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Review article

Nanoparticles in Biomedicine and Biosciences: Design, Mechanism, and Their Applications

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ABSTRACT

Nanotechnology is one of the promising sciences that has progressed rapidly in the last fifty years. It is used in many biomedical fields, including drug delivery, disease diagnosis, and vaccination. There are many examples of nanoparticles (NPs), PEGylated liposomal doxorubicin, albumin-bound paclitaxel and ionizable lipid NP mRNA Covid-19 vaccines. This article focuses on NP classification, synthesis, and properties and tests their translation into drug delivery, imaging, cancer therapy, gene therapy, regenerative medicine, and antimicrobial applications. This review article also highlighted the relationship between structure and function of NPs, leading to the study of biodistribution, protein corona formation and targeting, all of which shed light on toxicology mechanisms, the regulatory framework and its persistent barriers, including reproducibility, immunogenicity and cost impact on the application and synthesis of NPs. This article also investigated the publications that deal with the role of AI in NP design, personalized nanomedicine, multifunctional smart systems, and in conjunction with CRISPR-based gene editing. All these are also discussed as pathways to overcome the limitations. This article tries to reach the aims by consolidating materials design, bioscientific interaction, and clinical translation within a single framework. The aim of the manuscript is to provide researchers and clinicians with information for advancing nanoparticle-based technologies from the bench to the bedside of patients.

Keywords: Biomedicine & Biosciences; Drug delivery; Lipid Nanoparticles; Nanoparticles, Nanomedicine, Nanotoxicology.

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1. INTRODUCTION

The idea of nanotechnology began with the lecture presented by Dr. Richard Feynm's in 1959, entitled "There is plenty of room at the bottom". In this lecture, Feynman highlighted the manipulation of matter at the atomic and molecular scales [1]. The word nanotechnology was formalized by Norio Taniguchi and expanded by K. Eric Drexler, who redesigned the molecular model of the nanoparticles [2]. The application of this science is evident when nanoparticles are controlled and used in medicine and pharmacology to deliver macromolecular therapeutics, e.g., proteins and nucleic acids [3]. Advances in this field have improved others, such as lipid chemistry, culminating in PEGylated liposomes, which led to the approval of the first nanoparticle drug, Doxil®, in 1995 [4], and albumin-bound paclitaxel (Abraxane, 2005) [5]. In the last ten years, there has been significant development in inorganic and quantum-dot nanoparticles for imaging and therapy [6], which has improved the mRNA COVID-19 vaccines (2020-2021), making it the most important development in nanomedicine (Fig.1) [7].

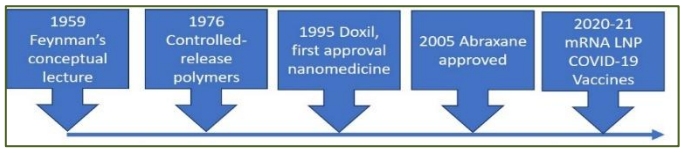

Fig 1. Timeline highlighting key milestones in the development of nanomedicine and nanoparticle-based therapeutics (1959–2021).

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Nanoparticles are categorized into core classification based on their composition in various classes namely; organic nanoparticles (liposomes, polymer nanoparticles, dendrimers and micelles); inorganic nanoparticles (gold, iron oxides and silica) [8]; carbon-based nanoparticles (carbon nanotubes, graphene and fullerenes); lipid-based nanoparticles (mainly ionizable lipid nanoparticles for mRNA delivery) [9], and hybrid nanoparticles which are made of more than one type of component to serve multiple functionalities like imaging and therapeutics in the same particle [10]. The classification is presented through the detailed (Fig. 2) showing detailed physicochemical properties of the nanoparticles discussed above.

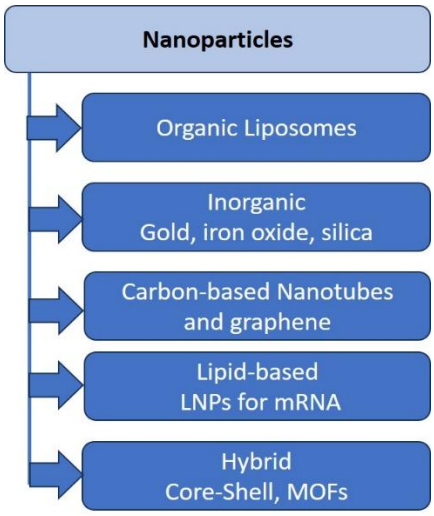

Fig 2. Classification of nanoparticles used in biomedicine and biosciences.

There are many research articles that have been done in relation to every single type of nanoparticle; however, there is still no unified synthesis covering all areas from design to biomedical applications. The current paper summarizes the existing knowledge in relation to the structure-functions of nanoparticles in order to define the process of biodistribution, targeting and ensuring safety [11]. At the same time, it focuses on the relations between nanoparticles and gene therapy, immunotherapy and computer-aided design of nanoparticles. Therefore, the author in the current review wishes to analyze what has been done so far and what challenges still remain, such as the reproducibility and immunogenicity of nanoparticles, as well as issues of regulation in this area.

2. CLASSIFICATION of NANOPARTICLES

2.1. Organic Nanoparticles

The organic nanoparticles that comprise liposomes, polymeric nanoparticles, dendrimers, and micelles, are considered to be the most clinically relevant type because they are biodegradable and have tunable surface chemistry. Liposomes, which consist of lipid bilayer membranes, can entrap both hydrophilic and lipophilic drugs and serve as the basis for PEGylated formulations such as Doxil [12]. Polymeric nanoparticles (e.g., PLGA) have definite degradation rates, while dendrimers-based systems have well-defined structures that enable multivalent conjugation of drugs or genes [13]. Micelles, which are made of amphiphilic block copolymers, work best in solubilizing poorly soluble compounds (Table 1).

2.2. Inorganic Nanoparticles

The utility of inorganic nanoparticles, such as gold, silver, iron oxide and silica nanoparticles, depends on their inherent physical properties, instead of how they degrade chemically. Gold nanoparticles are very useful in biosensing devices and photothermic therapy due to the ability to manipulate their surface plasmon resonance [14]. Silver nanoparticles are primarily effective due to their antimicrobial property, while SPIONs are used as a magnetic resonance imaging (MRI) contrast agent or have use in focused hyperthermic therapy [15]. The mesoporous silica nanoparticles have a very high surface area which allows for effective drug loading (Table 1).

2.3. Carbon-Based Nanoparticles

The highly interesting nanoparticles are carbon nanotubes, graphene, and fullerenes, which form a unique class of structures with remarkable mechanical strength and conductivity. Single- and multi-walled carbon nanotubes, as well as graphene derivatives, are being intensively studied for biosensing, scaffolding, and as vehicles for drug/gene delivery because of their large surface areas and ability to be functionalized [16]. However, worries about their persistence in living organisms and clearance are still under investigation.

Table 1. Classification of nanoparticles with representative physicochemical properties, primary biomedical applications, and examples.

Category	Representative types	Typical size range	Key physicochemical properties	Examples
Organic	Liposomes, polymeric NPs, dendrimers, micelles	20-200 nm	Biodegradable; tunable surface chemistry; high drug-loading capacity	PEGylated liposomes (Doxil); PLGA nanoparticles; PAMAM dendrimers
Inorganic	Gold, iron oxide, silica, silver	1-100 nm	High density; magnetic or plasmonic properties; chemical stability	Gold nanoparticles; superparamagnetic iron oxide nanoparticles (SPIONs); mesoporous silica
Carbon-based	Carbon nanotubes, graphene, fullerenes	1-100 nm	High surface area; electrical conductivity; mechanical strength	Single-walled carbon nanotubes; graphene oxide; C_{60} fullerenes
Lipid-based	Solid lipid nanoparticles, nanostructured lipid carriers, ionizable LNPs	50-200 nm	Biocompatible; efficient nucleic acid encapsulation; low immunogenicity	mRNA-LNP vaccines (Pfizer–BioNTech, Moderna)
Hybrid/composite	Core–shell, polymer–lipid, metal–organic frameworks	10-200 nm	Combines multiple functionalities; tunable release kinetics	Lipid–polymer hybrid nanoparticles; metal–organic frameworks (MOFs)

2.4. Lipid-Based Nanoparticles

Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) integrate the compatibility of lipids both biocompatibility and enhanced stability as compared to liposomes. Ionizable lipid nanoparticles have gained it fame lately with mRNA-based COVID-19 vaccines being the example why it more suitable for nucleic acids drug delivery systems since it allows for effective endosomal trafficking [7,17].

2.5. Hybrid and Composite Nanoparticles

Composite and hybrid systems such as metal-organic frameworks and lipid-polymer hybrids consist of various materials within one platform in order to combine diagnosis and therapy [10,12]. These theranostic systems symbolize the cutting edge of rational nanoparticle design. The properties of the given theranostic systems are modified for various types of applications as seen in Table 1 and Fig 2.

3. SYNTHESIS AND STRUCTURAL METHODS

3.1. Top-Down Approaches

The top-down methods use in preparing nanoparticles through physical or mechanical means. The methods include lithographic techniques (electron beam lithography and soft lithography), which allow the production of nanoparticles. Mechanical milling is a method that relies on repeated fracture and cold welding of powders in order to arrive at the required size of nanoparticles. In this case, however, top-down methods are energy-intensive, with a tendency to get structural imperfections, and poor efficiency in the production of sub-50 nm particles for their use in biomedical purposes [18,19] (Table 2, Fig 3).

3.2. Bottom-Up Approaches

Strategies that depend on nucleation and growth are more effective in particle size uniformization since they build nanoparticles from a molecular and/or ionic source. The sol-gel technique derives its effectiveness from the Stober procedure in which monodisperse silica nanoparticles are formed through alkaline reaction of various alkoxysilanes. Thereafter, people use chemical reduction methods to prepare noble metals' nanoparticles though they sometimes require the use of organic solvents and this may hinder biocompatibility due to impurities remaining in the final product [20] (Table 2, Fig 3).

3.3. Green/Biological Synthesis of Nanoparticles

Green synthesis involves using plant extracts, microorganisms, and bioolecules as the reducing agents in place of hazardous chemical reductants. Phytochemicals like polyphenols and flavonoids help reduce the metal ions and stabilize the surface of the nanoparticles produced; in this method, the biosynthesis processes involving bacteria, algae, and fungi are expanded [21]. However, there are still many difficulties associated with this technique including variability associated with biological materials as well as the lack of thorough understanding of the mechanism of the reduction process (Table 2, Fig 3).

3.4. Surface Functionalization and Bioconjugation Strategies

Irrespective of synthesis method involved, biomedical properties of nanoparticles strongly rely on post-synthesis modifications done to their surfaces. The most common method of preventing opsonization and achieving long half-lives of nanoparticles' blood circulation is their PEGylation, which allows incorporating a hydrophilic barrier [22].

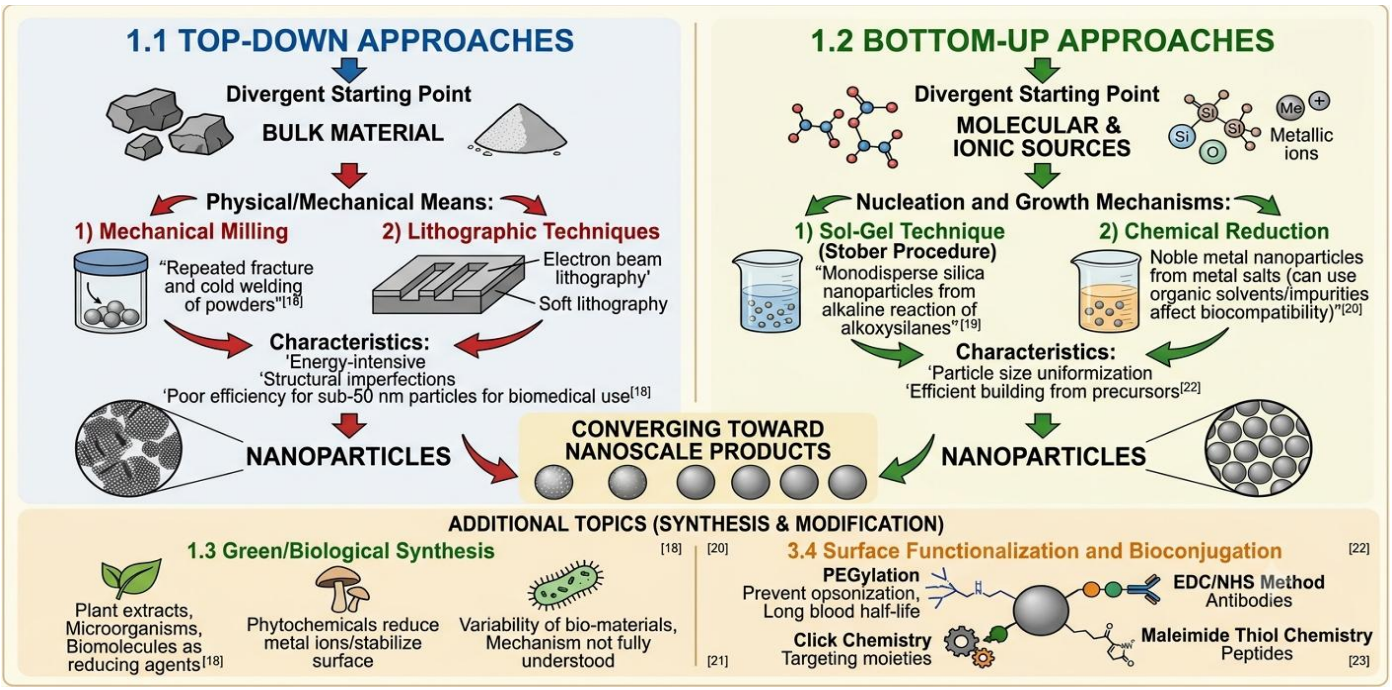

Fig 3. Figure 3. Scheme of representations of paths of synthesis and functionalization of nanoparticles. A schematic representation of the contradictory paths of synthesis and functionalization of the nanoparticles, such as top-down bulk disintegration and bottom-up molecular assembly processes leading to the same nanoscale material, along with the alternative green synthesis option and clinical surface functionalization methods. The numbers in the figure represent publication references.

Table 2. Comparison of nanoparticle synthesis methods: advantages, limitations, and scalability.

Method	Category	Advantages	Limitations	Scalability
Lithography	Top-down	High pattern precision; reproducible geometry	Expensive equipment; low throughput; limited to planar/thin-film formats	Low (research-scale)
Mechanical milling	Top-down	Simple; solvent-free; suitable for hard/metallic materials	Broad size distribution; defect and contamination introduction	High (industrial)
Sol-gel	Bottom-up	Mild conditions; tunable porosity and monodispersity	Requires precise hydrolysis control; solvent residues	Moderate–High
Chemical reduction	Bottom-up	Fine size/shape control; well-established protocols	Toxic reagents/capping agents; purification burden	Moderate
Green/biological synthesis	Bottom-up	Low toxicity; environmentally sustainable; cost-effective	Batch variability; poorly defined mechanism; slower kinetics	Low–Moderate
Surface functionalization/bioconjugation	Post-synthetic	Improves biocompatibility, targeting, and circulation time	Adds process complexity; potential loss of ligand activity	Moderate

There are several bioconjugation chemistries, including 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide/N-hydroxysuccinimide (EDC/NHS) method, maleimide thiol chemistry and click chemistry, which are used to covalently bind various molecules (e.g. targeting moieties, antibodies, peptides) to nanoparticles; each chemistry has its own pros and cons concerning efficiency of conjugation process, stability, orientations, etc [23]. All mentioned functionalization methods unite both chemistry and practical application of nanoparticles (Table 2, Fig 3).

4. PHYSIOCHEMICAL PROPERTIES RELATED to BIOMEDICAL APPLICATIONS

4.1. Physical Properties

The size of a nanoparticle is important since it affects how long the particle is able to circulate, exit the bloodstream, be taken up by cells and establishes how fast it can be removed from the body. Nanoparticles smaller than 8 nm tend to be cleared through the kidneys very quickly while those larger than 200 nm are eliminated through the mononuclear phagocyte system of the body. It was found that the shape of nanoparticles independently affects the manner in which the particle behaves in an organism: elongated and rod-shaped particles were observed to have a lowered uptake via macrophages when compared to similarly sized spherical nanoparticles [24-26].

4.2. Surface Chemistry and Functionalization

Apart from the gross geometry, the type of molecules on the surface of a nanoparticle influences its behavior. The presence of hydrophilic polymer coatings, predominantly polyethylene glycol (PEG), restricts the adsorption of plasma proteins by the nanoparticle and the recognition by phagocytes, thereby increasing half-life in circulation when compared with non-coated particles [27]. Targeting efficiency is also dependent on the degree of density of ligands on the functionalized surface because high density of ligands can hinder receptor binding due to steric hindrance or force ligand binding to take place in off-target cells through avidity effects [28]. New alternatives to PEG that are "stealth" are also being developed, which include zwitterionic and polysarcosine coatings.

4.3. Stability, Biocompatibility, and Biodegradability.

Colloids must remain stable during their storage and subsequent injection to allow for reliable pharmacokinetics. Aggregation can change the size of the particles, activate the body complement, and cause tissue embolism. Biocompatibility and biodegradability depend on the type of the core; organic and lipid-based materials usually degrade through either hydrolysis or enzymatic route while inorganic and carbon-based nanoparticles do not easily degrade and can accumulate in tissues [29]. Therefore, rational design is being more and more focused on the use of biodegradable scaffolds or the use of ever-degrading inorganic core nanomaterials as a way to avoid toxicity while maintaining activity.

4.4. Protein Corona Creation and Bioscience Interactions

When exposed to biological fluids, nanoparticles quickly adsorb proteins from plasma to form a "protein corona," thus changing the biological identity of nanoparticles and making it very different from its original properties in many respects [30]. The protein composition of the corona changes over time after initially forming a dynamic layer, which is replaced first by the most thermodynamically favorable proteins [31]. Almost everything that is adsorbed influences circulation half-life, uptake, recognition by immune cells, targeting, etc.

5. NANOPARTICLES in DRUG DELIVERY

5.1. Mechanism of Loading and Release

Medicines are incorporated into nanoparticles through various methods, including encapsulation, surface adsorption, or conjugation, which depend on the solubility of the drug, the chemistry of the carrier, and the kinetics of its release. The release of drug substances from nanoparticles occurs via diffusion, erosion of the material, desorption from the surface or a combination of these methods [32]. Polymers and lipids are able to provide a biphasic profile with an initial burst release and subsequent slow diffusion.

5.2. Passive vs. Active Targeting (EPR Effect, Ligand-Receptor Targeting)

Passive targeting makes use of the enhanced permeability and retention (EPR) effect – a process whereby the presence of leaky capillaries and poor drainage mechanisms leads to preferential particle accumulation in the tumor [33]. However, experience gained from research in this field has shown that there is much variation in the EPR level from tumor to tumor and from patient to patient, which limits the extent to which it can be assumed that the EPR effect is applicable in all cases of clinical application. Active targeting, instead, uses ligands containing antibodies, peptides and some special molecules that can bind to the receptors presented in excess in target cells, thus providing for higher efficiency of particle uptake as well as enhanced specificity of activity [34].

5.3. Stimuli-Responsive (pH, Redox, Thermal, Enzymatic)

Stimuli-responsive (smart) nanoparticles are designed to release encapsulated cargoes in response to internal or external signals. pH-responsive systems harness the acidic tumor microenvironment or endosomal/lysosomal compartments to facilitate a protonation-induced disassembly, while redox-responsive carriers rely on disulfide bonds that can be broken by high levels of glutathione (GSH) in the cells [35]. Thermoresponsive systems typically developed using materials that have adjustable lower critical solution temperature (LCST) thermoresponsive polymers allow drug release upon heating [35]. Enzyme-responsive systems rely on unhealthy proteases found in tumors that break the peptide or ester linkers. With these mechanisms, you can increase the spatiotemporal control in drug release compared to passive diffusion protocols.

5.4. Case Studies: FDA-Approved Nanomedicines

Clinical translation finds its best example in products that are approved in the field of nanoparticles. Doxil is a PEGylated liposomal version of doxorubicin and is the classical model of passive EPR-mediated targeting with lesser cardiotoxicity than the free drug. Abraxane consists of paclitaxel nanoparticles bound to albumin and has led to improved drug solubility and delivery, without using toxic solvents usually employed in conventional paclitaxel products [4,5]. Onpattro (patisiran) is a therapeutic type of siRNA [36]. It displayed the clinical significance of nucleic acid delivery through ionizable lipid nanoparticles and, consequently, allowed the later possibility to use this delivery system in mRNA vaccines against COVID-19 (Table 3) [7].

6. NANOPARTICLES IN DIAGNOSIS

6.1. Nanoparticles in MRI, CT and Ultrasound

Contrast agents based on nanoparticles increase the sensitivity and specificity of imaging techniques by concentrating the materials producing signals in the diseased tissues, as compared to using small molecules that are spread across the entire body. In magnetic resonance imaging (MRI), specially designed nanoparticles can provide either T1- or T2-weighted imaging results by the selection of nanoparticle core and coating material, making these agents usable for both lymph node staging and tracking of macrophages in inflammation. In computed tomography CT imaging, nanoparticles made of elements with high atomic number such as gold and bismuth provide long-term vascular imaging and additional advantages over iodine contrast agents, in addition to enabling differentiated spectral CT images for several simultaneously injected contrasts [37]. In the case of ultrasound imaging, both gas-filled microbubbles and nanobubbles produce stronger sound signals in the ultrasound imaging, and can be also designed for special usage cases like imaging of inflammatory markers or localized drug delivery (Table 4) [38].

Table 3. Clinically approved nanoparticle-based drugs with representative indications.

Product	Nanoparticle type	Active agent	Indication
Doxil/Caelyx	PEGylated liposome	Doxorubicin	Ovarian cancer, Kaposi's sarcoma, multiple myeloma
Abraxane	Albumin-bound nanoparticle	Paclitaxel	Breast, lung, pancreatic cancer
Onpattro	Ionizable lipid nanoparticle	Patisiran (siRNA)	Hereditary transthyretin amyloidosis
Comirnaty/Spikevax	Ionizable lipid nanoparticle	mRNA	COVID-19 prophylaxis
Marqibo	Liposome	Vincristine	Acute lymphoblastic leukemia

6.2. Fluorescent and Quantum Dot-Based Picturing

Because of their size-tunable emission spectra, relatively high quantum yield, and intermediate photostability, semiconductor quantum dots have shown promise for their use in multiplexed optical imaging and long-term individual tracking of single molecules in living tissues. However, due to the possible toxic effects associated with heavy-metal-containing cores (e.g., cadmium), researchers are now actively pursuing other options to enhance biocompatibility of quantum dot technologies [39].

6.3. Biosensors and Diagnosis

The use of nanoparticles plays a crucial role in the development of innovative biosensing devices as it allows for boosting the effectiveness of detection by facilitating a significant increase in the surface area compared to its volume and availability of variable properties in optical and electrochemical fields. Various types of lateral flow systems as well as electrochemical sensors based on either gold nanoparticles or magnetic ones are capable of supplying colorimetric or impedance-based results when determining nucleic acids, pathogens, and proteins with significant accuracy [40,41]. In order to provide reliable instant biosensing solutions, it is essential to implement the principles of nanoparticle-based detection platforms allowing the performance of assays at the clinical level without application of complex laboratory equipment [41].

Table 4. Comparison of imaging modalities enhanced by nanoparticles.

Modality	Representative nanoparticle agents	Key advantages	Key limitations
MRI	Iron oxide nanoparticles, gadolinium-based nanocarriers	High soft-tissue resolution; no ionizing radiation	Long acquisition time; limited sensitivity
CT	Gold, bismuth, iodinated nanoparticle agents	Fast acquisition; excellent spatial resolution	Ionizing radiation; renal clearance concerns
Ultrasound	Micro-/nanobubbles	Real-time, low-cost, portable	Limited penetration depth; operator dependence
Optical/fluorescence	Quantum dots, dye-loaded nanoparticles	High sensitivity; multiplexing capability	Limited tissue penetration; potential heavy-metal toxicity

6.4. Theranostic Nanoparticles

Theranostic nanoparticles include in one entity both the ability of imaging and the mode of treatment [42]. To achieve this goal, a specific design is implemented and involves using an imaging component (such as a magnetic core, a radiolabel, or a fluorophore) combined with a drug compound on one nanoparticle platform, which could be applied to the process of patient selection for treatment. Although theranostic nanoparticles have been proven effective under laboratory conditions, their practical application is limited because of the difficulties connected with the regulation of combination products and the difficulty of achieving the desired functionality on a large scale [43].

7. NANOPARTICLE in CANCER THERAPY

7.1. Active and Passive in Tumor Targeting Strategies

As mentioned before in our discourse regarding the Enhanced Permeability and Retention (EPR)-mediated passive accumulation and ligand-directed active targeting, tumor-specific delivery also has to overcome certain limitations posed by the tumor microenvironment itself. Factors such as the dense composition of the stroma, high interstitial fluid pressure, and uneven blood flow distribution can hinder the penetration of nanoparticles beyond the perivascular zone, thus limiting its therapeutic efficacy [44]. Therefore, a more successful strategy would involve the combination of specific surface ligands with methods enhancing penetration of the nanoparticles through the use of tumor-penetrating peptides or other processes, in order to get the therapeutic agents beyond blood vessels into the tumor tissue.

7.2. Nanoparticle and Chemotherapy

On top of its capability for the single-agent reformulation, nanoparticle carriers bring a rational integration of chemotherapy by co-encapsulating the drugs in a constant synergistic ratio which cannot be achieved by free-drug administration in vivo. The product known as CPX-351, a liposomal combination of cytarabine and daunorubicin in the ratio of 5:1, exhibited a greater degree of effectiveness than the standard treatment for high-risk acute myeloid leukemia thanks to its ability to keep the synergistic ratio intact while in elongated circulation [45]. Nevertheless, nanoparticle carriers remain useful in the treatment of multidrug-resistance cells through evasion of P-glycoprotein-P-glycoprotein mediated drug efflux through endocytosis instead of passive drug entrance, thus ensuring the possibility for the drugs to enter the resistant tumor cells.

7.3. Photodynamic and photothermal Therapy.

The nanoparticles, which have great ability to absorb the infrared light in the near-infrared region, such as gold nanoshells and golden nanorods, are applied in the photothermal method in order for their function to transform this light into heat, which is enough for tumor cell killing while not harming the nearby healthy tissue [46,47]. However in photodynamic procedure the nanoparticles serve for transportation of the photosensitizing agents that can produce toxic reactive oxygen species after being irradiated [48]. The porphyosome nanoparticles make it possible to integrate both methods into the same nanoparticles due to their properties of autoquenching when aggregated.

7.4. In Immunotherapy and Vaccine Delivery

Utilization of nanoparticles has shifted from purely inflicting death on cancer cells to modifying the immune system's response against tumors or cancers. Researchers have experimented with lipid nanoparticle-based RNA vaccines containing instructions on how to manufacture proteins allowing immune cells to differentiate between normal and neoplastic cells (tumors) [49]. These trials have produced T cell responses in patients whom they were being tested on, leading them to believe that it can help to treat future malignancies and cancers too [50-52]

8. NANOPARTICLES in GENE THERAPY and VACCINE DELIVERY

8.1. Lipid Nanoparticles for mRNA/siRNA Delivery

It is common for liposoms (LNPs) used in clinical practice to consist of more than one ingredient like an ionizable fat, a phospho-lipid on the base of which other substances can be added, cholesterol, and a PEGylated fat molecule. Each of these components serves its unique purpose in the delivery of nucleic acids [53]. The ionizable fat does not exert any harmful effects at the body temperature but in the acidic conditions of the endosome, it gain protons leading to the formation of a lipid bilayer that causes disruption of the membrane and release of an important cargo of the liposome [54]. Cholesterol increases hardness of the particle and facilitates merging with the cell membrane, the phospho-lipid takes care of the structure of the liposome, while the PEGylated liposome deals with the size of liposomes (Fig 4).

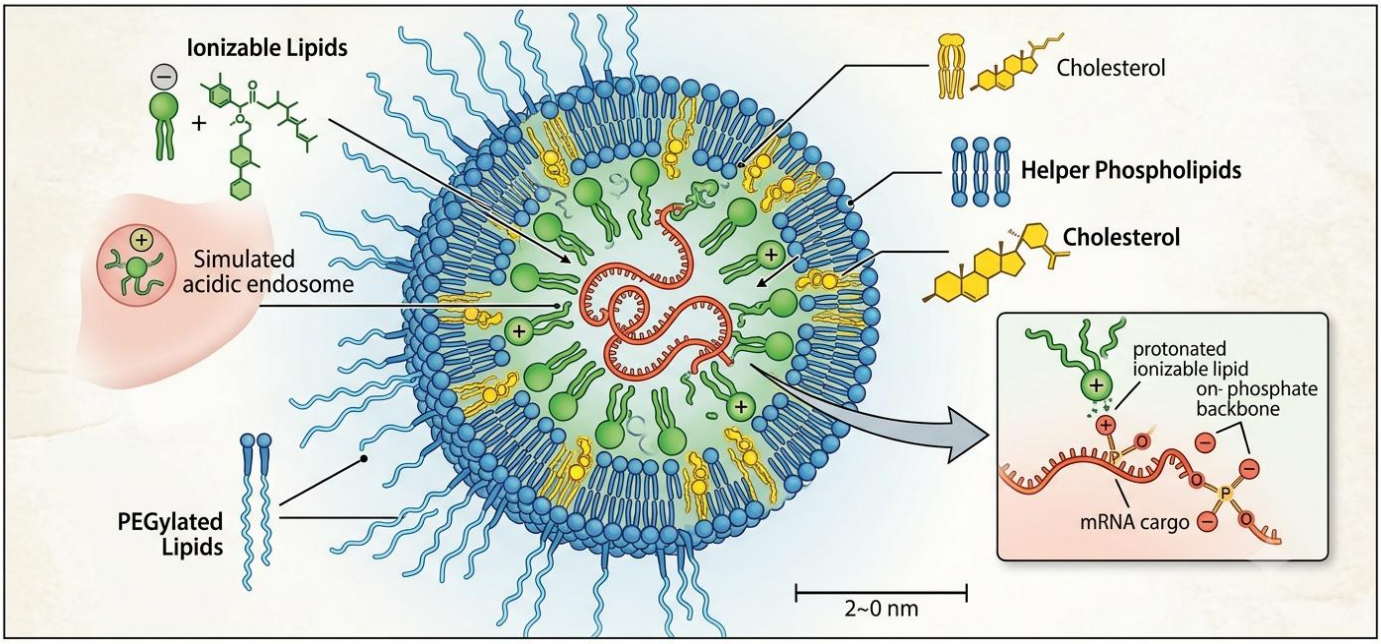

Fig 4. The structure of a lipid nanoparticle mRNA complex. This image showing the ionizable lipid, helper phospholipid, cholesterol, and PEGylated lipid components organized around an encapsulted mRNA core.

8.2. Polymeric Vectors for Gene Delivery.

Cationic polymers provide an alternative and often a less expensive option for nucleic acid delivery by way of the electrostatic condensation of anionic nucleic acid into polyplexes. Polyethylenimine (PEI) is one of the earliest and most popular types of synthetic vectors which achieve high transfection efficiency through the claimed proton sponge mechanism whereby the vector provides much buffering capacity for the endosome and thus results in its swelling and rupture. However, PEI and its analogues may not always be efficient due to their high charge density which leads to cell damage and activation of the complement cascade [55,56].

8.3. Case study: Covid 19 mRNA Vaccine Nanoparticle Platforms

Both the Pfizer-BioNTech and Moderna vaccines against COVID-19 marked the first time that the concept of ionizable LNP-mRNA was proven on such a vast scale. The mRNA molecules used in these vaccines were nucleoside-modified, comprised of the viral Sars-Cov-2 spike protein. The studies conducted in regards to these mRNA vaccines clearly indicated that the lipid form of micelles should play a crucial role in determining the properties of the whole system. The analysis of the structure and stability of these molecules showed that the efficacy of the formulation depends on the composition of lipids and the process parameters (the rate of microfluidic mixing, etc.).

9. NANOPARTICLES IN REGENERATIVE MEDICINE

9.1. Scaffold-Based Nanoparticle (NP) system

Nanoparticles have found a role in tissue engineering scaffolds by offering spatially controllable chemical and mechanical signals for tissue regeneration. The application of nanoparticles, carrying growth factors, in electrospun fibers or hydrogels will make it possible to use a controlled release of morphogens like BMPs or VEGF in tissue engineering scaffold applications, rather than the standard bolus injection, which is characterized by fast systemic distribution and elimination of drugs [58]. Besides working as passive drug reservoirs, nanoparticles used in engineering scaffolds can affect mechanical properties, surface structure, and electrical conductivity of the scaffold, which help engage cells more effectively into tissue reparation process. The combination of nanoparticles and scaffold technology allows designers to divide mechanical properties from bioactive signals.

9.2. NPs in Stem Cell Differentiation.

Nanoparticles play a dual role: they help in delivering the differentiation causing materials as well as they perform the physical and the magnetic stimulation. The concept of nanoparticles in the field of stem cells deals with the use of nanoparticles in the manipulation and storage of the stem cells in a controlled manner through a process called magnetically induced mechanotransduction [59]. Even if there is no application of the magnetic field, it has been revealed that by just changing the size and chemistry of the nanoparticle, it can shun the path of the differentiation: gold nanoparticles of definite size have shown to cause the osteogenic differentiation of the human stem cells through the activation of p38 pathway [60]. Thus, it further demonstrates that the nanoparticle can be used as the instructive agents, substituting the other traditional soluble factors through the use of nanoparticles.

9.3. NPs for Wound Healing and Antimicrobial Effect.

Nanoparticle-based wound dressing fulfills two important needs of tissue healing -to prevent infections and speed wound healing. Among all antimicrobial nanomaterials, silver nanoparticles are the most used and have a wide spectrum of antimicrobial actions due to ion release, reactive oxygen species

production, and direct cell membrane destruction. This is probably due to the very effective action of these nanoparticles against multidrug resistant bacteria. In addition to the antimicrobial action, nanoparticle-based dressing is capable to induce angiogenesis, influence inflammatory processes of tissue and deliver some growth factors that are necessary for re-epithelialization of the wound [61,62]. Antimicrobial action and pro-regenerative effects in these dressings are combined together but there are many combinations of nanoparticles with certain functionalities present in a single dressing.

10. ANTIMICROBIAL APPLICATION

10.1. Mechanism of Antimicrobial Effect.

Nanoparticles function by employing various mechanisms to kill bacteria rather than the typical monomodal system that is seen in traditional antibiotics. One of the modes of actions involves the production of reactive oxygen species (ROS) where the surfaces of redox active or photocatalytic nanoparticles cause the degradation of lipid, nucleic acid, and proteins in microbes through the action of radicals and hydrogen peroxide [62]. In addition, bacterial cell membranes can be compromised by the electrostatic influence of nanoparticles as well as dissolved metal ions to cause the leakage of cellular materials and cell death. Moreover, the phenomenon of particle-induced intracellular ion release may also cause damage through enzymatic and respiratory chain disturbance discovered in metal nanoparticles that discharge bioactive ions after absorption into bacteria cells [63, 64]. Since all these mechanisms happen simultaneously in different cellular parts, there is greater challenge for bacteria to develop any sort of resistance as compared to conventional antibiotics.

10.2. Metal NPs against Pathogens.

Metals and their oxide nanoparticles form a well-researched group of antimicrobial compounds. One significant example includes the nanoparticles of zinc oxide which possess high activity levels. In what way is the activity of zinc oxide nanoparticles explained? Primarily, this efficacy is determined by reactive oxygen species (ROS) production, zinc ion dissociation, and possible disruption of membranes. The activity of nanoparticles depends on their size, character, and amount of defects present on their surfaces. In a similar way, it has been shown that copper oxide nanoparticles can destroy different microorganisms because they have high activity levels. On the contrary, the use of titanium dioxide nanoparticles is limited because they are less effective in terms of their action when there is no presence of ultraviolet or visible light. Silver nanoparticles turn to be a most successful as an antimicrobial material [65]. It has been shown that their efficacy does not depend on the type of bacteria under consideration including Gram-positive and Gram-negative bacteria (Table 5).

10.3. NPs and Antibiotic Resistance Isolates

These multi-target mechanisms described above make nanoparticles very appealing when it comes to fighting against multidrug-resistant (MDR) pathogens like Methicillin-resistant Staphylococcus aureus (MRSA) and carbapenem-resistant Enterobacteriaceae, as traditional antibiotics against these pathogens have become less and less effective [66]. Nanoparticles can also enhance the efficacy of antibiotics if used in combination with antibiotics since they make it possible to accumulate the drugs inside the cells. They help to inhibit the functioning of efflux pumps or to destroy protective biofilms that protect resistant bacteria from antibiotic penetration [66]. Besides, nanoparticles have a potential in terms of antivirals due to their ability to impede the entry of viruses into the organism by binding to their receptors.

11. TOXICOLOGY, BIOSAFETY, and BIODISTRIBUTION

11.1. Mechanism of Nanotoxicity.

Nanoparticle toxicity comes from their physicochemical properties, specifically the size, surface reactivity, charge, and dissolution characteristics, and not just the chemistry of the bulk material or the chemical structure of their whole [68]. Oxidative stress is one of the main mechanisms implicated in this toxicity. In this process, excess reactive oxygen species generated on the surface of nanoparticles overwhelm the capacity of cells to defend themselves from oxidative stress, leading to the damage of cell membrane lipids, proteins, and DNA [69]. The oxidative stress can initiate cascade of inflammation reactions, including activation of NF-κB and release of proinflammatory cytokines, especially when nanoparticles cells recognize by phagocytosis [68]. Genotoxicity caused by nanoparticles includes not only the DNA strand breaks and chromosomal changes but also oxidative DNA damage which is especially found among the nonbiodegradable nanoparticles or the nanoparticles remaining in human tissues for a long time thus creating risk of the mutagenic or carcinogenic effects [69].

Table 5. Antimicrobial efficacy of representative nanoparticle types against common pathogens.

Nanoparticle type	Primary mechanism	Effective against	Notes
Silver (Ag)	Ion release; membrane disruption; ROS	Gram-positive and Gram-negative bacteria, fungi	Broadest clinical use (wound dressings, coatings)
Zinc oxide (ZnO)	ROS generation; Zn^{2+} release; membrane damage	*E. coli*, *S. aureus*, fungal pathogens	Activity size- and morphology-dependent
Copper oxide (CuO)	Ion release; ROS; enzyme inhibition	Broad-spectrum bacteria, some viruses	Lower cost alternative to silver
Titanium dioxide (TiO_2)	Photocatalytic ROS generation	Bacteria, biofilms	Requires UV/visible light activation
Gold (Au, functionalized)	Membrane disruption; carrier for antibiotics	MDR Gram-negative bacteria	Primarily as antibiotic-potentiating carrier

11.2. Toxicity Assessment Models.

Standard in vitro cytotoxicity testing, modeled after pharmaceutical testing (for instance, MTT, LDH release), needs validation for the testing of nanoparticles because nanoparticles can interfere with the assay reagents or optical detection systems that can mislead the test results [70]. Therefore, it is recommended that additional tests that measure oxidative stress, membrane stability, and genotoxicity be conducted in conjunction with the standard viability tests in order to come up with a complete toxicological profile. In vivo studies are needed since there are certain systemic effects that cannot be captured in a cell culture such as immune cell involvement, accumulation of drugs in organs, and chronic exposure effects.

11.3. Biodistribution and Clearance

When the nanoparticles are administered through systemic administration, they follow an efficient distribution mechanism which is dependent on the clearance pathways. For instance, those that are below the renal filtration threshold (~8 nm) are quickly cleared via the kidneys. Furthermore, the bigger particles, on the other hand, accumulate in the liver and spleen because they are taken up by the resident macrophage cells in the mononuclear phagocyte system (MPS) [71]. On the other hand, a lot of the non-biodegradable nanoparticles including inorganic and carbon-based materials may exist for a very long time in these organs even if they do not cause acute toxicity. Different from these, biodegradable organic and lipid-based particles are typically cleared through the process of metabolic degradation which works efficiently (Table 6).

Table 6. Summary of toxicity findings across representative nanoparticle types.

Nanoparticle type	Primary toxicity concern	Key evidence
Gold	Generally low acute toxicity; size-dependent accumulation	Persistence in liver/spleen at small sizes [71]
Silver	Oxidative stress; cytotoxicity at high dose	ROS-mediated damage in vitro [69]
Iron oxide (SPIONs)	Generally biocompatible; degradable	Metabolized via iron storage pathways [71]
Carbon nanotubes	Inflammation; fibrosis; genotoxicity	Asbestos-like effects reported with long, rigid tubes [68,69]
Quantum dots (Cd-based)	Heavy-metal cytotoxicity	Cd^{2+} release linked to oxidative/genotoxic damage [69]
Polymeric/lipid NPs	Low toxicity; biodegradable	Rapid clearance via hydrolysis/enzymatic degradation [70]

11.4. Consideration of Regulatory (FDA and EMA).

Both the FDA and EMA have developed guidance documents specific to nanomedicine in relation to the characterization of drugs, ensuring manufacturing consistency, and conducting nonclinical safety evaluations, which implies an understanding that current frameworks for controlling small molecules are unsatisfactory for regulating products based on nanoparticles. Regulatory challenges that continue to exist include the development of harmonized international regulations regarding the requirements for the characterization of nanoparticles and other aspects of drug development (Table 6).

12. CHALLENGES and LIMITATIONS

12.1. Reproducibility Problems and Scale-Up.

A chronic bottleneck is the translation of nanoparticle synthesis from the laboratory scale to reproducible clinical-grade manufacturing. As mixing kinetics, heat transfer and nucleation dynamics scale non-linearly with reactor size [73], batch-to-batch variability is often elevated in terms of size, polydispersity and drug-loading efficacy when synthesis transitions from milliliter to industrial volumes. These manufacturing inconsistencies complicate regulatory approval (which requires rigidly specified critical quality attributes) and comparability across clinical trial batches, leading to the striking underperformance of nanoparticle formulations in transitioning from preclinical promise to approved product [73].

12.2. Immunogenicity and Safety Concerns.

Repeated application of nanoparticle therapeutics has been shown to result in unexpected immune effects that are detrimental to the achievement of desired outcomes and safety of the therapy. The phenomenon of accelerated blood clearance (ABC), in which the immune system produces anti-PEG IgM antibodies in response to the initial dose of PEGylated nanoparticles, gives rise to immune-mediated clearance of subsequent doses of the same drug. The phenomenon is illustrative of the way in which the immune system renders chronic treatment with certain drugs ineffective [74]. The effect of chronic exposure to PEGylated nanoparticles on human health is under-investigated as most preclinical safety studies do not investigate effects of nanoparticle exposure lasting for several years.

12.3. Ethical Challenges and Regulatory.

Moreover, agencies have not yet established fully harmonized international standards for the characterization of nanoparticles [72], making development and approval challenging to manage in an international context. Specifically, high manufacturing costs need to be balanced against equitable access in nanomedicine, informed consent is further complicated by the use of novel materials with poorly characterized long-term risk profiles and ethical governance needs to encompass nanoparticle-based genetic and enhancement technologies as inherent capabilities expand [75]. Because risk-benefit determinations for novel nanomaterials must be made under greater uncertainty than traditional pharmaceuticals, these ethical dimensions also intersect with regulatory policy.

12.4. Clinical Defects and Cost-Effectiveness.

Huge problems such as an enormous costs and high technology involved in creating complex multicomponent nanosystems make impossible inclusion of highly sophisticated nanoparticle systems into the market and hinder any input of new nanoparticles into clinical practices.virtual nanoparticles are the last category the world of nanopharmaceuticals needs today

because production of these nanoparticles requires large amount of money and the prevailing attitude of companies producing drugs according to the design of safety and efficacy [76].

13. FUTURE PERSPECTIVES

13.1. AI-Assisted NP Design.

Machine learning techniques are being utilized on a larger scale for speeding up the discovery and optimization of nanoparticles, doing away with the traditional repeated testing of formulations with the help of trial-and-error methods. Instead, predictions are based on scientific principles and known relationships between material properties and resultant properties like size, stability, drug-loading capacity, and biocompatibility. By combining high-throughput experimental data with predictive models, new formulations can be chosen prior to their actual materialization, reducing the search for a formulation from many possibilities to a few lead formulations [77].

13.2. Personalized Nanomedicine.

The developments in the field of nanoparticle engineering and precision medicine will allow us to manufacture drugs that are personalized according to patient needs, ranging from production of vaccines targeted to individual mutants of cancer cells to designing different models of nanoparticles for different types of tumors. This is going to be achieved through the use of modern production systems that would allow getting drugs manufactured at small quantities still maintaining the same quality of production as in traditional pharmaceutical practices [78].

13.3. Smart NP system

Inspired by recent advances in stimuli-responsive and theranostic technologies, innovative nanoparticle systems are evolving toward novel integration level where active targeting, imaging, dose release, and immediate feedback can be operated in a single system in an adaptive fashion. In particular, the new systems will make it possible for nanomedicine to go beyond its current use of fixed, programmed carriers and start operating as “smart” therapeutic agents capable of detecting and responding to the disease process at the site affected; however, the more complex the design of the new systems becomes, the more difficult it will be to manufacture them according to regulations in the future [79].

13.4. Connection with CRISPR and Gene-Editing

Lipid nanoparticles and other kinds of nanoparticle transportation methods are becoming a potential alternative to viral delivery systems of CRISPR/Cas9 and other genetic engineering techniques due to their relatively low toxicity and flexibility in carrying different types of biological materials [80, 81]. In order to exploit genetic modification technology in other organs and tissues it is important to continue improving the methods of targeting specific tissues and ensuring more efficient release of drug above mentioned systems.

14. CONCLUSION

Nanoparticle technologies have transitioned from being merely concepts to being part of modern medical practices in many fields such as cancer, infectious diseases, genetic engineering, diagnostic practices, and tissue regeneration. The differences in organic, inorganic, carbon, lipid, and hybrid technologies used in nanoparticles show that this branch of science can modify the characteristics of the materials for different biological purposes. That make medicines with different properties. Several studies showed the possibility of using them in passive tumor accumulation due to the EPR effect, and in triggered and responsive discharge. The same material complexity that makes nanoparticles so versatile leads to basic challenges that have not been solved for a long time. The first issue is the ability to conduct mass production of nanoparticle pharmaceuticals in compliance with all rules and regulations. One more major challenge is the lack of complete understanding of the long-term effects of the developed products on the body. Moreover, there are no developed principles for safe mass production of drug substances for humans and animals, and it is complicated to regulate the existing protocols.

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Author contributions

Al-Mutalib LAA. Conceptualization, Methodology, Investigation, Data curation, Formal analysis, Literature review, Visualization, Writing – original draft, Writing – review & editing.

The author reviewed and approved the final manuscript and agreed to be accountable for all aspects of the work.

AI declaration

The authors used Claude AI to improve the manuscript's academic tone and readability. The authors also used Gemini Pro to help in preparing parts of the graphical abstract and other figures (3 & 4). After using this tool/service, the authors reviewed and edited the content as needed and took full responsibility for the publication's content.

Data availability

Data will be made available on request.

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