts, P., Stevens, R., Dause, R., Perkins, W.R. and Janoff, A.S., **1997.** Enhancement of the in vivo circulation lifetime of l-α-distearoylphosphatidylcholine liposomes: importance of liposomal aggregation versus complements opsonization. *Biochimica et Biophysica Acta (BBA)-Biomembranes*, *1329*(2), pp.370-382.

[34] Roberts, R., Henderson, R.D. and Wigle, E.D., **1975.** Esophageal disease as a cause of severe retrosternal chest pain. *Chest*, *67*(5), pp.523-526.

[35] Ishida, T. and Kiwada, H., **2008.** Accelerated blood clearance (ABC) phenomenon upon repeated injection of PEGylated liposomes. *International Journal of Pharmaceutics*, *354*(1-2), pp.56-62.

[36] Acharya, P., Jayaprakasha, G.K., Crosby, K.M., Jifon, J.L. and Patil, B.S., **2019.** Green-synthesized nanoparticles enhanced seedling growth, yield, and quality of onion (Allium cepa L.). *ACS Sustainable Chemistry & Engineering*, *7*(17), pp.14580-14590

[37] Eds. Zhao, Y., Zhang, Z. and Feng, W., **2016.** Toxicology of Nanomaterials. Wiley-VCH Verlag GmbH & Co. KGaA.

[38] Lee, D., Rubner, M.F. and Cohen, R.E., **2006.** All-nanoparticle thin-film coatings. *Nano Letters*, *6*(10), pp.2305-2312.

[39] Kumar, S., Rani, R., Dilbaghi, N., Tankeshwar, K. and Kim, K.H., **2017.** Carbon nanotubes: a novel material for multifaceted applications in human healthcare. *Chemical Society Reviews*, *46*(1), pp.158-196.

[40] Zhang, S., Li, J., Lykotrafitis, G., Bao, G. and Suresh, S., **2009.** Size-dependent endocytosis of nanoparticles. *Advanced Materials (Deerfield Beach, Fla.)*, *21*, p.419.

[41] Liu, H.H., Surawanvijit, S., Rallo, R., Orkoulas, G. and Cohen, Y., **2011.** Analysis of nanoparticle agglomeration in aqueous suspensions via constant-number Monte Carlo simulation. *Environmental Science & Technology*, *45*(21), pp.9284-9292.

[42] Elci, S.G., Jiang, Y., Yan, B., Kim, S.T., Saha, K., Moyano, D.F., Yesilbag Tonga, G., Jackson, L.C., Rotello, V.M. and Vachet, R.W., **2016.** Surface charge controls the suborgan biodistributions of gold nanoparticles. *ACS Nano*, *10*(5), pp.5536-5542.

[43] Blanco, E., Shen, H. and Ferrari, M., **2015.** Principles of nanoparticle design for overcoming biological barriers to drug delivery. *Nature Biotechnology*, *33*(9), pp.941-951.

[44] Horcajada, P., Chalati, T., Serre, C., Gillet, B., Sebrie, C., Baati, T., Eubank, J.F., Heurtaux, D., Clayette, P., Kreuz, C. and Chang, J.S., **2010.** Porous metal–organic-framework nanoscale carriers as a potential platform for drug delivery and imaging. *Nature materials*, *9*(2), pp.172-178.

[45] Wuttke, S., Braig, S., Preiß, T., Zimpel, A., Sicklinger, J., Bellomo, C., Rädler, J.O., Vollmar, A.M. and Bein, T., **2015.** MOF nanoparticles coated by lipid bilayers and their uptake by cancer cells. *Chemical Communications*, *51*(87), pp.15752-15755.

[46] Liu, X., Zhang, F., Jing, X., Pan, M., Liu, P., Li, W., Zhu, B., Li, J., Chen, H., Wang, L. and Lin, J., **2018.** Complex silica composite nanomaterials templated with DNA origami. *Nature*, *559*(7715), pp.593-598.

[47] Rühle, B., Saint-Cricq, P. and Zink, J.I., **2016.** Externally controlled nanomachines on mesoporous silica nanoparticles for biomedical applications. *ChemPhysChem*, *17*(12), pp.1769-1779.

[48] Manzano, M. and Vallet-Regí, M., **2019.** Ultrasound responsive mesoporous silica nanoparticles for biomedical applications. *Chemical Communications*, *55*(19), pp.2731-2740.

[49] Wyatt, P.J., **2014.** Measurement of special nanoparticle structures by light scattering. *Analytical chemistry*, *86*(15), pp.7171-7183.

[50] Li, N., Zhao, P. and Astruc, D., **2014.** Anisotropic gold nanoparticles: synthesis, properties, applications, and toxicity. *Angewandte Chemie International Edition*, *53*(7), pp.1756-1789.

[51] Talamini, L., Violatto, M.B., Cai, Q., Monopoli, M.P., Kantner, K., Krpetic, Z., Perez-Potti, A., Cookman, J., Garry, D., Silveira, C.P. and Boselli, L., **2017.** Influence of size and shape on the anatomical distribution of endotoxin-free gold nanoparticles. *ACS Nano*, *11*(6), pp.5519-5529.

[52] Banerjee, A., Qi, J., Gogoi, R., Wong, J. and Mitragotri, S., **2016.** Role of nanoparticle size, shape and surface chemistry in oral drug delivery. *Journal of Controlled Release*, *238*, pp.176-185.

[53] Forestiere, C., Miano, G., Boriskina, S.V. and Negro, L.D., **2009.** The role of nanoparticle shapes and deterministic aperiodicity for the design of nanoplasmonic arrays. *Optics express*, *17*(12), pp.9648-9661.

[54] Orendorff, C.J., Sau, T.K. and Murphy, C.J., **2006.** Shape-dependent plasmon-resonant gold nanoparticles. *small*, *2*(5), pp.636-639.

[55] Park, J., Elmlund, H., Ercius, P., Yuk, J.M., Limmer, D.T., Chen, Q., Kim, K., Han, S.H., Weitz, D.A., Zettl, A. and Alivisatos, A.P., **2015.** 3D structure of individual nanocrystals in solution by electron microscopy. *Science*, *349*(6245), pp.290-295.

[56] Ercius, P., Alaidi, O., Rames, M.J. and Ren, G., **2015.** Electron tomography: a three-dimensional analytic tool for hard and soft materials research. *Advanced Materials*, *27*(38), pp.5638-5663.

[57] Baeza, A., Ruiz-Molina, D. and Vallet-Regí, M., **2017.** Recent advances in porous nanoparticles for drug delivery in antitumoral applications: inorganic nanoparticles and nanoscale metal-organic frameworks. *Expert opinion on drug delivery*, *14*(6), pp.783-796.

[58] Kulkarni, V.S., 2009. *Handbook of non-invasive drug delivery systems: science and technology*. Elsevier.

[59] Liu, J., Wu, C., Xiao, D., Kopold, P., Gu, L., van Aken, P.A., Maier, J. and Yu, Y., **2016.** MOF-derived hollow Co9S8 nanoparticles embedded in graphitic carbon nanocages with superior Li-ion storage. *Small*, *12*(17), pp.2354-2364.

[60] Min, Y., Caster, J.M., Eblan, M.J. and Wang, A.Z., **2015.** Clinical translation of nanomedicine. *Chemical reviews*, *115*(19), pp.11147-11190.

[61] Cabral, H., Miyata, K., Osada, K. and Kataoka, K., **2018.** Block copolymer micelles in nanomedicine applications. *Chemical reviews*, *118*(14), pp.6844-6892.

[62] Shi, J., Kantoff, P.W., Wooster, R. and Farokhzad, O.C., **2017.** Cancer nanomedicine: progress, challenges and opportunities. *Nature reviews cancer*, *17*(1), pp.20-37.

[63] Wang, A.Z., Langer, R. and Farokhzad, O.C., **2012.** Nanoparticle delivery of cancer drugs. *Annual review of medicine*, *63*(1), pp.185-198.

[64] Lee, N., Yoo, D., Ling, D., Cho, M.H., Hyeon, T. and Cheon, J., **2015.** Iron oxide based nanoparticles for multimodal imaging and magnetoresponsive therapy. *Chemical reviews*, *115*(19), pp.10637-10689.

[65] Li, Z., Clemens, D.L., Lee, B.Y., Dillon, B.J., Horwitz, M.A. and Zink, J.I., **2015.** Mesoporous silica nanoparticles with pH-sensitive nanovalves for delivery of moxifloxacin provide improved treatment of lethal pneumonic tularemia. *ACS nano*, *9*(11), pp.10778-10789.

[66] Rühle, B., Saint-Cricq, P. and Zink, J.I., **2016.** Externally controlled nanomachines on mesoporous silica nanoparticles for biomedical applications. *ChemPhysChem*, *17*(12), pp.1769-1779.

[67] Nielsen, E., **2008.** *Nanotechnology and its impact on consumers*. Consumers Council of Canada.

[68] Bawarski, W.E., Chidlowsky, E., Bharali, D.J. and Mousa, S.A., **2008.** Emerging nanopharmaceuticals. *Nanomedicine: Nanotechnology, Biology and Medicine*, *4*(4), pp.273-282.

[69] Kostarelos, K., Bianco, A. and Prato, M.A.U.R.I.Z.I.O., **2009.** Promises, facts and challenges for carbon nanotubes in imaging and therapeutics. *Nature nanotechnology*, *4*(10), pp.627-633.

[70] Oberdorster, G., Maynard, A., Donaldson, K., Castronova, V., Fitzpatrick, J., Ausman, K., Carter, J., Karn, B., Kreyling, W., Lai, D. and Olin, S., **2005.** ILSI Research Foundation: Principles for characterising the potential human health effects from exposure to nanomaterials: elements of a screening strategy. *Part Fibre Toxicol*, *2*(8). Pp. 1-35

[71] Sezer, A.D. ed., **2014.** *Application of nanotechnology in drug delivery*. BoD–Books on Demand.

[72] Oroojalian, F., Charbgoo, F., Hashemi, M., Amani, A., Yazdian-Robati, R., Mokhtarzadeh, A., Ramezani, M. and Hamblin, M.R., **2020.** Recent advances in nanotechnology-based drug delivery systems for the kidney. *Journal of Controlled Release*, *321*, pp.442-462.

[73] Sahu, T., Ratre, Y.K., Chauhan, S., Bhaskar, L.V.K.S., Nair, M.P. and Verma, H.K., **2021.** Nanotechnology based drug delivery system: Current strategies and emerging therapeutic potential for medical science. *Journal of Drug Delivery Science and Technology*, *63*, p.102487.

[74] Malik, S., Niazi, M., Khan, M., Rauff, B., Anwar, S., Amin, F. and Hanif, R., **2023.** Cytotoxicity study of gold nanoparticle synthesis using Aloe vera, honey, and Gymnema sylvestre leaf extract. *ACS omega*, *8*(7), pp.6325-6336.

[75] Enrico, C., **2019.** Nanotechnology-based drug delivery of natural compounds and phytochemicals for the treatment of cancer and other diseases. *Studies in natural products chemistry*, *62*, pp.91-123.

[76] Liu, J., Xie, G., Lv, S., Xiong, Q. and Xu, H., **2023.** Recent applications of rolling circle amplification in

biosensors and DNA nanotechnology. *TrAC Trends in Analytical Chemistry*, *160*, p.116953.

[77] Dang, Y. and Guan, J., **2020.** Nanoparticle-based drug delivery systems for cancer therapy. *Smart Materials in Medicine*, *1*, pp.10-19.

[78] Rajput, A., Shevalkar, G., Pardeshi, K. and Pingale, P., **2023.** Computational nanoscience and technology. *OpenNano*, *12*, p.100147.

[79] Chouhan, A.S. and Rangi, N., **2023.** A Research on Future Scenario in the Field of Role of Nanorobotics a Device for Diagnosis and Treatment. *Glob. Acad. J. Med. Sci*, *5*, pp.85-95. **23**

[80] DeLuca, M., Shi, Z., Castro, C.E. and Arya, G., **2020.** Dynamic DNA nanotechnology: toward functional nanoscale devices. *Nanoscale Horizons*, *5*(2), pp.182-201.

[81] Kim, J. and Franco, E., **2020.** RNA nanotechnology in synthetic biology. *Current opinion in biotechnology*, *63*, pp.135-141.

[82] Yu, C., Li, L., Hu, P., Yang, Y., Wei, W., Deng, X., Wang, L., Tay, F.R. and Ma, J., **2021.** Recent advances in stimulus-responsive nanocarriers for gene therapy. *Advanced Science*, *8*(14), p.2100540.

[83] Hu, Q., Li, H., Wang, L., Gu, H. and Fan, C., **2018**. DNA nanotechnology-enabled drug delivery systems. *Chemical reviews*, *119*(10), pp.6459-6506.

[84] Jiang, Y., Fan, M., Yang, Z., Liu, X., Xu, Z., Liu, S., Feng, G., Tang, S., Li, Z., Zhang, Y. and Chen, S., **2022.** Recent advances in nanotechnology approaches for non-viral gene therapy. *Biomaterials Science*, *10*(24), pp.6862-6892.

[85] Chen, X., Wang, L. and Lou, J., **2020.** Nanotechnology strategies for the analysis of circulating tumor DNA: A review. *Medical science monitor: International medical journal of experimental and clinical research*, *26*, pp. e921040-1.

[86] Javaid, M., Haleem, A., Singh, R.P., Rab, S. and Suman, R., **2021.** Exploring the potential of nanosensors: A brief overview. *Sensors International*, 2, p.100130.

[87] Cheng, M. and Dou, H., **2022.** Nano-assemblies based on biomacromolecules to overcome cancer drug resistance. *Polymer International*, *71*(4), pp.371-378.

[88] Idrees, H., Zaidi, S.Z.J., Sabir, A., Khan, R.U., Zhang, X. and Hassan, S.U., **2020.** A review of biodegradable natural polymer-based nanoparticles for drug delivery applications. *Nanomaterials*, *10*(10), p.1970.

[89] Jahangirian, H., Lemraski, E.G., Webster, T.J., Rafiee-Moghaddam, R. and Abdollahi, Y., **2017.** A review of drug delivery systems based on nanotechnology and green chemistry: green nanomedicine. *International journal of nanomedicine*, pp.2957-2978.

[90] Kanwar, R., Rathee, J., Salunke, D.B. and Mehta, S.K., **2019.** Green nanotechnology-driven drug delivery assemblies. *ACS omega*, *4*(5), pp.8804-8815.

[91] Rehan, F., Zhang, M., Fang, J. and Greish, K., **2024.** Therapeutic applications of nanomedicine: recent developments and future perspectives. *Molecules*, *29*(9), p.2073.

[92] Baig, N., Kammakakam, I. and Falath, W., **2021.** **24** Nanomaterials: A review of synthesis methods, properties, recent progress, and challenges. *Materials Advances*, *2*(6), pp.1821-1871.

[93] Ma, X., Tian, Y., Yang, R., Wang, H., Allahou, L.W., Chang, J., Williams, G., Knowles, J.C. and Poma, A., **2024.** Nanotechnology in healthcare, and its safety and environmental risks. *Journal of Nanobiotechnology*, *22*(1), p.715.

[94] Zhu, H., Li, B., Chan, C.Y., Ling, B.L.Q., Tor, J., Oh, X.Y., Jiang, W., Ye, E., Li, Z. and Loh, X.J., **2023.** Advances in Single-component inorganic nanostructures for photoacoustic imaging guided photothermal therapy. *Advanced Drug Delivery Reviews*, *192*, p.114644.

[95] Ying, S., Guan, Z., Ofoegbu, P.C., Clubb, P., Rico, C., He, F. and Hong, J., **2022**. Green synthesis of nanoparticles: Current developments and limitations. *Environmental Technology & Innovation*, *26*, p.102336.

[96] Vijayaraghavan, K. and Ashokkumar, T., **2017.** Plant-mediated biosynthesis of metallic nanoparticles: A review of literature, factors affecting synthesis, characterization techniques and applications. *Journal of Environmental Chemical Engineering*, *5*(5), pp.4866-4883.

[97] Khandel, P., Yadaw, R.K., Soni, D.K., Kanwar, L. and Shahi, S.K., **2018.** Biogenesis of metal nanoparticles and their pharmacological applications: present status and application prospects. *Journal of Nanostructure in Chemistry*, *8*, pp.217-254.

[98] Sin Cheow, W., Xu, R. and Hadinoto, K., **2013**. Towards sustainability: new approaches to nano-drug preparation. *Current Pharmaceutical Design*, *19*(35), pp.6229-6245.

[99] Patra, J.K., Das, G., Fraceto, L.F., Campos, E.V.R., Rodriguez-Torres, M.D.P., Acosta-Torres, L.S., Diaz-Torres, L.A., Grillo, R., Swamy, M.K., Sharma, S. and Habtemariam, S., **2018.** Nano based drug delivery

systems: recent developments and future prospects. *Journal of Nanobiotechnology*, *16*, pp.1-33.

[100] Mondal, P., Anweshan, A. and Purkait, M.K., **2020.** Green synthesis and environmental application of iron-based nanomaterials and nanocomposite: A review. *Chemosphere*, *259*, p.127509.

[101] Trivedi, R., Upadhyay, T.K., Mujahid, M.H., Khan, F., Pandey, P., Sharangi, A.B., Muzammil, K., Nasir, N., Hassan, A., Alabdallah, N.M. and Anwar, S., **2022.** Recent advancements in plant-derived nanomaterials research for biomedical applications. *Processes*, *10*(2), p.338.

[102] Csóka, I., Ismail, R., Jójárt-Laczkovich, O. and Pallagi, E., **2021.** Regulatory considerations, challenges and risk-based approach in nanomedicine development. *Current Medicinal Chemistry*, *28*(36), pp.7461-7476.

[103] Malik, R. and Patil, S., **2020.** Nanotechnology: Regulatory outlook on nanomaterials and nanomedicines in United States, Europe and India. *Applied Clinical Research, Clinical Trials and Regulatory Affairs*, *7*(3), pp.225-236.

[104] Sainz, V., Conniot, J., Matos, A.I., Peres, C., Zupanǒiǒ, E., Moura, L., Silva, L.C., Florindo, H.F. and Gaspar, R.S., **2015.** Regulatory aspects on nanomedicines. *Biochemical and Biophysical Research Communications*, *468*(3), pp.504-510.

[105] European Medicines Agency (2023) *Guideline on the quality requirements for nanomedicines*. EMA/CHMP/130299/2022.

[106] Shi, J., Kantoff, P.W., Wooster, R. and Farokhzad, O.C., **2017.** Cancer nanomedicine: progress, challenges and opportunities. *Nature Reviews Cancer*, *17*(1), pp.20-37.

[107] Pozzi, D. and Caracciolo, G., **2023**. Looking back, moving forward: lipid nanoparticles as a promising frontier in gene delivery. *ACS Pharmacology & Translational Science*, *6*(11), pp.1561-1573.

[108] Mitchell, M.J., Billingsley, M.M., Haley, R.M., Wechsler, M.E., Peppas, N.A. and Langer, R., **2021**. Engineering precision nanoparticles for drug delivery. *Nature Reviews Drug Discovery*, *20*(2), pp.101-124.

[109] Geraci, C.L. and Castranova, V., **2010**. Challenges in assessing nanomaterial toxicology: a personal perspective. *Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology*, *2*(6), pp.569-577.

[110] Anselmo, A.C. and Mitragotri, S., **2019**. Nanoparticles in the clinic: An update. *Bioengineering & Translational Medicine*, *4*(3), p.e10143.

[111] Satalkar, P., Elger, B.S., Hunziker, P. and Shaw, D., **2016**. Challenges of clinical translation in nanomedicine: A qualitative study. *Nanomedicine: Nanotechnology, Biology and Medicine*, *12*(4), pp.893-900.

[112] Yin, H., Kanasty, R.L., Eltoukhy, A.A., Vegas, A.J., Dorkin, J.R. and Anderson, D.G**., 2014**. Non-viral vectors for gene-based therapy. *Nature Reviews Genetics*, *15*(8), pp.541-555.