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# Recent Advances in Nanomedicine: Enhancing Drug Delivery and Diagnosis through Nanotechnology

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## Abstract
*Nano-medicine is an evolving field that utilizes nano-scale materials to enhance diagnostic tools and deliver therapeutic agents with high precision to specific target sites. This approach is particularly beneficial for treating chronic diseases, offering targeted and controlled drug delivery. Recent advancements in nanotechnology have led to significant improvements in the effectiveness of both new and existing drugs, including natural products, and in the selective diagnosis of diseases using molecular markers. The field is marked by numerous applications, including chemotherapeutic, biological, and immunotherapeutic agents. The review discusses the opportunities, challenges, and future perspectives of nano-medicine in drug delivery, from synthetic and natural sources to clinical applications.*
***Keywords:*** *Advances in nanomedicine, challenges in clinical application, diagnostics, drug delivery and nanotechnology.*

## 1. Introduction
Since ancient times, plant-based natural products have been extensively utilized as remedies for various diseases. The foundation of many modern medicines can be traced back to herbs, grounded in traditional knowledge and practices. It is estimated that about 25% of the major pharmaceutical compounds and their derivatives in use today are sourced from natural resources. Natural compounds, with their diverse molecular structures, provide a valuable foundation for the development of new drugs. A recent trend in drug discovery involving natural products is the design of synthetically accessible lead molecules that replicate the chemistry of their natural counterparts. Natural products are particularly valued for their remarkable features, including exceptional chemical diversity, specific chemical and biological properties, macromolecular specificity, and reduced toxicity. These attributes make them excellent candidates for novel drug discovery. Additionally, computational studies have advanced our understanding of molecular interactions, paving the way for innovations in target-based drug discovery and drug delivery systems. Despite these advantages, pharmaceutical companies often hesitate to invest heavily in natural product-based drug discovery and delivery systems. Instead, they frequently turn to existing chemical compound libraries in search of new drugs. Nevertheless, natural compounds are increasingly being screened for their potential to treat major diseases, such as cancer, diabetes, cardiovascular conditions, inflammatory disorders, and microbial infections. The appeal of natural drugs lies in their unique benefits, including lower toxicity, fewer side effects, affordability, and promising therapeutic potential. However, challenges related to the biocompatibility and toxicity of natural compounds remains significant obstacles to their use as medicines. Nanotechnology has demonstrated its ability to bridge the gap between biological and physical sciences by utilizing nano-structures and nano-phases across various scientific disciplines, particularly in nano-medicine and nano-based drug delivery systems, where these particles hold significant interest. Nano--materials are typically defined as materials with dimensions ranging from 1 to 100 nanometers, which are crucial in advancing the field of nano-medicine. Applications of nano-materials span a wide range, including biosensors,

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micro-fluidics, drug delivery, microarray tests, and tissue engineering. Nanotechnology involves the use of therapeutic agents at the nano-scale to develop nano-medicines. The field of biomedicine, which includes nano-biotechnology, drug delivery, biosensors, and tissue engineering, has been significantly advanced through the use of nano-particles. Since nano-particles are materials engineered at the atomic or molecular scale, they are often small nano-spheres. This small size allows them to navigate the human body more efficiently compared to larger materials. Nano-scale particles also exhibit distinctive structural, chemical, mechanical, magnetic, electrical, and biological properties. Nanotechnology presents numerous advantages in the treatment of chronic diseases through the precise and targeted delivery of medications. However, there is a significant concern regarding the toxicity of nanostructures due to the current lack of comprehensive understanding in this area. This concern highlights the need for further research to enhance the safety and effectiveness of these technologies, ensuring they can be safely applied in medical practice. Consequently, careful design of nano-particles could help address the issues related to their application. In light of these considerations, this review intends to explore various nano-based drug delivery systems, the important applications of nano-medicines derived from natural compounds, and aspects like bioavailability, targeting, controlled release, as well as the challenges associated with the use of nano-materials in medicine. [1-5]

## 2. Drug Delivery Systems

In recent years, significant progress has been made in the development of delivery systems designed to transport therapeutic agents or naturally-derived active compounds to specific target sites for the treatment of various ailments. While several drug delivery systems have been successfully implemented, certain challenges persist, highlighting the need for more advanced technologies to ensure precise delivery to target sites. Consequently, nano-based drug delivery systems are being actively researched as they promise to enhance the effectiveness and precision of drug delivery.

## 3. Nano-Technology-Based Techniques In Drug Design

Nano-medicine is a branch of medicine that applies nanotechnology to the prevention and treatment of various diseases by utilizing nano-scale materials, such as biocompatible nano-particles and nano-robots, for a range of applications including diagnosis, drug delivery, sensory functions, and actuation within living organisms. Drugs with very low solubility often face several biopharmaceutical challenges, such as limited bioavailability after oral intake, reduced ability to penetrate outer membranes, the need for higher doses in intravenous administration, and undesirable side effects typical of traditional vaccination methods. However, these limitations can be effectively addressed through the application of nanotechnology in drug delivery systems. Designing drugs at the nano-scale has been extensively researched and represents the most advanced technology in nano-particle applications, offering potential benefits like the ability to modify properties such as solubility, drug release profiles, diffusivity, bioavailability, and immunogenicity. These improvements can lead to the development of more convenient administration routes, reduced toxicity, fewer side effects, better bio-distribution, and an extended drug lifecycle. Engineered drug delivery systems are either targeted to specific locations or designed for the controlled release of therapeutic agents at particular sites. Their formation typically involves self-assembly, where well-defined structures or patterns are spontaneously created from building blocks. Additionally, these systems must overcome challenges such as opsonization and sequestration by the mononuclear phagocyte system. Nanostructures deliver drugs through two main methods: passive delivery and self-delivery. In passive delivery, drugs are incorporated into the inner cavity of the nanostructure, primarily through the hydrophobic effect. When these nanostructures are directed to specific sites, the intended drug dosage is released due to the low concentration of the drug encapsulated in the hydrophobic environment. On the other hand, in self-delivery, drugs are directly conjugated to the carrier nanostructure material, facilitating easy delivery. The timing of drug release

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is critical in this approach; if the drug dissociates from the carrier too quickly, it may not reach the target site, whereas delayed release can reduce its bioactivity and efficacy. Targeting of drugs is another important aspect of nano-material-based drug delivery systems, which can be classified into active and passive targeting. In active targeting, molecules like antibodies and peptides are attached to the drug delivery system, allowing them to anchor to receptor structures at the target site. In passive targeting, the drug carrier complex circulates through the bloodstream and is directed to the target site by affinity or binding, influenced by factors such as pH, temperature, molecular size, and shape. Key targets in the body include receptors on cell membranes, lipid components of the cell membrane, and antigens or proteins on cell surfaces. Currently, most nanotechnology-based drug delivery systems are focused on targeting and treating cancer. [6-10]

## 4. Drug Design and Delivery Process and Mechanism

The evolution of nano-medicine, coupled with advancements in drug discovery, design, and delivery systems, has led to the proposal of numerous therapeutic approaches and the examination of traditional clinical diagnostic methods, all aimed at enhancing drug specificity and diagnostic accuracy. For instance, new routes of drug administration are being explored, with a focus on ensuring that these drugs act specifically in targeted regions, thereby reducing toxicity and improving bioavailability within the body. In this regard, drug design has emerged as a promising area, characterized by the discovery of novel lead compounds based on an understanding of biological targets. The advancement of computer science and the improvement of experimental procedures for the classification and purification of proteins, peptides, and other biological targets are crucial for the growth of this field. Additionally, many studies and reviews in this area emphasize the rational design of various molecules and highlight the importance of studying different mechanisms of drug release. Furthermore, natural products offer viable and innovative solutions to address challenges in drug design and serve as valuable inspirations for discovering drugs with desired physicochemical properties. Moreover, drug delivery systems have gained significant attention in recent years. These systems can be readily developed and are capable of promoting the modified release of active ingredients within the body. For instance, Chen et al. reviewed the use of nano-carriers for imaging and sensory applications and discussed their therapeutic effects. Similarly, Pelaz et al. provided a comprehensive overview of the applications of nano-carriers in nano-medicine and discussed emerging opportunities and challenges in this sector. Although various nano-carriers exist with different drug release profiles, ongoing strategies are being developed to enhance the specificity of nanostructures for targeting specific regions within the body. Additionally, efforts are being made to reduce immunogenicity by coating or chemically functionalizing nanostructures with various substances, such as polymers, natural polysaccharides, antibodies, cell membranes, tunable surfactants, peptides, and more. In instances where drugs lack binding affinity for a specific target or cannot cross barriers like the blood-brain barrier or the blood-cerebrospinal fluid barrier, ligand-modified nano-carriers are employed to traverse the cell membrane, enabling targeted and controlled drug delivery in a specific environment. [11-15]

## 5. Nanoparticles used in Drug Delivery

A variety of biopolymeric materials are utilized in drug delivery systems, each with distinct properties that make them suitable for different applications. Chitosan is known for its muco-adhesive properties, allowing it to act within tight epithelial junctions. Consequently, chitosan-based nano-materials are widely employed in sustained drug release systems for various epithelial types, including buccal, intestinal, nasal, ocular, and pulmonary tissues. For example, Silva et al. prepared and assessed the efficacy of a 0.75% w/w isotonic solution of hydroxyl-propyl methylcellulose (HPMC) containing chitosan /sodium tri-polyphosphate/hyaluronic acid nano-particles for delivering the antibiotic ceftazidime to the eye. The rheological synergism parameter was determined by measuring the viscosity of the nano-particles in contact with mucin in varying mass proportions. The lowest viscosity was noted when chitosan nano-particles interacted with mucin.

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Despite this, the nano-particles exhibited muco-adhesion, resulting in strong interaction with the ocular mucosa and prolonged antibiotic release. This suggests that these nano-particles could extend the drug's lifespan in the eye. Additionally, the nano-particles demonstrated no cyto-toxicity in the two cell lines tested and were able to maintain their antibacterial activity, making them a promising formulation for ocular drug delivery with enhanced muco-adhesive properties. Another bio-polymeric material used in drug delivery is alginate. This biopolymer contains terminal carboxyl groups, classifying it as an anionic muco-adhesive polymer. Alginate is known for its superior muco-adhesive strength compared to cationic and neutral polymers. For example, Patil and Devarajan developed insulin-loaded alginate nano-particles incorporating nicotinamide as a permeation enhancer. This formulation was designed to reduce serum glucose levels and increase serum insulin levels in diabetic rats. Cellulose and its derivatives are widely used in drug delivery systems, primarily for modifying the solubility and gelation properties of drugs, which in turn helps control their release profiles. Elseoud et al. studied the use of cellulose nanocrystals and chitosan nano-particles for the oral delivery of repaglinide, an anti-hyperglycemic agent. The chitosan nanoparticles exhibited a mean size of 197 nm, while the hybrid nano-particles made from chitosan and cellulose nano-crystals containing RPG had a mean diameter ranging from 251 to 310 nm. The presence of hydrogen bonds between the cellulose nano-crystals and the drug led to a sustained release of RPG. Additionally, the nano-particles made with oxidized cellulose nano-crystals showed a slower release compared to those made with native cellulose nano-crystals. Liposomes are widely utilized in both the pharmaceutical and cosmetics industries for transporting a variety of molecules and are among the most extensively researched drug delivery systems. They represent a sophisticated formulation strategy designed to enhance drug delivery. Liposomes are spherical vesicles made up of phospholipids and steroids, typically ranging in size from 50 to 450 nm. They are considered effective drug delivery vehicles because their membrane structure closely resembles that of cell membranes, facilitating drug incorporation. Liposomes have been shown to stabilize therapeutic compounds, enhance their bio-distribution, accommodate both hydrophilic and hydrophobic drugs, and exhibit biocompatibility and biodegradability. There are four main types of liposomes: (1) Conventional liposomes, which consist of a lipid bilayer that can be anionic, cationic, or neutral, and are made of cholesterol and phospholipids. This bilayer surrounds an aqueous core, allowing both the lipid layer and the aqueous space to be filled with hydrophobic or hydrophilic substances, respectively. Polymeric Micelles are nanostructures composed of amphiphilic block copolymers that spontaneously self-assemble into a core-shell structure in aqueous solutions. The hydrophobic core of these micelles can encapsulate hydrophobic drugs such as camptothecin, docetaxel, and paclitaxel, while the hydrophilic shell ensures the system's solubility in water and stabilizes the core. Typically less than 100 nm in size, polymeric micelles have a narrow size distribution to prevent rapid renal excretion, allowing them to accumulate in tumor tissues via the enhanced permeability and retention effect. Additionally, the polymeric shell reduces non-specific interactions with biological components. These nanostructures hold significant potential for delivering hydrophobic drugs, as their core structure enhances the stability and bioavailability of these drugs. Dendrimers are highly branched, monodisperse, well-defined, and three-dimensional structures. These globular-shaped molecules feature surfaces that can be easily and precisely functionalized, making them excellent candidates for drug delivery applications. Dendrimers can be synthesized using two main approaches: the divergent method, where the dendrimer is built from the core outward, and the convergent method, which starts from the outer edges of the Dendrimer. They are classified into various types based on their functional groups, including PAMAM, PPI, liquid crystalline, core-shell, chiral, peptide, glycol-dendrimers, and PAMAMOS. Among these, PAMAM dendrimers are the most studied for oral drug delivery due to their water solubility and ability to pass through epithelial

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tissues, enhancing drug transfer via the paracellular route. However, Dendrimers face limitations in clinical applications due to the presence of amine groups, which are positively charged and potentially toxic. To address this issue, Dendrimers are often modified to reduce or eliminate toxicity. Drug loading in Dendrimers is achieved through several mechanisms, including simple encapsulation, electrostatic interaction, and covalent conjugation. Nano-crystals are solid drug particles with dimensions within the 1000 nm range, composed of 100% drug material without any attached carrier molecules. These nano-crystals are typically stabilized using polymeric steric stabilizers or surfactants. A suspension of nano-crystals in a liquid medium, known as a nano-suspension, is often prepared by adding a surfactant agent. The dispersing medium can be water, or other aqueous or non-aqueous liquids, such as liquid polyethylene glycol or oils. Nano-crystals have unique properties that address challenges like enhanced saturation solubility, increased dissolution rate, and improved adhesion to surfaces or cell membranes. The synthesis of nano-crystals is generally categorized into two approaches: top-down and bottom-up. The top-down approach includes techniques such as sono-crystallization, precipitation, high-gravity controlled precipitation technology, multi-inlet vortex mixing, and limited impinging liquid jet precipitation. However, this method can be costly due to the use of organic solvents and their subsequent removal. The bottom-up approach involves grinding processes combined with high-pressure homogenization. Metallic Nano-particles have gained significant attention in recent years for various medical applications, including bioimaging, biosensing, targeted and sustained drug delivery, hyperthermia, and photoablation therapy. The ability to modify and functionalize these nano-particles with specific functional groups enhances their capacity to bind with antibodies, drugs, and other ligands, making them increasingly promising for biomedical uses. While gold, silver, iron, and copper nano-particles are among the most studied, there is growing interest in other metallic nano-particles such as zinc oxide, titanium dioxide, platinum, selenium, gadolinium, palladium, and cerium dioxide, among others. Quantum Dots (QDs) are semiconductor nano-crystals with diameters ranging from 2 to 10 nm, and their optical properties, such as absorbance and photoluminescence, depend on their size. QDs have attracted significant interest in nano-medicine due to their unique characteristics. Unlike conventional organic dyes, QDs can emit light in the near-infrared region (< 650 nm), which is advantageous for biomedical imaging because it reduces tissue absorption and light scattering. Additionally, QDs of different sizes and compositions can be excited by the same light source to produce distinct emission colors across a broad spectral range, making them ideal for multiplex imaging. In medicine, QDs are extensively studied for their applications in targeted drug delivery, sensors, and bioimaging. A considerable amount of research is available on the use of QDs as contrast agents for in vivo imaging. [16-19]

## 6. Natural Product-Based Nano-Technology

According to the World Health Organization (WHO), traditional medicine addresses the basic health needs of about 80% of the population in developing countries. Recent scientific efforts are focusing on the study of bioactive compounds, their chemical compositions, and pharmacological potentials from various plant species. The goal is to develop novel active ingredients that have fewer side effects compared to existing drugs. Plants have long been recognized as rich sources of medicinally valuable natural compounds and continue to offer significant potential for discovering new and effective drugs. However, discovering active compounds from natural sources poses challenges due to the variability in metabolite composition in response to stress. Consequently, the pharmaceutical industry has shifted towards developing synthetic compounds. Despite this trend, the number of synthetic drugs being marketed is decreasing, leading to a renewed interest in natural product-based active compounds, despite the associated challenges. Natural product-based materials fall into two categories: (1) those designed for targeted delivery to specific locations to treat various diseases, and (2) those primarily used in synthesis processes. A significant portion of research focuses on developing treatments for cancer, which is

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currently the leading cause of death worldwide. Different types of cancer affect various organs, underscoring the importance of creating alternative medicines that specifically target cancerous cells. Despite this focus, research is also exploring nano-medicine applications for other diseases. These delivery systems are categorized based on factors such as surface charge, particle size, size distribution, shape, stability, encapsulation capacity, and biological activity, and are utilized according to their specific needs. Nano-particles have been synthesized using natural products, including metallic, metal oxide, and sulfide nano-particles. These can be produced through various microorganisms, such as bacteria, fungi, algae, and yeast, or through plant extracts. In the first method, microorganisms are cultivated in an appropriate growth medium and then introduced to a metal precursor solution, allowing for incubation to produce nano-particles either intra-cellularly or extra-cellularly. In the second method, plant extracts are combined with metal precursors and incubated at room or elevated temperatures, or exposed to light to initiate nano-particle synthesis.

Currently, natural product-based materials are highly valued for creating new nano-formulations due to their appealing characteristics, such as biodegradability, biocompatibility, availability, renewability, and low toxicity. These biomaterials can also undergo chemical modifications, providing unique and advantageous properties for nano-medicine applications. Various nano-particles, including gold, silver, cadmium sulfide, and titanium dioxide, have been synthesized using different bacteria.

## 7. Products Currently In The Market

In the field of medical nanotechnology, there are currently 51 products being used in clinical practice. These nano-medicines are primarily developed for drugs with low aqueous solubility and high toxicity. The nano-formulations are designed to mitigate toxicity while enhancing the pharmacokinetic properties of these drugs. Recent reviews by Caster et al.indicate that while only a few nano-medicines have received FDA approval, numerous initiatives are underway, with many in clinical trials, suggesting that more nanotechnology-based drugs will soon enter the market. Of these, 18 are focused on chemotherapeutics, 15 on antimicrobial agents, 28 on various medical applications including psychological conditions and autoimmune diseases, and 30 on nucleic acid-based therapies. Given the swift advancements in nanotechnology and its promising applications in nano-medicine, there is an urgent need for a more comprehensive and unified regulatory framework. Governments around the world should collaborate to establish new, stringent protocols specifically designed to address safety concerns. This will ensure that nano-medicines are released safely and provide meaningful benefits to patients.

## 8. Future Prospects Of Nano- Drug Delivery Systems

Nano-medicine stands as one of the most exciting research fields today. Over the past two decades, extensive research has resulted in the filing of 1,500 patents and the completion of numerous clinical trials. Cancer exemplifies a disease where both diagnosis and treatment have greatly benefited from nanotechnology. By utilizing various nano-particles to deliver precise amounts of medication to cancerous cells while sparing healthy cells, nano-medicine and advanced drug delivery systems are set to be a major focus of research and development for the foreseeable future. Future research will likely focus on developing materials with improved uniformity, drug loading, and release capabilities. Significant advancements in the use of metal-based nano-particles for diagnostic applications have also been highlighted in this review. Metals like gold and silver are showing promise in both diagnostic and therapeutic contexts, potentially broadening the scope of nano-medicines. A notable area of interest is gold nano-particles, which are effectively absorbed by soft tumor tissues and can enhance the effectiveness of radiation-based heat therapies, such as those using near-infrared radiations, for targeted tumor destruction. The development of nano-robots and nano-devices for tissue diagnosis and repair, which could be controlled externally, has generated considerable excitement. Although this concept is still in the realm of future possibilities, it could become a reality soon. Despite their potential benefits, it is important to conduct thorough long-

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term studies to assess the possible risks of nano-medicines to both human health and the environment. Understanding the potential acute and chronic toxicity of new nano-materials is essential. Furthermore, as nano-medicines become more prevalent, research into their cost-effectiveness will be crucial to ensure they are accessible to a broader population.

## Conclusion

In summary, this review highlights the latest advancements in nano-medicine, focusing on technological innovations in drug delivery and diagnostic methods. It explores various nano-scale materials, including nano-robots and nano-sensors, which are utilized for targeted delivery, sensing, or activation within living systems. Initially, nanotechnology aimed at improving drug solubility, absorption, bioavailability, and controlled release. Although the development of nano-drugs involves significant uncertainties and the discovery of pharmacologically active natural compounds is less common today compared to 50 years ago, enhancing the efficacy of existing natural bioactive compounds through nanotechnology has become increasingly prevalent. Notable examples include the therapeutic applications of nanotechnology for compounds such as berberine, curcumin, ellagic acid, resveratrol, and quercetin. The effectiveness of these natural products has been significantly enhanced using various nano-carriers, including gold, silver, cadmium sulfide, and titanium dioxide nano-particles, as well as solid lipid nano-particles, crystalline nano-particles, liposomes, micelles, super-paramagnetic iron oxide nano-particles, and dendrimers. There has been a sustained demand for novel natural biomaterials due to their advantages of being biodegradable, biocompatible, readily available, renewable, and low in toxicity. Research is currently focused on improving the stability of these natural biopolymers, such as polysaccharides and proteins, in industrial processing environments and biological matrices. Advanced techniques like cross-linking are being explored to enhance their stability and functionality. Regulatory mechanisms for nano-medicines, along with comprehensive safety and toxicity assessments, will be a focus of future development. Despite these challenges, nano-medicine has already transformed drug discovery and delivery in biological systems. Advances in this field have enhanced our capacity to diagnose diseases and have made the integration of diagnosis and therapy a practical reality. A significant area of interest in recent nano-medicine development is the integration of therapy and diagnosis, known as theranostics, with cancer as a prominent example. Notable examples include:

- Oleic acid-coated iron oxide nanoparticles used for diagnostic applications via near-infrared imaging.
- Photodynamic detection of colorectal cancer using alginate and folic acid-based chitosan nanoparticles.
- Utilization of cathepsin B-targeted fluorogenic peptide probes conjugated to glycol chitosan nanoparticles for metastatic processes.
- Iron oxide-coated hyaluronic acid used as a biopolymeric material in cancer therapy.
- Application of dextran among other materials in similar contexts.

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