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The Role of Novel Nanomaterials in Biomedical Applications

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Abstract

Nanotechnology is an innovative field of science that has revolutionized numerous biomedical applications, including drug delivery, gene transfer, disease diagnostics, imaging, theranostics, tissue engineering, biosensor development, and biocatalysis techniques. This field deals with small sized materials called nanomaterials, which can be metals, polymers, or semiconductors, having different properties that scientists use according to their requirements. They possess properties like high surface area, biocompatibility, and antioxidant capability and are also antimicrobial. These properties have enhanced their ability to diagnose the disease early, especially helping drug delivery to precise targets where they can release drugs only when specifically stimulated. Nanomaterials have improved the precision and efficacy of cancer treatments, imaging techniques, and regenerative medicine. Biosensors and biocatalysts utilizing nanomaterials have significantly enhanced the sensitivity and efficiency of diagnostics and industrial applications.

Despite these advancements, challenges like toxicity, accumulation in biological systems, and environmental impacts still exist that raise concerns regarding biocompatibility and safety and need to be catered prior to large scale applications and marketing.

Keywords: *Nanotechnology, Theranostics, Nanomaterials, Biosensors, Biocompatibility*

Introduction

Nanotechnology has endured exponential growth in the last decade and has offered several benefits. Employing nano-scaled particles ranging between 1 and 100nm in one dimension has revolutionized almost every walk of life [1]. Particularly, nanoparticles have attained special attention in biomedical field because of their specific characteristics like antimicrobial activity [2], antioxidant properties, catalytic activity [3], loading capacity [4], anti-inflammatory properties [5], and many other. Nanotechnology covers a wide range of application from diagnostics to imaging, therapeutics, regenerative medicines and personalized medicines.

Nanoparticles have played a key role in all these applications because of their size, biocompatibility, and large surface area [6]. They are able to carry the drug to the specific target points thus making targeted drug delivery possible. In addition they can they are also effective in transporting the protein, DNA, and hydrophobic drug molecules which are difficult to deliver with conventional tools and solvents (Figure 1) [7]. Interestingly, more than ninety nano-drugs are available in the market [8] and many in progress.

Although nanotechnology offers a lot of improvement in biomedical field, there are still some concerns. The main factor that needs to be consider is accumulation of nanoparticles in living organisms because of their size and ability to cross the biological barrier [9]. Research should be conducted to make biodegradable nanoparticles through green synthesis so that nanoparticles could not get accumulated and cause further problems. Many efforts are going on to overcome this issue. For example green synthesis of metal nanoparticles using plant growth promoting rhizobacteria that offers eco-friendly and sustainable approach is under research [10]. The other major concerns related to nanoparticles are their cytotoxicity and their impact on the natural ecosystem because of their size. To overcome this problem regulations and policies are made by different organizations at national and international level [11].

The present review explores the history, classification, production methods, future perspective, challenges and the applications of nanoparticles in the biomedical field.it emphasize the role of nanoparticles in different biomedical techniques and approaches like drug delivery, diagnostics and imaging. It provides an understanding of the importance of nanoparticles in tissue engineering and regenerative medicine and how they can help in the treatment and diagnosis of different diseases. But their limitations like cytotoxicity, accumulation and manufacturing of these nanoparticles from laboratory to large scale up industry is still associated with difference of opinions, though researchers are going on to overcome these challenges and to exploit their full potential.

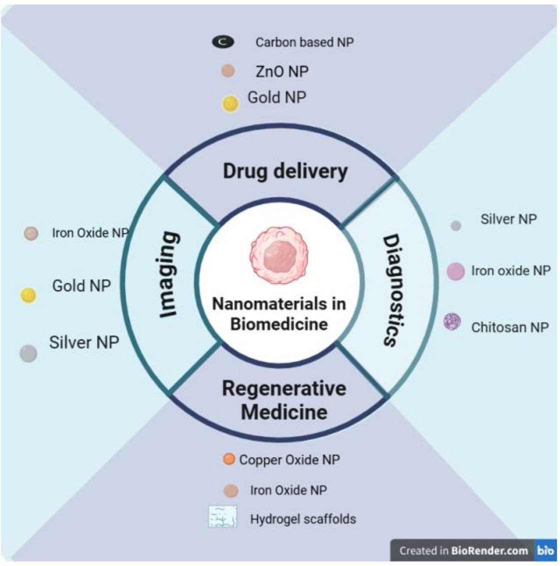

Figure 1: overview of Nano-materials in Biomedicine (This diagram has been prepared by BioRender https://BioRender.com)

3. History of Nanomaterials in Biomedicine

- ***Brief history of nanomaterials in biomedical research***

One of the earliest examples of nanotechnology is the Lycurgus cup produced in 4th century by Romans. It was renowned due to its dichroic nature (appears green in regular light or red or purple when light shines through it). It possessed this ability because the materials used to construct it were gold or silver nanoparticles [12]. Nevertheless, the proper scientific study of nanoparticles began in 1857, when Michael Faraday highlighted his work at the Royal Society of London that nanoscale material behave differently than those at larger level. For example gold looks yellow in bulky form, as opposed to its nanoscale counterpart that exist in either red or purple colour [13]. Moving forward, in 1959, Richard Feynman's statement caught attention of the research community, stating "There is Plenty of Room at the Bottom" during his lecture at the American Physical Society meeting. He even mentioned the use of tiny robots in medicine to examine, treat, or support damaged organs [14]. Interestingly, in 1981, Gerd Binning and Heinrich Rohrer developed the Scanning Tunneling Microscope (STM) by which scientist were able to scan the individual atom, and in 1986 the more advanced version of STM, the Atomic Force Microscope (AFM) was invented by Calvin Quate and Christoph Gerber, which further enhanced the ability to observe and manipulate the nanoscale structures at atomic levels [15]. These inventions led to the progress of nanotechnology in many disciplines including biomedicine.

In 1991, Drexler, Peterson and Pergamit published a book "Unbounding the Future: the Nanotechnology Revolution" in which the term “nano medicine” was presumably used for the first time [16]. Similarly, in the early 20th century, the concept of magic bullets was introduced by Paul Ehrlich's for targeted drug delivery inspired by the concept of "Freikugeln" in the opera Der Freischutz, resulting in the creation of nanoparticles in medicine. In the late 1960s , the first nanoparticle was created by Professor Speiser's team for assisting in therapeutics [17]. It was experimentally proven that insulin nano capsules showed long term results, both subcutaneously ($P<0.001$) and through intragastrical routes ($P<0.001$) on glycemia as compared to regular insulin [18].

- ***Milestones in nanomaterial applications for healthcare and treatment***

Another breakthrough was reported at the beginning of 2005 the first economical drug product using nanoparticles (Abraxane™, a composition of human serum albumin nanoparticles with paclitaxel) introduced on the market by US company, Abraxis Oncology [17]. In 1995 doxil became the first FDA approved drug and sales in USA and Europe in 1996 [19]. There are a number of other nano drugs which were approved by FDA after that, for example DaunoXome® approved in 1996, Visudyne® approved in 2000, NanoTherm® approves in 2003, DepoDur® approved in 2004, Cimzia® approved in 2008, Feraheme™ (Ferumoxytol) approved in 2009, Marqibo® and Opaxio® approved in 2012, and Kadcyla® approved in 2013 [20]. All these achievements proved very beneficial especially in the field of biomedicine.

Classification and production of nanoparticles

Nanomaterial classification is crucial for understanding their diverse properties, maximizing their applications, and determining their regulatory and potential interactions with biological systems. Nanomaterials have diversity in their structures, compositions, and functionalities, that's why they are categorized using various criteria. This classification is based on the material they are made of, along with their properties in order to identify the most suitable nanomaterials for specific biomedical applications.

Types of Nanomaterials

Nanomaterials are being classified based on their composition, having specific properties. The primary classifications include metallic nanomaterials, polymeric nanoparticles, carbon-based nanomaterials, hybrid nanomaterials, and supramolecular nanomaterials (Figure 2). These categories are distinguished by their unique physicochemical properties making them suitable for different biomedical applications. These include several categories, that have been discussed in the next section.

Metallic nanomaterial

Metallic nanomaterials are known for their biocompatibility, thermal conductivity, and have potential multifunctional applications. The most commonly used nanomaterials include gold, silver, and iron oxide nanomaterials. Gold nanomaterials exhibit a strong surface plasmon resonance (SPR) that have applications for the treatment of cancer, theranostics, photothermal therapy (PTT), biosensing, and imaging. [21]. Silver nanoparticles have antimicrobial properties making them beneficial against bacteria, algae, and fungi. [22, 23] [24]. Iron oxide nanomaterials have superparamagnetic properties, making them efficient in targeted drug delivery.[25] Recently nanomaterials are being made by combining two metals, such as gold-silver or gold-platinum, having increased catalytic activity and stability that can be used for Multi-Modal Therapies and Imaging.

Polymeric nanoparticles

Polymeric Nanomaterial are constructed from polymers like polyethylene glycol (PEG) or polylactide-co-glycolide (PLGA), have applications in the *in vitro* transfer of therapeutic and diagnostic agents because of their bio-resorbability, tunable properties, and ability to encapsulate diverse therapeutic agents. While non-biodegradable polymers such as PolyMethyl MethAcrylate (PMMA) have been explored, their non-biocompatibility poses significant limitations, making them less favorable for biomedical applications. [26], which necessitates the need for biodegradable nanoparticle production. They are made from polylactic acid (PLA), polyglycolic acid (PGA), poly(lactic-co-glycolic acid) (PLGA), and polycaprolactone (PCL) that degrades into a-toxic byproduct[27].They are used for targeted nano-delivery of cancer therapeutics [28], as effective gene-transfer material [29] and in vaccination protocols to enhance the delivery and efficacy [30]. Dendrimers are synthesized using organic polymers and are well-defined, monodispersed, and have multiple functional groups that allow surface modification. They also have many biomedical applications including targeted drug delivery. [31].

Carbon-based nanomaterials

Carbon-based nanomaterials are diverse in nature because carbon possesses various allotropes. They have many applications because of their physiochemical properties, such as high mechanical strength, surface area electric conductivity, and biocompatibility. These include fullerenes, graphene, quantum dots**,** graphene oxide, carbon nanofiber, and carbon nanotubes. Fullerenes are spherical molecules composed of carbon, C_{60} can intermediate photosensitized reaction as they absorb a broad spectrum of light this ability makes them beneficial in photodynamic cancer therapy. [32]. Carbon quantum dots (CQDs) are spherical and smaller than 9nm in diameter. They have absorbance, photoluminescence, and photoinduced electron transfer properties making them advantageous in bioimaging and therapeutics. [33]. Carbon-based nanomaterials because of their versatility in structure and properties have numerous biomedical applications.

Hybrid Nanomaterials

Hybrid nanomaterials are made from two distinct types of material on a nanoscale level in order to enhance properties of both. This category includes organic-inorganic hybrids, Polymer-Metal hybrids, Carbon-Based hybrids and interestingly due to their synergistic properties. All of these have vast applications in biomedical science.

Supramolecular Nanomaterial

Supramolecular means more complex than a molecule. Supramolecular-based nanomaterials (SMBNs) are made by self-assembling molecules that do not have covalent interactions. SMDNs rely on dynamic and reversible interactions, causing them to have highly organized, self-assembling structures such as micelles, nanotubes [34], nanospheres, nanocapsules, and hydrogels [35]. They are further classified based on the building blocks like peptide amphiphiles, cyclodextrins, amyloid protein, and supramolecular polymers. Their functionality at the nanoscale level; makes them significant in the biomedical field.

Production Methods

For the production of nanomaterials, it is important to understand that their synthesis involves techniques designed to control their size, shape, and surface properties at the nanoscale. Various methods are employed to tailor nanomaterials for specific applications, particularly in the biomedical field (Figure 2).

Top-down approaches are commonly used, which involve breaking down bulk materials into nanoscale particles through physical or mechanical methods. The method includes mechanical milling, lithography, particle beam lithography [36], photolithography, and Laser ablation to produce nanoscale structures.

When bulk structures are broken then **Bottom-up approaches** are used which are more precise and specified. The bottom-up approach involves the building up of particles on the nanoscale by using atoms and molecules as a building unit. Chemical Vapor Deposition (CVD) is a method in which thin film is obtained by a chemical reaction of gaseous precursors. [37].Spray pyrolysis is a method in which solution is atomized in fine droplets and is rapidly heated to evaporate solvent and left outs are nanoparticles [37]. Sol-Gel Process involves the conversion of polymers into fine gels of the polymer into fine gels and then drying or calcination to yield nanoparticles [38].

Biological systems are also being utilized, such as microbes [39], plant extracts, or enzymes, to produce nanoparticles in an eco-friendly manner through bottom-up approach. Moreover, Bottom-up approaches are widely adopted for their ability to produce nanoparticles with high precision and scalability.

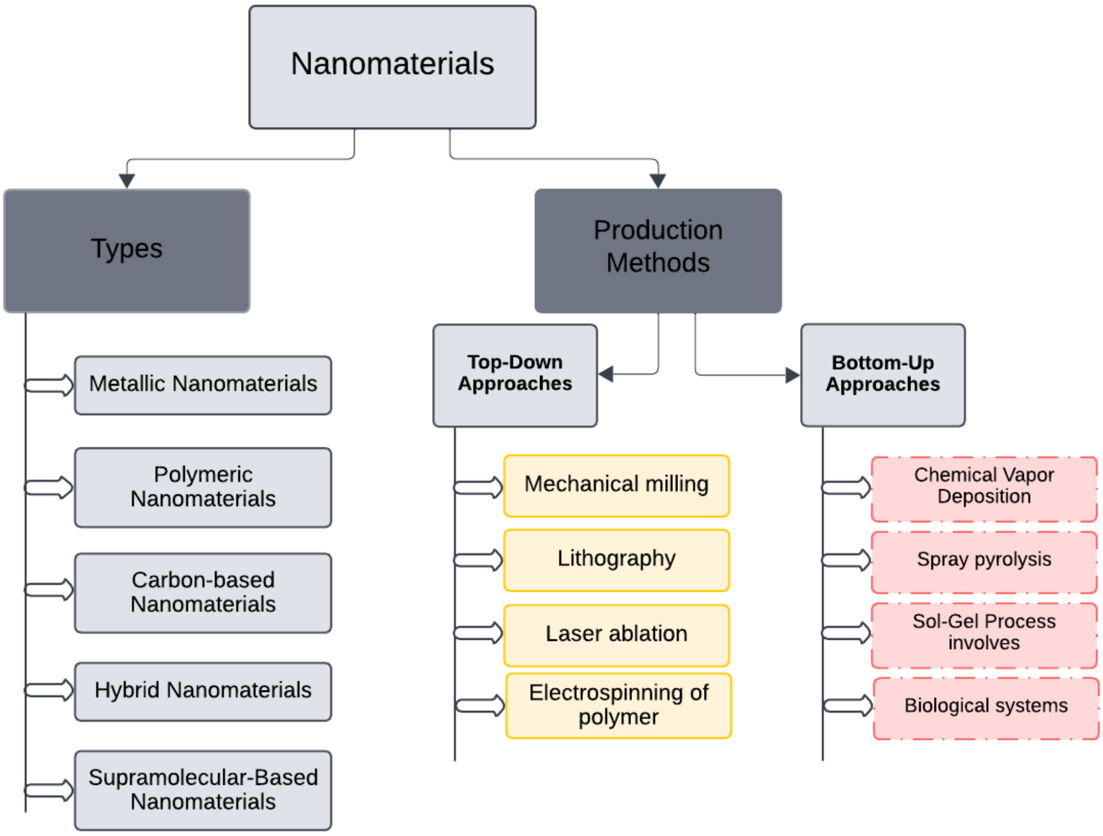

Figure 2: Classification and Synthesis Methods of Nanomaterials

Emerging Nanomaterials in Biomedical Research

Nanomaterials have revolutionized biomedical research due to their properties, biocompatibility, and efficiency. Some newly emerging nanomaterials include silicon Nanoparticles (SiNPs) and sustainable and biodegradable nanomaterials. We have explained them briefly in the following sections:

Silicon Nanoparticles (SiNPs)

Silicon is the most abundant electropositive element in the Earth's crust. It is biocompatible and bio-durable, having properties like hydrophobicity, chemical stability, thermal stability, and low surface tension. Particularly, Gadolinium silicate-coated porous silicon nanoparticles are used as tumo- targeting agent [40], Gadolinium silicate-coated porous silicon nanoparticles are used as an MRI contrast agent and drug delivery carrier [41] , and as biosensors [42].

Sustainable and Biodegradable Nanomaterials

As environmental concerns grow, sustainable and biodegradable nanomaterials have emerged as vital alternatives to conventional materials. These nanomaterials, including cellulose nanocrystals, chitosan, and PolyLactic Acid (PLA), are derived from renewable resources and designed to degrade into non-toxic byproducts. In drug delivery, biodegradable nanomaterials enable sustained drug release, reducing the need for repeated dosing and invasive retrieval after treatment. In regenerative medicine, these materials act as scaffolds for tissue repair, gradually degrading as new tissue forms [23]. These sustainable materials also hold potential in bioimaging [24] and diagnostics, where biodegradable agents offer lower toxicity and better clearance from the body. Their alignment with green chemistry principles ensures they meet both biomedical needs and environmental sustainability goals.

Key Biomedical Applications of Nanomaterials

Nanotechnology has transformed the biomedical field by introducing the innovative ways in the early diagnosis and treatment of diseases (Figure 3). Here is the crux of some vital biomedical applications of nanotechnology:

Drug Delivery System

Most therapeutics and treatment options involve non-targeted drug delivery systems that cause several side effects. In the case of cancer, chemotherapy is one of the most used treatment options but because of its non-targeted nature, it causes some detrimental side effects in the patients. They may face problems like constipation, vomiting, diarrhea, and thrombocytopenia due to toxicity of chemotherapeutic drugs [43].

To solve this problem nanotechnology has played a key role by lowering the side effects and selectively targeting the cancer cells. Literature shows that Mg^{+} doped ZnO nanoparticles have been used for the optimization of drug delivery especially in case of gastric cancer [44]. Research shows that Carbon-based nano-materials drug delivery systems are capable of targeted treatment of solid tumors [45]. Likewise, gold nanoparticles are used as drug carriers in the treatment of rheumatoid arthritis and increased the therapeutic efficiency of the drug [46].

Diagnostics and imaging

Early diagnosis of disease is the most important step for the recovery from that particular disease. In case of cancer the main reason of death is the late diagnosis [47]. This may be because we still do not have advanced diagnosis protocols. One of the main techniques that is used is magnetic resonance imaging which has high resolution but less specificity and the other diagnostic assay is Polymerase Chain Reaction (PCR) that provide specificity but is time taking [48].

In this hour of need, magnetic and fluorescent nanoparticles provide a potential solution to this problem using optical fluorescence imaging using gold nanoparticles (AuNPs). With their biocompatibility, high surface area, fluorescence and their ability to bind to biological element they are widely used in optical fluorescence imaging [6]. For instance, 5-HT-Fe3O4-Cy7 nanoparticles (5HFeC NPs) are used in imaging for accurate detection of Atherosclerotic plaque. This is done by targeting active myeloperoxidase using fluorescence imaging [49]. For fast fluorescence imaging and antibacterial treatment of bacterial keratitis novel NTR-responsive copper-based nanoparticles (Cu2-xSe@BSA@NTRP) were designed, which shows significant efficacy (95%) and significant re-epithelialization against *E. coli* and *S. aureus* ($p < 0.05/0.01$) for the cure of corneas infection [50]. Moreover, other nanaparticles are being widely incorporated in imaging techniques such as magnetic resonance imaging (MRI), fluorescence-labelled imaging, Computed Tomography (CT), and others for more accurate detection and diagnosis of diseases. Studies show that porous and solid gold nanoparticles improved the detection of lung cancer [51]. Thus, in diagnostics and imaging, nanoparticles are providing solutions to the current limitations of various techniques by accurate and targeted diagnosis.

Theranostics

Theranostics is an advance field of medicine combining both diagnostics and treatment therapies. Nanoparticles showed great advancement in theranostics as they provide accurate and targeted diagnosis and treatment options [52]. Studies show that gold quantum dot nanoparticles inhibit the growth of tumor cells by reducing the metastatic events thus are used in cancer therapy [53]. Carbon nanotubes because of their surface area, mechanical strength, thermal and electrical conductivity and stability are used as drug carrier and also as imaging contrast agent [54]. Another nanomaterial chitosome(liposome nanoparticles coated with chitosan) loaded with luteolin are used for brain targeted delivery to treat Alzheimer [55]. In cancer theranostics, gold nanoparticles manufactures through green nanotechnology showed long term and efficient therapies as they excel the targeted drug delivery and diagnostic imaging [56]. **Mn:ZnS Quantum Dots@Cellulose Nanofibrils (CNFs) Hydrogel Biosensor** detects glutathione (GSH) in blood plasma effieciently with high sensitivity and providing uncontaminated detection [57].

Although nanoparticles are of great use and provide broad spectrum of biomedical application, but toxicity and biocompatibility of nanoparticles should be considered very carefully.

Tissue Engineering and regenerative medicine

Tissue engineering and regenerative medicines (TERM) involve the repairing and replacement of damaged cells or tissues. Nanoparticles offer a great help by their unique properties like surface area, biocompatibility, and antimicrobial properties [58]. In TERM one of the most important studies involve extracellular matrix (ECM) as it regulates the cell function [59].

Nanoparticles play a key role in TERM as they can mimic the properties of ECM by facilitating the growth of cells. Several strategies are used to mimic the properties of ECM, one of which is multifunctional scaffolds that are designed to support the cell growth and proliferation to form desired tissues [60]. For example, β-TCP/BG_Cu (β-tricalcium phosphate/bioactive glass coated with copper oxide nanoparticles) proved to be promising as multifunctional scaffold in bone regeneration and exhibit strong antimicrobial activity while maintaining cell viability in bone tissue engineering [61].

Likewise, Iron Oxide derived nanoparticles are used in the magnetothermal approach in stem cell therapy and tissue engineering for in-vivo tracking, and magnetic targeting of transplanted stem cells specially in mesenchymal stem cells without disrupting proliferation and differentiation [62]. Further, researchers found potential in hydrogels and gold nanoparticles in cardiac and nerve tissue engineering because of their properties like structural support, and self-healing properties. Besides their applications, it is necessary to evaluate the functionality and optimization of nanoparticles to fully achieve the desired results [63].

Biosensors and Diagnostics

A biosensor is an electronic device that helps in identifying the biological component through a transducer by producing the signal and is widely used in diagnostics and therapeutics [64]. Due to the broad range of applications of the nanoparticles, they are being used in biosensors for diagnostic purposes by increasing sensitivity and specificity. Studies show that biosensors made of micro screen printed electrodes (µSPE) and modified Au-Pt nanoparticles are used in the detection of glucose level with fast response, higher sensitivity, and wide concentration range from 0.1nM to 500µM [65]. Biosensors with nanoparticles are also being used to increase the precision and reliability of early detection of various diseases. Electrochemical biosensors with an array of modifying carbon nanotubes are developed for the detection of multiple biomarkers like C- reaction protein (CRP), carbohydrate antigen 125 (CA125), carcinoembryonic antigen (CEA) in human serum plasma for cancer detection [66]. For the early detection of diabetes, scientist used the machine learning (ML) tool, the techniques involved for its early detection with high accuracy are k-nearest neighbor (KNN) and Random Forest algorithm. Experiment shown that k-nearest neighbor (KNN) achieved an accuracy of 98% while Random Forest algorithm shows an accuracy of 87% for early diagnosis of diabetes [67] [68] Despite their promising applications, there are certain limitations related to nanoparticles like reproducibility, cost issues, and time that are the main concerns of research.

Biocatalyst

Biocatalysts are biological molecules or enzymes that speed up the rate of chemical reaction by lowering the activation energy and thus increasing the efficiency and specificity. It is often facilitated by enzyme immobilization, a technique used in industrial processes for the stability and further recovery of enzymes [69]. Magnetic nanoparticles like magnetite Fe3O4 are being used in enzyme immobilization due to their strong magnetic properties, low toxicity, and biocompatibility with biological materials [70].

Nano-biocatalysts are being used in various fields such as drug delivery, pharmaceutical, waste treatment, biofuel, etc. Nano porous core shell particles like lipid polymer hybrid particles shows potential in drug delivery [71]. Glucose oxidase enzyme immobilized on selenium nanoparticles are used in biosensors for determination of glucose in body fluids. Literature reports show that cellulases immobilized on gold coated magnetic silica nanoparticles are used in the generation of biofuels [72]. They also have been used in biomedicine. It is reported that folic acid-functionalized chitosan nanaoparticles are used to deliver catalase in case of spinal cord injury because the efficacy of drug was limited in that particular disease [73].

While using nanomaterial in any application, their toxicity, and biodegradability should be considered for safe and eco-friendly use.

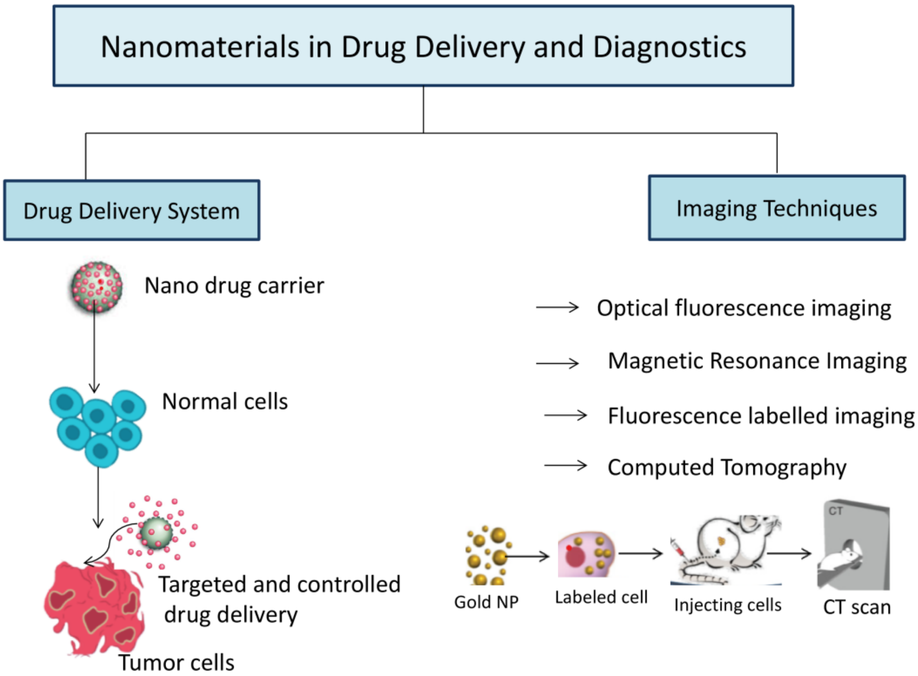

Figure 3: Nanomaterial Applications in Drug Delivery and Diagnostics

Stimuli-Responsive Nanomaterials

Stimuli-responsive nanomaterials (SRNs), also termed " Smart Nanomaterials," have significant biomedical applications due to their ability to change physiochemical properties according to stimuli. This is beneficial for drug delivery as it prevents the untimely release of drugs, for diagnosis, wound healing, etc (Table 1). Nevertheless, designing nanoparticles that respond to specific stimuli after entering the complex and dynamic biological system is challenging and needs attention.

Interestingly**,** SRNs are designed for precise drug delivery and releasing therapeutic drugs upon the onset of specific stimuli. These stimuli are categorized as internal (e.g., pH, redox, enzymatic activity, and ionic strength) and external (e.g., temperature, light, magnetic fields, and ultrasound), some of their examples and biomedical applications are enlisted in Table 2.

Table 1: Stimuli-responsive Nanomaterials and their Biomedical Applications

Stimulus Type	Stimulus	Nanomaterials	Biomedical Applications	References
Internal	pH	PEGylated DOX-MSNs, poly(l-histidine) grafted carbon nanotube	Release drug on specific pH environment for targeted Drug delivery	[74] , [75]
		ZIF-8 (Zeolitic Imidazolate Framework-8)	Metal-organic framework use for Drug Delivery and Bioimaging	[76]
	Redox	PEGylated mesoporous silica core-shell redox-responsive nanoparticles	Paclitaxel delivery for breast cancer	[77]
	Enzymatic	Hyaluronic Acid-Coated Nanomedicine	Use in Cancer therapy, release drug in the presence of hyaluronidase	[78, 79]
	Ionic Strength	chitosan nanoparticles	Influences aggregation and stability by screening electrostatic interactions	[80]
External	Temperature	poly (N-isopropyl acrylamide) nanoparticles	delivery of simvastatin acid in hyperthermic conditions	[81]
	Light	chitosan nanoparticles	drug targeting towards MDA-MB-453 cells	[82]

	Magnetic Field	Fe_3O_4-CA nanoparticles	magnetically active scaffolds Changes in gene expression profile of normal human fibroblasts	[83]
	Ultrasound	microbubbles (MBs) coated Cu-Se nanoparticles	anticancer activity in human ovarian cancer cells	[84]

RNMs (Responsive Nanomaterials) in Disease Detection and Treatment

Introduction to RNMs

Responsive nanomaterials are being created to developed innovative unique functionalities [11]. Responsive nanomaterials are a flexible and energetic type of materials that have the ability to respond to various stimuli, making them very useful in areas such as medicine, sensing and imaging. These abilities make them efficient and enhanced their functionality.

Table 2: Responsive nanomaterials and their Biomedical Applications

Types	**Bio Relevant Stimuli**	**Applications**	**Ref**
Biologically Responsive Nanomaterials	• PH • redox potentials	• Biosensing • bioimaging • photoacoustic imaging	[85]
Optical Responsive Nanomaterials	• Temperature • pH • ionic strength • humidity	• Biomedicine sensing • photocatalysis	[86]
Enzyme-Responsive Nanomaterials	• Temperature • light • magnetic field • ultrasound • light	• theranostics	[87]
ZnO-Based Responsive Nanomaterials	• light, • ultrasound • electricity • magnetic field	• anticancer • antimicrobial • biosensors • tooth bleaching	[88]

Electrochemically Responsive Nanomaterials	• Temperature • pH	• daptive materials • responsive • electrochromic • architectures	[89]
Target-Responsive Nanomaterials	• Electrochemical and Optical/Colorimetric stimuli	• drug delivery • bioimaging • sensing	[90]
Cellulose-Based Responsive Nanomaterials	• Humidity • pH • pressure, • electricity	• Ctuators • sensors • smart coatings • nanogenerators	[91]
Polymeric Responsive Nanomaterials	• Temperature • pH • light • magnetic or electric fields	• drug delivery • sensors • separation membranes • catalysis	[92]
Stimuli-Responsive Nanomaterials	• PH • temperature • light • enzyme presence	• Drug delivery	[93]

Challenges and Limitations in Nano medicine

Toxicity and Biocompatibility Concerns

Nanoparticles are of great interest in biomedical research, improved diagnostics and treatment therapies. However there are several concerns related to nanoparticles especially toxic effect of nanoparticles like silica nanoparticles which are most widely used as drug carrier [94]. Studies show that SiNPs can induce cytokine response in bronchial cells (BEAS-2B, HBEC3-KT) [95] which can lead to chronic inflammation.

Another main concern is the biocompatibility of nanoparticles which includes several factors like accumulation, size, shape, surface chemistry and physicochemical properties [96]. Accumulation of metal oxide nanoparticles can lead to oxidative stress induction and apoptosis. As CuO NP was found as anticancer agent [97] and was widely used, they were studied to check the toxicity and biocompatibility and studies found that they were cytotoxic and can cause increase in reactive oxygen species (ROS) generation [98].

So considering these limitations there should be careful selection and preparation of nanoparticles in diagnostics and treatment otherwise these nanoparticles can be damaging and even lethal.

Manufacturing and scalability

Key parameters of nanoparticles that are used in biomedical research are size, shape, morphology, size distribution, targetability and functionality [99]. Keeping in mind all these points, there are two main challenges in manufacturing and scalability of nanoparticles that are size and cost. In biomedical research, achieving a consistent size and managing interfacial bonding hindering is a major task. Further challenges involve aggregation, contamination, degradation, and low yield during the production of nanoparticles [100].

Also large scale production of nanomedicines leads to various challenges and limitations. Studies show that large scale production of nanomedicine from a laboratory batch results in decreased size due to increase in impeller speed and agitation time [101].

Another challenge in the manufacturing of nanoparticles is to produce biosynthesized nanoparticles that are environment friendly and safe to use as cleaner and safer environment has become our top priority [102].

Regulatory and Ethical Issues

For the safe and sustainable integration of nanotechnology in the society, regulatory policies are must for safeguarding human health, preserving environment and building public trust [103]. The extensive use of nanoparticles (e.g., AgNPs, AuNPs, ZnONPs) can potentially damage the environment due to their ability to interact with living organisms and wildlife, especially in the absence of regulations or policies governing their use [11]. So, now nanoparticles and nanomedicine undergo approval process to ensure their safety, efficacy, and quality by regulatory bodies FDA, the European Medicines Agency (EMA), and China's National Medical Products Administration (NMPA). From 2003-2011, the United States took initiative for regulatory measures in nanotechnology like the 2007 EPA Nanotechnology White Paper, 2009 Nanomaterials Research Strategy, and the 2011 Nanotechnology EHS Research Strategy [104]. Thus, before implementation of any application of nanotechnology regulatory and ethical values should be considered.

Future Perspectives and Unexplored Areas in Nanomedicine

Nano medicine is considered an encouraging candidate for upcoming medical studies because of its widespread applications such as antibacterial activities against bacterial infections [105], for efficient immunosuppression retrogression [106], for treatment of post-surgery tumors such as tumor recurrence and lung cancer [107]. Nanomaterials have gained a significant research interest as the next generation of tissue repair materials, which are developed in tissue engineering and therapeutic regeneration to restore, maintain or enhance the capability of harmed tissues and organs [108]. These progressive steps highlight the therapeutic and diagnostic ability of novel Nano medicines while clearing the path for upcoming clinical deployments.

- ***Advances in Smart and Stimuli-Responsive Nano materials for precision medicine.***

The nanoparticles are designed in such a way that they are able to respond to specific triggers Such as NIR light, PH changes, and reducing agents. Due to these triggers the nanoparticles can release drugs into the cells where the cancer cells are present in the body. When nanoparticles are exposed to NIR light, they heat up and causes photo-induced hyperthermia which can lead to kill cancer cell more effectively [109]. In the coming days, investigating novel stimuli and improving stimuli-responsive nanomaterials will not only create novel opportunities in nano medicine but also facilitating more targeted, beneficial and personalized cancer treatments.

- ***Potential for Sustainable and Green Nano materials in reducing environmental impact***

By searching for natural reducers and stabilizers, there is an increasing demand for nano materials. It cause reduction in Non-green methods for example chemicals that are toxic for natural systems as well as toxic for human health [110]. For instance, for the formation of $TiO2$ nanoparticles the extract of Annona muricata L., that possess a significant antioxidant power, has been found to be a Potent reducing agent [111]. Similarly, ZnO nanoparticles which are synthesized by *Bauhinia forficata* extract show excellent photocatalytic activity under UV light emphasizing its capability for ecological cleanup and effluent rectification. This methodology can lead to the degradation of many dyes including methylene blue (98.0 %), methyl orange (84.4 %), rhodamine-B (94.64 %), Congo red (95.5 %), and malachite green (98.2 %), respectively [110]. Collectively this study tells the importance of green or sustainable nano materials in reducing environmental impact, on the other hand making progress in technologies develop for clean energy, and pollution control.

- ***Emerging applications in Personalized Medicine and real-time health monitoring.***

Small size of nanomaterials makes them differ significantly from their Larger-scale materials, it can lead to new opportunities for developing novel therapies, targeted drug delivery systems, and sensitive diagnostic tools. Moreover, with the help of Nanotechnology-based sensors and devices we can assess the medical condition of patient immediately, which allow quick diagnosis and personalized care strategies. Over time nanotechnology may pave the way for creation of nanorobots to remove cancerous growths or to carry the drugs to designated area that can move through the circulatory system [112]. For better individualized care nano based gene therapy provides targeted DNA repair allowing personalized cares and real time health monitoring.

Conclusion

Nanotechnology promises to have a great effect on the progress of novel theranostic, diagnostic, imaging, regenerative medicine and therapeutic strategies. A lot of drugs facilitated by nanomaterials had been introduced in the market which showed very positive impact on modern biomedical science. Through focused and systematic release, nanomaterials not only enhance the drug delivery system but also play vital role in early disease detection by using gold nanoparticles through diagnostic, biosensors or bioimaging and also contributed to regenerative medicine and tissue engineering. However, issues such as toxic effect of nanoparticles, biocompatibility, aggregation, contamination, degradation, scalability remain key challenges to their widespread use. Moreover, regulatory and ethical hurdles need to be tackled for the safe and sustainable integration of nanotechnology in the biomedical industry

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