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Review Article

Nanoparticles in Biology: Applications, Mechanisms and Future Directions

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Abstract
Nanoparticles have emerged as an evolutionary tool in the world of modern biology because of their extraordinary physiochemical characteristics, tunable surface chemistry, and ability to engage with biological systems at the molecular level. This review represents current innovations in the design, functionalization, and implementation of nanoparticles in an extensive range of biological fields. Their key applications include targeted drug delivery, bio-sensing, gene delivery, regenerative and personalized medicine, and remodeling of the cellular microenvironment. In this review, we will demonstrate basic interaction processes such as cellular uptake pathways, intracellular trafficking, nano-bio interface dynamics, and biodistribution, which play a vital role in the efficacy and safety of medicine. Particular attention is on biocompatibility, immunological mechanisms, and toxicity strategies in order to enhance selectivity and biological performance. Advanced directions, including smart stimuli-responsive nanoparticles, nano-bio hybrid systems, tailored bioinspired nanomaterials, and their uses in personalized and precise medicine, have been discussed. A detailed description of the present landscape and future applications of nanoparticles in biology, with an emphasis on their growing contributions in next-generation diagnostics and therapeutic advancements, has been demonstrated.

INTRODUCTION

Nanotechnology is a multidisciplinary science whereby matter is manipulated at the atomic and molecular level, typically less than 100 nanometers [1]. The technology harnesses distinctive physical, chemical, and biological characteristics at the nanoscale, allowing the design and engineering of materials, devices, and systems with operational capabilities beyond the standard range. The development history of nanotechnology has been marked by breakthroughs, such as visualization tools of atomic scale like the Scanning Tunneling Microscope, in addition to the formalization of the idea of molecular nanotechnology that aims at the assembly of matter molecule by molecule [2]. Material characteristics in this scale that include reactivity, mechanical strength, electrical conductivity, and optical behavior vary greatly compared to the properties in bulk forms, thereby providing numerous opportunities to be used in industries [3].

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Nanotechnology is rapidly establishing innovation in medicine, electronics, environmental science, energy, and manufacturing. Within the health field, it has revolutionized drug delivery and diagnostics. These nanoscale materials also find applications in environmental engineering, in the areas of advanced filtration, monitoring, and pollution control [4]. Various types of nanoparticles are being prepared with various applications, including those of antimicrobial agents, functional food additives, and environmental remediation, among others, of metallic, semiconductor, polymeric, and carbon-based nanoparticles. Coupled with immense potential, it also presents health, environmental, and even regulatory risks, welcoming the emergence of new subfields such as nanotoxicology and nanomedicine to facilitate safe and responsible application [5].

Nanoparticles have gained significant relevance in the biological sciences due to their distinct physiochemical characteristics and nanoscale dimensions that closely resemble biological molecules, including proteins and DNA [6]. These similarities of size permit nanoparticles to be coupled with biological systems specifically and make them potent means of studying and manipulating cellular processes. They have an extensive use in

bioimaging and biosensing, where the fluorescent or magnetic characteristics of nanoparticles offer a mechanism for visualizing and tracing biological molecules and cells with high specificity, along with sensitivity. Nanoparticles may be functionalized with biological components, including antibodies or ligands, which recognize particular cells or tissues, hence enhancing their applications in diagnostics and targeted therapy [7]. In the field of medicine, nanoparticles have revolutionized the drug delivery system through controlled, targeted, and sustained release of therapeutics, leading to the improved effectiveness of drugs while reducing their adverse effects. They facilitate the transfer of drugs through different biological barriers, such as the blood-brain barrier, which is significant in the treatment of neurological diseases. Besides that, nanoparticles such as silver, gold, and magnetic nanoparticles have natural antimicrobial, anti-inflammatory, and imaging properties, and thus have expanded their uses in wound healing, cancer, and regenerative medicine [8]. In addition to therapeutic applications, nanoparticles find applications in gene delivery, hyperthermia therapy, tissue engineering, and thus are versatile in biological studies and clinical practices. Recent studies take advantage of nanoparticles in the study of cellular signaling pathways and protein-protein interactions at the subcellular level, and advance our knowledge related to complex biological processes and disease pathogenesis. Their use in biology requires close attention to their biocompatibility and potential toxicity; therefore, a lot of research is underway on the path towards safe design and functionalization [9]. In general, nanoparticles are critical constituents of contemporary biological sciences that will further advance the field of diagnostics, therapeutics, and fundamental research due to their versatile, and adaptable nature [10].

This review article is a systematic investigation of the applications of nanoparticles in life sciences, which ranges from a variety of applications to underlying mechanisms and future perspectives [11]. More recent advances have been discussed in terms of the development and application of nanoparticle-based drug delivery, biosensing, molecular imaging, gene therapy, tissue engineering, and antimicrobial therapy. Putting together the information of the past decade, this review points to several good therapeutic opportunities, but also to problems of functionalization, biocompatibility, and specific targeting of nanoparticles in the complex *in vivo* environment [12]. This involves explaining how nanoparticles have also enhanced the accuracy and efficiency of interventions and diagnostics in the biological field; clarifying the physical and cellular mechanisms by which nanoparticles interact with biological systems and explaining the existing gaps and barriers to translation. Review also covers developing and future directions, including stimuli-responsive nanoparticles, nanotheranostics, and discussions on safety, ethical, and regulatory considerations critical to responsible translation and development [13]. Overall, this review intends to act as a comprehensive reference for the direction of further research and innovation applying nanoparticles to solve pivotal biomedical and biological problems.

Classification and Types of Nanoparticles

Organic Nanoparticles

Organic nanoparticles represent a special class of nanoparticles that are mainly composed of organic compounds and are non-toxic, biodegradable, and highly versatile in applications in biomedicine as mentioned in Figure 1 [14]. Examples include liposomes, dendrimers, and polymeric nanoparticles, all with unique structural features and functional capabilities. Liposomes are spherical vesicles formed from lipid bilayers that can encapsulate hydrophilic as well as hydrophobic substances, and, for this reason, they represent one of the best carriers in drug delivery and gene therapy [15]. They are biocompatible and can withstand the degradation of encapsulated agents, besides being able to release them in specific locations. Dendrimers are highly branched and three-dimensional polymeric materials with many reactive functional groups that can be functionalized to a desired chemical reaction, making them more useful in molecular recognition, sensing, and reaching drug targets [16]. Their internal cavities have capability of encapsulating molecules or therapeutic agents, thereby providing regulated release profiles and enhanced stability. Polymeric nanoparticles, which are made of biocompatible and biodegradable polymers like PLGA, are stable nanocarriers whose size and surface charge can be regulated, as well as the kinetics of drug release. These characteristics facilitate the effective transport of pharmaceuticals, genes, and imaging agents, which are characterized by lower toxicity and improved targeting potential [17]. Together, organic nanoparticles offer affordable platforms to be used in biomedical research as they can be customized in terms of physicochemical characteristics, high biocompatibility, and molecular-scale interactions with biological systems [18]. Their capability in surface modification, controlled drug release, and immunogenicity makes them useful in diagnostics, therapeutic, and regenerative medicine. Their structure and actions are under continuous optimization in contemporary research in terms of achieving their maximum efficacy and minimizing the possible side effects and toxicity [19].

Inorganic Nanoparticles

Inorganic nanoparticles are a prominent class of nanoparticles that are basically made of metals, metal oxides, and other inorganic elements [20]. They lack carbon-based structures and are well-known for their

unique physiochemical characteristics, which include high surface area, optical, catalytic, and magnetic properties. Gold, silver, silica, and magnetic nanoparticles are the most common types of inorganic nanoparticles that have certain merits with respect to various applications [21]. Gold nanoparticles are highly biocompatible products with superior optical properties (including surface plasmon resonance), easy biomolecule functionalization, and are therefore suitable in biomedicine, diagnostics, and drug delivery [22]. Due to strong antimicrobial and anti-inflammatory properties of silver nanoparticles, their applications in wound healing, coatings, and medical devices are extremely important. Silver nanoparticles have good surface chemistry, and they are chemically and thermally stable, possess a large surface area, which makes them an excellent carrier for drug delivery as well as imaging agents. The magnetic nanoparticles, which are usually made of iron oxides including magnetite or maghemite, possess special magnetic properties that enable them to be applied in MRI, targeted drug delivery by magnetic guidance, cancer treatment by hyperthermia, and biosensing [23].

The fabrication along with the structure of inorganic nanoparticles decides the critical functionality, including size, surface charge, shape, and crystallinity [24]. The stability of these inorganic nanoparticles with controllable physical characteristics renders them useful in the field of medical imaging, diagnostics, therapeutics, catalysis, and environmental remediation [25]. Unluckily, majority of the inorganic nanoparticles have shown potential toxicity and other adverse impacts on the environment; hence, their creation as well as utilization must be carefully assessed to guarantee safety and effectiveness. To conclude, inorganic nanoparticles represent a significant element of nanotechnology that can provide wide-ranging capabilities and uses in the field of science and industry [26].

Carbon-based Nanoparticles

Carbon-based nanoparticles are one of the most significant groups of nanoparticles, which are mainly quite complex structure of carbon atoms in their allotropes and nanostructures [27]. These are carbon nanotubes (CNTs), graphene oxide, fullerenes, carbon nanohorns, carbon dots, and graphene derivatives, as mentioned in Figure 1. Carbon nanotubes are cylindrical constructions constructed out of rolled sheets of graphene and split into single-walled carbon nanotubes (SWCNTs) and multi-walled carbon nanotubes (MWCNTs) [28]. Their mechanical strength, electrical conductivity, and thermal stability are extraordinarily high, and thus they can be used in a wide variety of applications such as drug delivery, biosensing, tissue engineering, and cancer therapy. Graphene oxide is a derivative of graphene, which is made of a one-atom-thin layer of carbon atoms in a hexagonal lattice with oxygen-containing functional groups attached to its surface, making it highly dispersible in biological media and easily functional on its surface to be used in biomedical applications [29].

Other essential carbon-based nanoparticles are fullerenes, which are spherical carbon molecules, with the most popular form being C60, which is a Buckminsterfullerene, having properties of free radical scavengers and efficient drug carrier abilities [30]. Carbon dots, along with nano-diamonds, belong to this category and are used in bioimaging and biosensing because of their photoluminescence capabilities and biocompatibility. This type of structure, with distinct surface chemistry of carbon-based nanoparticles, is highly chemically stable, surface properties are adjustable, and it is highly biocompatible. As a result, carbon-based nanoparticles can be extensively used in targeted drug delivery, cancer therapy, molecular imaging, antimicrobial remedies, and tissue engineering [31]. Additionally, certain carbon-based nanomaterials can respond to external stimuli, which include temperature, pH or light, and thus change their physical or chemical behavior, which could be used in smart therapeutic systems to increase their functionality. Overall, carbon-based nanoparticles are multifunctional substances and possess an immense potential in biological and medical studies because of their exceptional characteristics and the vast scope of usage [32].

Hybrid Nanoparticles

Hybrid nanoparticles are a class of advanced nanoparticles that include the incorporation of two or more constituents, organic, inorganic, or both at the nanoscale, to synergistically merge their respective properties and address the shortcomings of each material [33]. In comparison to mere physical mixtures, these hybrid nanostructures have superior functionalities and novel properties as a result of close molecular or supra-molecular interactions in the interfaces of the constituent components. Common examples of such hybrid nanostructures consist of core-shell, yolk-shell, heterodimers, Janus particles, dot-in-nanotube systems, and nano branches, all tailor-made with the aim of ensuring ideal functionality in various properties with regard to stability, biocompatibility, active targeting, and multimodal functionality [34].

Hybrid nanoparticles also tend to have organic components that provide flexibility, tunable electrical characteristics, biocompatibility, and effective luminescence, whereas the inorganic components have additional properties like magnetic responsiveness, mechanical strength, electrical conductivity, and thermal stability [35]. All these features together offer wide usage of hybrid nanoparticles in biomedicine, such as targeting of drugs, phototherapy, image-guided therapy, and novel biomedical imaging [36]. Hybrid nanoparticles are designed to meet the objective of

multifunctionality, including therapeutic and diagnostic functions, and to optimize pharmacokinetics and biodistribution to enhance efficacy and safety. Therefore, it is the versatility and increased functionality of hybrid nanoparticles that render them promising candidates to address certain complex problems in the biomedical field that would not be addressed using traditional single-component nanoparticles [37].

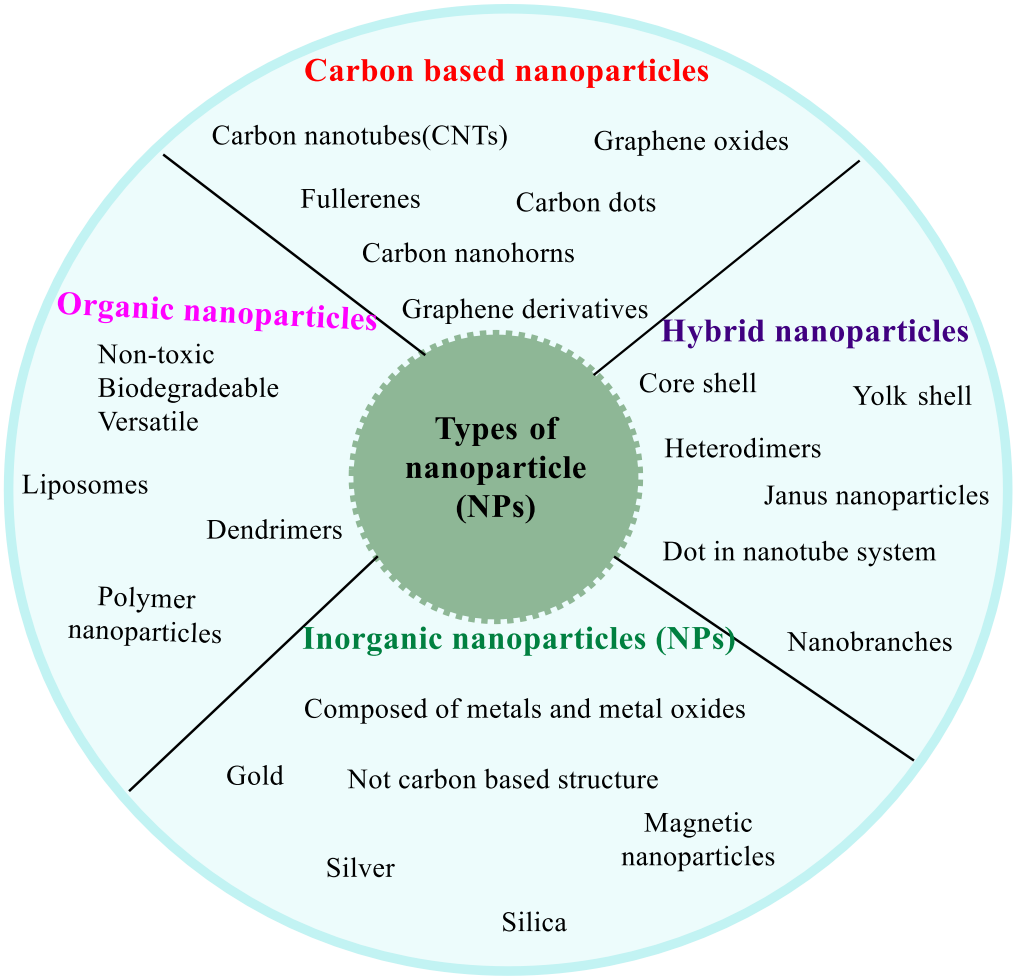

Figure 1: Types of nanoparticles and their characteristics

Synthesis and Functionalization

Bottom-Up and Top-Down Synthesis Methods

In the bottom-up strategy, nanostructures are created atom by atom or molecule by molecule, using processes that include CVD, sol-gel strategies, and molecular beam epitaxy [38]. This is indeed a constructive strategy that begins with basic building blocks, precursor atoms, or molecules, and develops them to nanoscale structures by carefully guided chemical and physical reactions. It allows for easy regulation of size, shape, and surface qualities [39]. As an example, the sol-gel technique makes use of chemical solutions as starting materials in the formation of metal oxides, and self-assembly is a self-organization of molecules into an ordered nanoarray [40]. This is quite a general approach and enables one to produce sophisticated functional nanomaterials with precisely engineered characteristics to be used in biomedicine, catalysis, and electronics. In the top-down approach, bulk materials are used and reduced in size by mechanical milling, lithography, etching, sputtering, etc., to nanosize. This is really a subtractive approach that involves breaking or carving larger pieces of material into smaller fragments, which, in many cases, results in imperfections or dispersity in size. Laser ablation and electron bombardment are also used to vaporize and subsequently condense bulk material into nanoparticles. Though top-down methods are less accurate at the atomic level, they are established in large-scale manufacturing and very effective for the preparation of nanostructured surfaces and thin films [41].

Surface Modification and Functionalization

Surface modification and functionalization are critical processes to enhance stability, biocompatibility, dispersibility and targeting interactions with biological systems. By attaching specific molecules, such as polymers, ligands, or biomolecules, to the nanoparticle surface, the physicochemical properties of nanoparticles can be finely tuned to realize their intended functionality [42]. Typical surface modification methods include covalent conjugation, in which functional groups such as amine, carboxyl, and thiol groups are chemically bound to the surface of nanoparticles to enable the binding of polymers or targeting ligands, as well as non-covalent interactions, which include hydrogen bonding and van der Waals interactions, which are less complex and less stable. As an example, polyethylene glycol (PEG), can be utilized to produce a hydrophilic stealth surface that decreases the aggregation of nanoparticles and evades the response of the immune system, which results in longer circulation times in the bloodstream [43]. Additional modifications may produce positive or negative charges in order to promote cellular uptake or permit muco-adhesion. More advanced functionalization entails the conjugation of antibodies, peptides, and other small molecules that facilitate selective targeting performance and result in enhanced distribution of nanoparticles to target tissues as well as cells to produce more significant therapeutic or diagnostic outcomes. Thus, surface modification is essential to maximize the efficacy and minimize the toxicity of nanoparticles while offering multifunctionality toward a variety of biomedical and engineering applications [9].

Bioconjugation Techniques

Bioconjugation techniques refer to the chemical or physical methods of attaching biomolecules, such as proteins, antibodies, peptides, or nucleic acids, onto nanoparticles for the formation of functionalized nanostructures with biomedical applications [44]. Common bioconjugation strategies include the formation of covalent bonds, which means that stable and specific linkages are provided by reactive functional groups of nanoparticles and biomolecules via chemistries like carbodiimide (EDC/NHS) coupling, maleimide-thiol reactions, or click chemistry. Covalent attachments give strong and durable conjugates suitable for *in vivo* applications. Conversely, non-covalent interactions like electrostatic forces, hydrogen bonding, and van der Waals forces can also provide other mild and reversible conjugations that usually preserve biological activity. Highly specific and one of the widely used is the avidin-biotin system, which uses the strongest known non-covalent interaction to connect biotinylated biomolecules with streptavidin-functionalized nanoparticles with very high affinity and specificity [45]. Overall, bioconjugation needs to be optimised very carefully to preserve the functionality of biomolecules, prevent aggregation of nanoparticles, and generate reproducible and stable bioconjugates. They would be applicable in focused drug delivery, biosensing, molecular imaging, and diagnostics. In the assessment of the successful conjugation, UV-Vis spectroscopy, dynamic light scattering, zeta potential, and electron microscopy are the characterization methods necessary to determine the quality of bioconjugates [46].

Interactions with Biological Systems

Cellular Uptake Mechanisms

The predominant endocytic pathways that are involved in internalization of nanoparticles into the cells include clathrin-mediated endocytosis, micropinocytosis, phagocytosis, caveolin-mediated endocytosis, and clathrin- and caveolin-independent routes [47]. These pathways involve invagination of the plasma membrane to internalize the nanoparticles to form vesicles, which convey the latter into the intracellular compartments. All the paths are dependent on the size of the nanoparticles, their shape, and real surface chemistry, and cell type. For example, smaller nanoparticles (usually less than 200 nm) most often penetrate by means of clathrin-coated pits, whereas larger ones may be engulfed by phagocytosis mainly within immune cells. Rarely under physiological conditions is direct penetration across the membrane with no vesicle formation seen. These pathways need to be understood for designing nanoparticles so that efficient cellular delivery with targeted effects will result [48].

Biodistribution and Pharmacokinetics

Nanoparticles, after being administered, distribute all over the body through the bloodstream. Their biodistribution depends on physicochemical properties such as size, shape, surface charge, and interactions with biological components [49]. Because of the recognition and clearance by the mononuclear phagocyte system, nanoparticles accumulate in organs with high macrophage activity, like the liver, spleen, and lymph nodes. The higher the nanoparticle size, the lower the kidney filtration rate, while larger nanoparticles are hepatically cleared. Pharmacokinetics involves the study of absorption, distribution, metabolism, and excretion (ADME) of nanoparticles. Mathematical modeling for describing nanoparticle distribution employs compartmental analysis representing blood, organs, and target tissues for predicting the fate of nanoparticles over time. Optimizing the properties of nanoparticles increases the circulation time, accumulation at target sites, and reduces off-target effects [50].

Toxicity and Immunogenicity

The contact of nanoparticles with biological systems may lead to immune reactions and make a toxic impact depending on their size, surface chemistry, composition, and dose [51]. Nanoparticles may cause oxidative stress, inflammation, or cytotoxicity by the formation of reactive oxygen species or destabilization of cell membranes. Nanoparticles can be recognized by the immune system and trigger the complement activation, cytokine release, or phagocytosis, which can undermine the efficacy of therapy or result in side effects [52]. These surface alterations minimize immunogenicity and enhance biocompatibility, i.e., by coating them with biocompatible polymers such as PEG. Toxicology (*in vitro* and *in vivo*) research fully describes the profiles of safety and assists in reducing the possible risks of clinical application [46].

Protein Corona Formation

After exposure to biological fluids, nanoparticles absorb a complicated and dynamic layer of proteins along with other biomolecules onto their surface, which is called the protein corona [53]. This corona alters the identity of the nanoparticle, therefore interfering with cellular recognition, biodistribution, and immune response. The corona makeup, however, is dependent on characteristics of the nanoparticles and the biological environment. The "hard" corona is composed of strongly bound proteins that have longer residence times, and the "soft" corona consists of loosely bound proteins that are in transient exchange. The formation of protein corona may mask the targeting ligand materials and interfere with cellular uptake mechanistic pathways. To understand and control the formation of corona via surface engineering is essential for optimization of the performance of nanoparticles in biological systems [54].

Applications in Biology and Medicine

Drug Delivery

Generally, nanoparticle-based drug delivery systems have become novel platforms in the field of biology and medicine that aim to enhance the accuracy and effectiveness of therapeutic substances through targeted delivery and controlled release processes [55]. Targeted drug delivery exploits the properties of nanoparticles to recognize and bind the specific cellular or tissue markers through the implementation of active targeting strategies. This can also be done by coating the surfaces of nanoparticles with ligands like antibodies and peptides or receptors that bind with small molecules that are overexpressed on target cells. In case of cancer therapy, nanoparticles can deliver chemotherapeutics directly to cancer cells by attaching to tumor-specific antigens and can therefore enhance the local concentration of drugs and reduce systemic toxicity [56]. Passive targeting, in its turn, also exploits enhanced permeability and retention effect (EPR) whereby nanoparticles are accumulated preferentially in tumor tissues because of leaky vasculature and inefficient lymphatic drainage [57]. Controlled release processes are an inherent attribute of nanoparticle drug delivery for the purpose of sustained and stimuli-responsive release of therapeutic substances, thereby improving treatment outcomes. The drugs may be programmed according to the diffusion, degradation, or environmental factors like pH, temperature, enzyme activity, or light exposure [58]. For instance, polymeric nanoparticles can be engineered to swell or degrade in the acidic tumor microenvironment or in the inflamed tissue, hence delivering their payload specifically at the site of disease. Drug release triggered by temperature is allowed since thermo-responsive polymers such as poly(N-isopropylacrylamide) can undergo phase transition at particular temperatures [59]. Nanoparticles can also be designed for the purpose of dual stimuli responsiveness, i.e., pH and temperature, which enables precise spatiotemporal control on drug delivery. These types of controlled release systems minimize the dosing frequency, thereby increasing patient compliance while reducing side effects of drugs via preventing the premature drug release, thereby maximizing the effect on the target site. Overall, targeted and controlled drug delivery systems based on nanoparticles are a significant move in the field of precision medicine, as they can be used to treat more complicated diseases in a safer and more efficient fashion [60].

Imaging and Diagnostics

Nanoparticles are employed in enhanced imaging and diagnostics based on their unique optical and magnetic features. These are quantum dots, fluorescent dyes encrusted into a silica or polymeric matrix, and up conversion nanoparticles that give bright, stable, and tunable emission indicators in fluorescence imaging [61]. On conjugation with targeting ligands (i.e., antibodies or peptides), they can permit high spatial resolution and detection sensitivity of a given biomolecule, cell, or tissue. NIRF nanoparticles allow better tissue penetration and minimize autofluorescence, therefore, increasing the accuracy of imaging. These nanoparticles will enable some of the drawbacks of traditional dyes, like photobleaching and poor signal intensity, to be overcome by enabling multifunctional fluorescent probes with long-term stability that can be used in real-time imaging *in vivo* [62]. Superparamagnetic nanoparticles and magnetic nanoparticles, particularly those that include iron oxides, find extensive application as MRI contrast agents because of the superparamagnetic behaviors, which lead to changes in relaxation time of neighboring protons and result in an increase in contrast, permitting a more complete delineation process of anatomical structures and pathological locations such as tumors or

inflammation [63]. Functionalization with targeting particles further leads to the localization of these nanoparticles at a particular site, thereby facilitating early diagnosis of disease. Besides imaging, nanoparticles may also be viewed as part of biosensing, where they may be used to enhance signal amplification or transduction in sensors that detect a wide range of biomolecules such as proteins, nucleic acids, or metabolites [64]. Gold nanoparticles, quantum dots, and carbon nanotubes enable the creation of electrochemical, optical, or plasmonic biosensors with increased sensitivity, specificity, and speed of response. Such nanoparticle-based biosensors show promise in applications related to diagnostics, environmental monitoring, and personalized medicine for the early detection of diseases and real-time health monitoring, as mentioned in Figure 2. Overall, nanoparticles have enhanced the sensitivity, specificity, and versatility of imaging and biosensing techniques, opening a new era of precision diagnostics with possibilities for combined therapeutic and diagnostic use (theranostics) [65].

Therapeutics

The advanced treatment modalities under discussion refer to photothermal and photodynamic therapies, in which nanoparticles play an important role in targeted and efficient cancer therapy, as discussed in Figure 2 [66]. Photothermal therapy is based on the underlying action of nanoparticles that can absorb near-infrared light and convert it into localized heat that induces hyperthermia, selectively destroying tumor cells while sparing the surrounding normal tissue [67]. Due to their strong NIR absorption and high photothermal conversion efficiency, gold nanostars, carbon-based nanoparticles, and semiconductor nanoparticles represent efficient photothermal agents. By functionalizing nanoparticles with targeting ligands, PTT can attain enhanced accumulation in tumor tissues, due to passive targeting given by the EPR effect, or active targeting, thereby maximizing therapeutic efficacy with minimum off-target effects [68]. Combination of photothermal and photodynamic therapy, involving the generation of reactive oxygen species in a light-activated manner, further enhances cancer cell killing via complementary mechanisms, including oxidative stress and thermal ablation. The use of biomimetic nanoparticles and dual-stimuli responsive carriers has been explored in recent studies for improved specificity and therapeutic outcomes with reduced systemic toxicity [69].

Nanoparticles are used as vectors in gene delivery and RNA interference for the safe and efficient intracellular delivery of nucleic acids to target cells, with the purpose of affecting gene expression. Nanoparticles protect fragile RNA or DNA molecules from enzymatic degradation and facilitate their cellular uptake by endocytosis, which enables them to escape from the endosome and release genetic material into the cytoplasm or nucleus. Delivery systems use organic nanoparticles such as polymeric and lipid-based nanoparticles, which may be functionalized for site-specific drug delivery with reduced off-target effects and improved therapeutic specificity [70]. This delivery system is used to silence post-transcriptionally acting genes of diseases by the action of RNA interference, by small interfering RNA or microRNA. Bioconjugation of nanoparticles to target ligands and protective coatings, including PEG, can be performed through the tunable surface chemistry of the nanoparticles to improve stability and decrease immunogenicity. Stimuli-reactive nanoparticles can also be designed to enable the release of genes under control of other environmental conditions, like pH or redox conditions. Such gene delivery systems have been promising in the treatment of genetic diseases, cancers, and viral infections with targeted genetic modulation with fewer adverse effects when compared to viral vectors [71].

Tissue Engineering and Regenerative Medicine

Scaffolds in tissue engineering are the three-dimensional materials that are designed to mimic the extracellular matrix (ECM), which permits cell attachment, promotes their proliferation and differentiation to facilitate tissue regeneration [72]. Nanoparticle-enhanced scaffolds combine improved mechanical characteristics, bioactivity, and adjustable porosity to produce a perfect microenvironment. The most used biomaterials are biocompatible natural and synthetic polymers such as chitosan, gelatin, polylactic acid, and polycaprolactone that are used in combination with graphene derivatives, carbon nanotubes, cellulose nanocrystals, and hydroxyapatite nanoparticles [73]. These nanocomposite scaffolds are described by an increased structural integrity as well as bio-functionality, which are closely linked with native tissues. Nanoparticles in the scaffold may be engineered as nano reservoirs in order to ensure the controlled release of different growth factors or drugs that might induce cellular responses and accelerate the healing process. The use of electrospinning and 3D printing technologies allows precise control over scaffold architecture, porosity, and surface topography, all features that are critical for promoting specific cellular behaviors and tissue in-growth [74].

Cell fate and behavior tracking after the process of translation is a crucial step in regenerative medicine to assess the treatment efficacy. Nanoparticles are also useful in cell tracking, as a contrast agent or label that can be tracked using different imaging modalities such as magnetic resonance imaging, fluorescence images, or computed tomography [75]. SPIONS, as well as quantum dots, are extensively deployed in order to ensure the tracking of stem cells or therapeutic cells *in vivo*. In addition to tracking, nanoparticles can also serve as guidance signals to control cell migration,

alignment and differentiation using bioactive molecules absorbed to surface or by controlling the mechanical and chemical characteristics of the scaffold [76]. As an example, orientations of nano-topographies stimulated by inclusions of carbon nanotubes or nanocellulose may facilitate directional cell growth, which is vital in most tissues, nerves, muscles, or tendons. In addition, the scaffolds containing stimulus-responsive nanoparticles can produce dynamic interactions with cells by releasing signaling molecules in response to environmental factors to regulate tissue regeneration. Such versatile nanoparticles are capable of two functions: improving the localization of regenerative therapy by combining therapeutic delivery with advanced imaging and cellular control [77].

Antimicrobial and Antiviral Applications

Nanoparticles are effective antimicrobial and antiviral agents due to a number of different avenues of action, thereby increasing their potential in the fight against pathogenic microorganisms and viruses [78]. The action that generally results in microbial inhibition typically consists of cell wall or cell membrane disruption, production of reactive oxygen species (ROS) that result in oxidative stress, enzyme inhibition, disruption of energy transduction, nucleic acids, and photocatalysis. Metal nanoparticles such as silver, copper, and zinc oxide induce the release of metal ions that adsorb onto the negatively charged bacterial cell walls, producing changes in the structure and permeability of the membrane, which lead to cell death [79]. The production of ROS also leads to oxidative damage of cellular components, such as proteins, lipids, and DNA, and puts the microbial cells into an oxidative stress condition that empowers the microbial antioxidant defenses. In addition, nanoparticles can stick to intracellular enzymes and nucleic acids, which disrupt microbial replication and metabolism, which are essential to life. Nanoparticles' size and shape affect the antimicrobial activity via analyzing the surface area's availability for purpose of interaction and penetration into microbial cells, and smaller nanoparticles have been observed to have higher activities due to the increased uptake of nanoparticles into microbial cells [80].

Nanoparticles in the antiviral therapy have been shown to act by preventing viral attachment and viral entry into the host cells, rupture of viral envelopes and capsids, possible generation of ROS, and disruption of machinery for viral replication [81]. The limitation of the size of the nanoparticles allows them to engage directly with the viral particles or host cells' receptors, hindering the infection process. For instance, AgNPs have been demonstrated to contribute successfully in averting the attachment of viruses to the host cell, like HIV, influenza, and coronaviruses, thereby reducing infectivity. Antimicrobial nanoparticles are also applied in the prevention or treatment of infection in wound healing and coating, and it enhances the wound healing process by decreasing the microbial loading and inflammation. Nanoparticle embedded wound dressings and coatings on medical devices offer constant antimicrobial release with barrier functions [82]. To illustrate this, silver nanoparticles embedded in dressings offer a broad-spectrum antibacterial activity while stimulating tissue regeneration and inhibiting biofilm growth. The antimicrobial coatings, which have good pathogen control, are also composed of other nanoparticles, including ZnO and CuO. The applications of functional properties of nanoparticles are used to provide localized, persistent antimicrobial effects, but avoid the systemic toxicity of traditional antibiotics. The above multifunctional applications of nanoparticles in antimicrobial wound care and surface coating, therefore, expand their use in the prevention of healthcare-associated infections and the fast and safe recovery [83].

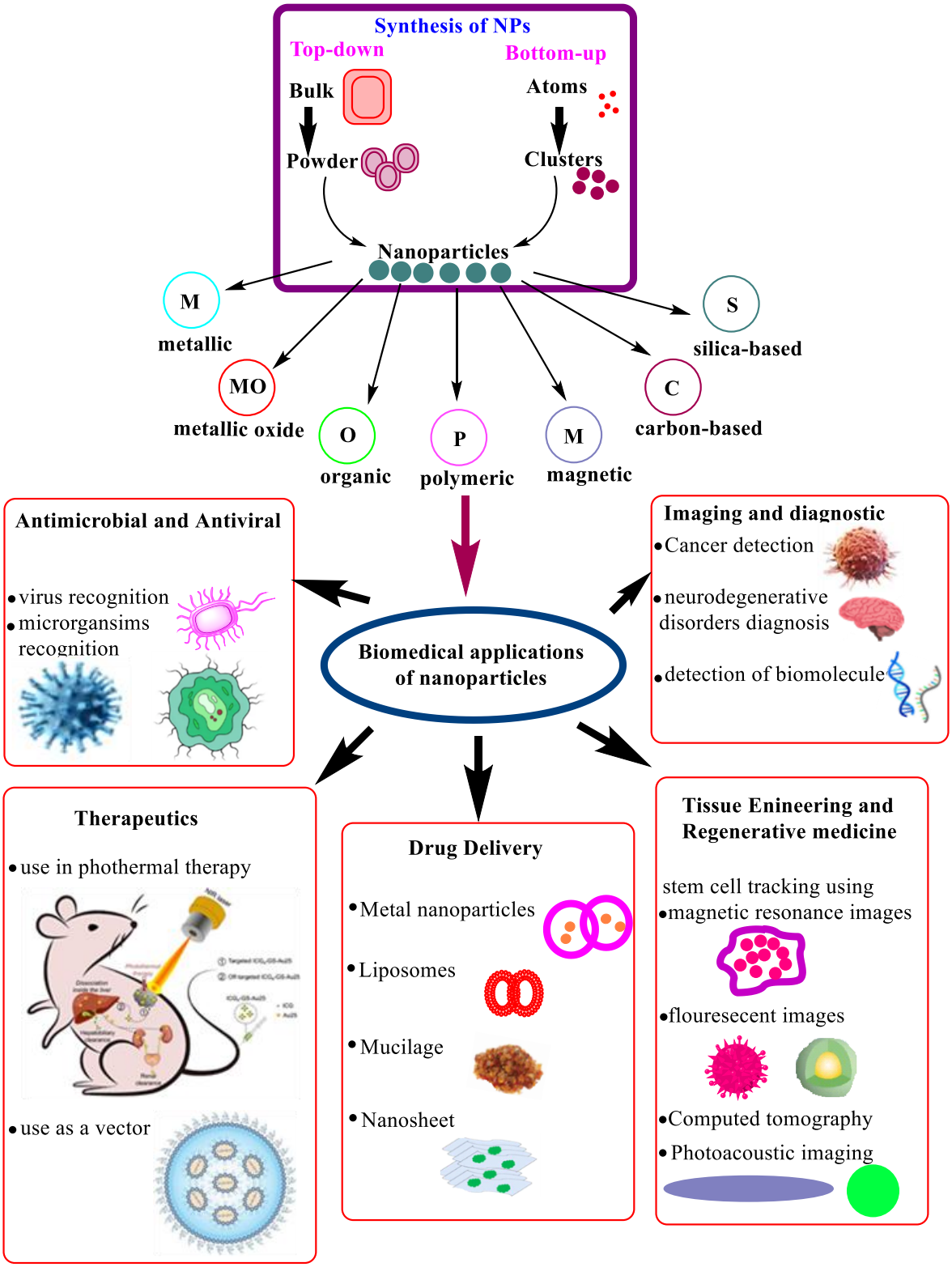

Figure 2: Synthesis of nanoparticles and their applications in the biomedical field

Environmental and Ethical Considerations

Ecotoxicology and Environmental Fate

The enhanced production and utilization of nanoparticles in various industrial sectors pose an essential concern about ecotoxicology and environmental fate. After entering the environment by manufacturing processes, product use, or disposal, nanoparticles experience complicated transformations that depend on physiochemical conditions, including pH, ionic strength, organic matter content, and exposure to light [84]. These aspects influence the nanoparticle aggregation, dissolution, chemical activity, and bioavailability, which ultimately govern their persistence in the environment and compartmental distribution, including the air, water, soil, and sediment. For instance, zinc oxide nanoparticles can flock in high salinity water or dissolve in acidic water, releasing toxic metal ions that are the sources of ecological toxicity. Subsequently, nanoparticles have the potential to bioaccumulate in organisms and move into food webs, leading to the emergence of oxidative stress, developmental defects, and behavioral shifts in aquatic and terrestrial organisms [85].

The ecotoxicological effects are related to the size of nanoparticles, concentration, coating, and duration of exposure, in which smaller particles tend to be more reactive and bioavailable. The existing issues are related to the fact that the fate and effect of nanoparticles are difficult to predict because of changing interactions with the environment and complicated exposure conditions. Mathematical fate models combining transport, transformation, and biological uptake stimulations that are being produced to fill these knowledge gaps and guide risk assessment methods [86]. With these complexities, stringent regulations, ecological surveillance, and production of safer nanoparticle designs with the least ecological footprints are indispensable. All these measures are supposed to strike a balance between technological progress and environmental safety and eco-friendly development and ensure that they use it responsibly to cause minimal harm to human health and the environment [87].

Ethical and Regulatory Issues in Biomedical Applications

Some of the ethical and regulatory concerns associated with biomedical uses of nanoparticles centered around the safety of patients, informed consent, data privacy, fair access, and responsible innovation. Because of the smaller (nanoscale) size, nanoparticles may have distinct toxicological profiles, which include potentially damaging DNA, toxicity of the pulmonary system, and immune system stimulation, which raises concerns about long-term health and unintended side effects [88]. Risk management and proper assessment are needed in order to weigh the benefits of nanoparticles in field of diagnostics, drug delivery, and regenerative medicine against possible harms. Ethical principles which include respect towards autonomy, beneficence, nonmaleficence, and justice, with a focus on the patient rights, risk-benefit assessment, and equal access to treatment. Informed consent is required, considering the complexity and novelty of nanomedical interventions.

Data privacy, along with data security, also causes challenges because of the widespread amassing of genetic and personal health data in the field of nanomedicine research. The worldwide regulatory systems are finding it difficult to match the fast-changing technological trends, and the international codes and collaborations to promote safety and effectiveness. Transparency in risks of communication and benefits to patients and society is essential to retain trust in innovation in nanomedicine while encouraging fair access and social justice [89]. The use of nanomaterials in research also requires ethical considerations, such as animal welfare and environmental control, taking into consideration potential risks and bioaccumulation of nanoparticles outside the clinical environment. Such multidimensional ethical and regulatory challenges involve a combined strategy using scientists, clinicians, ethicists, regulators, and public stakeholders in a responsible development of nanotechnology in medicine [90].

Challenges and Limitations

Toxicological issues present a major challenge and constraint of biomedical use of nanoparticles, necessitating deep and careful research on their safety and security profiles. The toxicity associated with nanoparticles can take place in different ways, with the development of reactive oxygen species (ROS) that create oxidative stress and cause cell damage and inflammation being the most common [46]. The build-up of ROS may also affect mitochondrial activity, cell membranes, and cause DNA damage, which adds to apoptosis or necrosis. In addition, nanoparticles can disrupt cellular signaling pathways, cell cycling, and epigenetics, which could lead to carcinogenesis or chronic health-related outcomes. Physicochemical characteristics of nanoparticles, such as size, shape, surface charges, composition, and functionalization, are important factors in the toxicity of nanoparticles. As an example, nanoparticles are more likely to enter cells and tissues, enhancing cellular toxicity risks, whereas surface charge affects cellular uptake and coordination with biomolecules, which may worsen adverse outcomes [91].

The routes in which nanoparticles may be bio-disturbed to critical organs with potential biodistribution, such as the liver, lungs, brain, spleen, and kidneys, after exposure include inhalation, ingestion, dermal contact, or intravenous administration [92]. The activation of

the immune system and inflammatory reactions should also be considered, and nanoparticles can trigger activation of the complement system or cytokine storms, further causing systemic toxicity. Also, other nanoparticles emit toxic ions on dissolution, which enhance adverse biological impacts. To investigate the toxicity of nanoparticles, it is necessary to use sophisticated *in vitro* and *in vivo* models such as cell cultures, animal models, and more organoids, which more closely mimic human physiology. Although nanoparticles have potential therapeutic uses, it is still urgent to comprehend their toxicity and to reduce it to achieve safe nanomedicines, to emphasize requirement of standardized assessment protocols, to design nanoparticles rationally to reduce their toxicity, and to regulate nanoparticles to ensure patient safety. Comprehensively, toxicological issues highlight the fact that the advantages of innovations based on the use of nanoparticles have to be weighed carefully to offset any biological hazards [93].

Scaling or transition of nanoparticles production from laboratory to industry is associated with many challenges in terms of reproducibility, complexity of the process, and quality control. Compared to traditional pharmaceutical compounds, nanoparticles are multicomponent systems with complex structures, and a correspondingly high level of control over size, shape, surface chemistry, and internal structure is required to preserve the functional properties of nanoparticle structures [94]. Scale-up mechanisms should preserve these important attributes to achieve efficacy and safety of the products. Small-scale synthesis methods, like sonication, milling, emulsification, or self-assembly, are frequently fated to fail when scaled to the large volumes of production, as the dynamics of the mixing process, temperature, and shear forces are likely to change, affecting particle size distribution and chemical composition. Very small differences in formulation ingredients or processing conditions, like polymer-to-drug ratio, type of solvent, concentration of emulsifier, temperature, and pH, may cause variation between batches of nanoparticles in terms of their performance [95].

Furthermore, extensive-scale production requires a high level of sterility and contamination control, either of biologic or nucleic acid-loaded nanoparticles, increasing technical and financial requirements. Sophisticated technologies at lab scale, e.g., microfluidics or high-pressure homogenization, might need considerable adjustment or substitution for industrial-scale production in order to sustain product uniformity [96]. The challenge leads to regulatory compliance, where aspects of reproducibility, robustness, and well-characterized critical quality attributes must be shown to meet the approval agencies. In addition, the production is complicated by the supply chain problems of raw materials and the scale of purification and sterilization procedures. Overall, one of the key obstacles to extensive commercialization and clinical translation of nanomedicines is the development of effective, scalable, and standardized manufacturing guidelines that could enable the production of nanoparticles with high quality and reproducible properties.

To solve these scale-up problems, interdisciplinary strategies with processing engineering, development of analytic methods, and quality control strategies should be used [97]. Regulatory hurdles are still a major obstacle to the clinical translation and commercialization of nanomedicines, because nanoparticle-based therapies are unique and difficult to regulate. In contrast to regular drugs or medical equipment, nanomedicines usually have hybrid properties lying between drugs, biologics, and devices, which make classification and regulatory approval processes challenging. The absence of standardized and specific recommendations engineered to nanomedicines poses uncertainty for developers on the preclinical and clinical information that is required on safety, quality control, efficacy, and pharmacokinetics [98]. Nanoparticles exhibit dynamic physicochemical properties, including size distribution, surface chemistry, and stability in physiological environments, making characterization difficult and impacting reproducibility and performance. Safety evaluation also requires a large number of toxicity and immunogenicity studies to comprehend the interaction of nanoparticles with biological systems and long-term consequences that may not be properly covered by traditional regulatory frameworks. Additionally, the scalability of manufacturing in conditions of Good Manufacturing Practice (GMP) with a consistent quality of batches further introduces another regulatory challenge. Regulatory bodies like the FDA and EMA promote early and sustained communication with developers to clarify the requirements, but globally harmonized regulatory standards are not established [99]. New approaches to these obstacles are emerging, such as the development of more sophisticated tools of nanoparticle characterization, cooperative platforms between regulators, researchers, and industry, and responsive clinical trial designs to nanomedicine behavior. Altogether, the process of nanomedicine regulation requires a multidisciplinary, multifaceted strategy to enable safe and effective bench-to-bedside translation of nanomedicines and innovation [35].

Future Perspectives

Smart and Responsive Nanoparticles

Advanced and responsive nanoparticles offer an innovative future in biomedical and nanomedicine applications, which provide a solution of highly precise, targeted, and controlled therapeutic strategies [10].

These nanoparticles are designed to react intelligently to internal biological signals like pH change, expression of enzymes, temperature, and redox conditions or external stimuli, which include magnetic field, light, and ultrasound, to change their behavior in real time. An illustration of this is the release of drugs specifically in the tumor microenvironment by pH- responsive nanoparticles, minimizing systemic toxicity while increasing therapeutic efficiency. Enzyme-responsive processes or systems release their payload while contacting disease-specific enzymes, allowing treatment to be highly localized. Non-invasive drug release and imaging can be achieved with external stimulus-responsive nanoparticles, including near-infrared light-activated particles, magnetic field-activated particles, and so on, creating opportunities to combine therapeutic and diagnostic (theranostic) uses [100]. Specificity can be increased further by surface functionalization with tumor-specific ligands, peptides, or antibodies, and therefore, the nanoparticles can actively target and attach to target cells with minimal off-target toxicity. Moreover, development in artificial intelligence, along with machine learning, is being combined with nanoparticles that are engineered to optimize their physiochemical characteristics and predict their interaction with the biological field, thereby enhancing the creation of personalized medicine. Materials such as gold nanoparticles, metal-organic frameworks, black phosphorus, and quantum dots have become the subject of active research in order to ensure diverse smart capabilities, such as targeted drug delivery, photothermal and photodynamic treatment, biosensing, and bioimaging [101]. In general, smart and responsive nanoparticles become a new era of versatile, dynamic nanomedicines that have the potential to transform treatment outcomes, reduce side effects, and create real-time monitoring capability, which is expected to radically change the future of precision healthcare [102].

Personalized Nanomedicine

Personalized nanomedicine is a novel strategy that focuses on the customization of medical therapy to the specific genetic, phenotypic, and environmental characteristics of patients with the objective of enhancing therapeutic efficiency while reducing adverse side effects [84]. This modality takes advantage of high-tech nanotechnology combined with artificial intelligence to create nanocarriers that can deliver drugs to target tissues or cells, depending upon biomarkers and mutations specific to patients. AI algorithms investigate complicated omics data and clinical measures to create formulations of optimized nanoparticles that increase targeting accuracy, drug uptake, and controlled release based on individual needs [103]. Such a tailored approach is especially promising in the treatment of complex diseases like cancer, neurodegenerative diseases, and rare genetic disorders, where drug response and metabolism vary widely. Nanotechnology-biosensors and imaging tools allow real-time monitoring of the reactions of the patients and allow an adaptive treatment regimen to be applied, which will guarantee dynamic changes in the treatment regimen to maximize the benefit and minimize the risks. Moreover, the autonomous nanorobots that operate on AI have the potential in the future to perform cellular intervention with high accuracy, such as delivering drugs, repairing tissues, and detecting disease markers at an entirely new scale. With the current trends in research and regulatory standards, personalized nanomedicine is going to revolutionize healthcare delivery as it makes treatment much safer, effective, and highly personalized, as well as enhances patient outcomes and quality of life [104].

Integration with AI and Biotechnology

Combining AI and biotechnology with nanomedicine will transform healthcare to the extent of allowing unparalleled accuracy, effectiveness, and customization of diagnostic and therapeutic approaches [105]. AI-based algorithms allow the design, optimization, and synthesis of nanoparticles, whose versions can be used in particular biomedical applications to enhance targeting accuracy, drug loading, release kinetics, and reduce toxicity. Machine learning models can be used to analyze datasets of omics technologies, imaging, and clinical parameters to determine disease biomarkers and predict nanoparticle behavior in complicated biological environments. This synergistic integration enables the creation of advanced nanomedicines that can be used for real-time analysis, adaptive treatment, and dynamic drug release based on patient-specific feedback [84].

The AI innovations in the field of biotechnology facilitate the development of advanced therapeutic agents and streamline the design of vaccines, along with nanotechnology, which provides diverse platforms for delivery and molecular identification. AI-enhanced imaging methods with nanoparticle contrast agents enhance disease detection sensitivity and spatial resolution that can be used to detect diseases earlier and plan their treatment more effectively. In addition, nanorobots and nano sensors controlled by AI will have a future perspective in terms of minimally invasive surgery, targeted therapy on a cellular level, and constant health tracking. The application of these combined technologies in an ethical manner will be achieved by using strong validation, data governance, and regulatory frameworks in order to provide safety, efficiency and equity. Generally, AI and biotechnology converging nanomedicine is a revolutionary frontier in personalized and precision medicine, and it is likely to improve the performance of patients and healthcare delivery considerably [106].

CONCLUSION

The nanomedicine field represents a frontier merging smart nanotechnology with biotechnology and AI to transform personalized medicine, along with disease management. Among others, it is possible to note that nanoparticles can efficiently deliver drugs, enhance imaging, and provide targeted treatments, which greatly enhance the effectiveness of the treatment and minimize side effects [107]. The integration of AI permits data-based optimization of nanoparticle design, real-time analysis, and adaptive treatment plans, specifically useful in areas of complicated disorders like cancer and neurodegenerative disorders. Furthermore, new smart and responsive nanoparticles that respond to certain biological or external stimuli enhance therapeutic control and diagnostic precision. The problem of ethics, regulation, and toxicity issues stresses the importance of careful assessment and responsible innovation. The challenges of scale-up and reproducibility in order to translate the nanomedicine from bench towards bedside remain, which require interdisciplinary cooperation, precise manufacturing, and guidelines [108].

In the future, nanomedicine research will rapidly grow towards more intelligent, multi-functional nanoplatforms incorporating AI, machine learning, and precision biotechnology. Such innovations are likely to deliver health care at a very personalized level as treatments can be adapted to specific molecular patterns and diverse disease conditions [109]. The non-invasive diagnostics, theranostics, and autonomous nanorobotics innovations will improve the detection of disease in its initial stages and make it possible to intervene in the cells in real-time. However, future studies should cover data privacy, ethical implementation, and harmonization of regulations around the world to enable safe and fair access. Nanotechnology, AI, and biotechnology may converge to create fundamental changes: Personalized nanomedicine is the foundation of the next-generation precision healthcare, and it must offer better patient outcomes, minimize healthcare burdens, and provide sustainable, innovative therapeutic modalities [108, 109].

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