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Review article

Advancements in nanostructured drug delivery systems: Innovations in targeted therapy and multifunctional nanomaterials

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ABSTRACT

Recent advancements in nanotechnology have highlighted the potential of nanoparticles in medical applications. This is especially true for targeted drug delivery systems. Nanoparticles offer unique characteristics, such as stable ligand interactions, varied sizes and shapes, and high carrier capacities. These features make them ideal for carrying both hydrophilic and hydrophobic substances in disease therapy. Novel therapeutic nanostructures have shown promise in targeted drug delivery. They offer superior carrier capacity, specific targeting, and low toxicity. These advancements have led to significant improvements in stability and absorption efficiency. They also enhance the ability to reach cellular and intracellular targets with greater effectiveness. However, there are complex issues regarding toxicity, safety, and production scale of nanoparticles. Resolving these problems could lead to clinical treatments based on laboratory successes. The next generation of medication delivery systems could benefit from personalized therapeutic techniques combined with smart nanomaterials. The main aim of this review is to explore recent developments in the design, synthesis, and optimization of therapeutic nanoparticles. This includes understanding their size, shape, and multifunctional properties to enhance the effectiveness of drug delivery. This review covers various methods for designing and characterizing nanoparticles. It focuses on optimizing nanostructures for enhanced drug delivery. The synthesis techniques, analysis methods, and potential modifications of nanoparticle characterization are discussed. Properly synthesized and optimized therapeutic nanoparticles represent a significant breakthrough in the field of drug delivery systems. Their ability to overcome the limitations of traditional therapies holds promise for future medical applications. Further research into their characterization and development will enhance clinical relevance and ensure safe, effective use in therapeutic settings.

1. Introduction

Rapidly emerging science uses nano-based drug discovery and delivery for both therapeutic and diagnostic purposes. Nanomedicines enhance the pharmacokinetic and pharmacodynamic properties of drug molecules. This enables effective drug therapy [1]. Encapsulated therapeutic nanoparticles release drugs in a controlled manner into the bloodstream. This achieves maximum bioavailability and ensures greater therapeutic efficacy. Liposomes in nanomedicines enhance the absorption, breakdown, distribution, and elimination of drugs from the body [2]. Many bacteria exhibit antimicrobial resistance, which decreases the effectiveness of antibiotics [3]. Therefore, we utilize nano-based antibacterial agents to treat bacterial infections that are resistant to conventional antibacterial drugs. Nanomedicines specifically target these conditions and inhibit the growth of bacteria, whether they are in a planktonic form or in a biofilm [4].

Nanoparticles can activate and functionalize their ligands to expand their therapeutic effects through targeted drug delivery. The shape and features of nanoparticles play a crucial role in determining how they spread throughout the body. It is essential for nanoparticles to target specific tissues and achieve therapeutic effectiveness. Compared to conventional drug delivery methods, this approach can reduce systemic toxicity and increase the intended effect. The physicochemical properties of nanoparticles also affect toxicity. Therefore, when conducting

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clinical research on nanomedicines, safety evaluation is essential. Computational modeling-based imaging techniques help improve the production and application of nano-based combination drugs [5]. Delivering drugs across the blood-brain barrier and the blood-placental barrier is crucial for treating neurological disorders and providing the fetus with essential nutrients [6]. Nanomedicine enables controlled distribution across biological membranes because of the particles' size and shape. Nanoparticles also possess special qualities that make them useful for diagnosing diseases using CT and MRI, as well as detecting biomarkers for atherosclerosis [7]. Recent innovative studies address both the difficulties and opportunities of using nanoparticles and developing CdS-based photocatalysts, offering a way forward for future research. The insights provided aim to speed up the development of durable and efficient CdS-based photocatalysts for sustainable hydrogen production [8]. Islam et al.'s study provides valuable insights into the mechanisms of visible light-responsive plasmonic photocatalysis. These results can guide the development of high-performance, next-generation photocatalysts [9]. Nanoparticles can also be utilized in drug delivery systems, resulting in groundbreaking research in the pharmaceutical and medical fields. The new CPA was tested for analytical performance, and several factors were optimized [10]. Researchers thoroughly examined the impact of pH, the concentration of Cu (II) ions, adsorption behavior, the effect of competing ions, and regeneration. The soft donor-functionalized composite [11]. Awual et al. provide a platform for detecting and removing heavy metal ions, especially in resource-limited areas [12]. It is important to assess the toxicokinetic properties of nanodrugs to ensure their safe use. This review mainly focuses on the types and designs of therapeutic nanoparticles. It emphasizes their role in targeted drug delivery systems for diagnosing and treating various diseases (Fig. 1).

2. Therapeutic aspects of nanoparticles

2.1. Lipid-based NPs

The creation of liposomes has led to their evolution from immunological and conventional liposomes to stimuli-responsive and actively targeted liposomes. Consequently, several liposomal-based drug delivery systems are already medically licensed to treat a range of conditions. Liposome-based NPs have the potential to enhance the pharmacokinetic properties of medications, including metabolism and absorption. Furthermore, liposome-based nanomedicine can serve as a drug delivery vehicle for cancer treatment due to its lower toxicity and biodegradability. Additionally, peptide-functionalized liposomes offer a wide range of applications in the delivery of diagnostic imaging agents, supporting the diagnosis of cancer at various stages. Moreover, liposome surfaces have various operationalized methods that provide improved target-mediated therapy. Therefore, this type of nanoparticle has numerous therapeutic applications, including antimicrobial activity, cancer diagnosis, and vaccine development [2]. Notably, lipid nanoparticle–mRNA vaccines are now in clinical use against coronavirus disease 2019 (COVID-19), marking a significant step forward for mRNA therapies. On this front, researchers are exploring the physiological barriers and practical routes of administration for lipid nanoparticle–mRNA systems, while also developing lipid nanoparticles for mRNA delivery. Finally, preclinical and clinical investigations using lipid nanoparticle–mRNA therapies for infectious diseases, cancer, and genetic abnormalities are highlighted, as well as good manufacturing technique, stability, storage, and safety [13].

2.2. Polymer-based NPs

Dendrimer-based therapeutic applications often utilize polymers because their highly branched structure allows for fine control over nanoparticle size. This branching supports the formation of cavities within dendrimer molecules, aiding in drug encapsulation and targeted delivery. Different dendrimer encapsulations allow precise delivery of gene therapies and vaccine activators to targeted sites [14,15]. To optimize biocompatibility, reduce toxicity, and ensure biodegradability in drug delivery, natural polymer-based or nanoparticle (NP)- based systems are often preferable alternatives to purely synthetic options [16]. Comparatively, synthetic polymer-based NPs, such as PCL and PLA, have lower immunogenicity and toxicity. In contrast, natural polymers like gelatin and chitosan, although potentially more toxic, are also effective carriers for drugs. Polymeric NPs act as matrix systems, forming nanocapsules or nanospheres, and enabling controlled and targeted drug release. These NPs can also modify ligand functional groups to enhance targeted therapeutic delivery. In contrast, silicon-based compounds are notable for their abundance, low toxicity, high conductivity, and affordability, making them attractive for biotechnology applications. For the broader use of silicon-based heterojunctions, synthesis methods must strike a balance between ease, cost, and environmental impact [17].

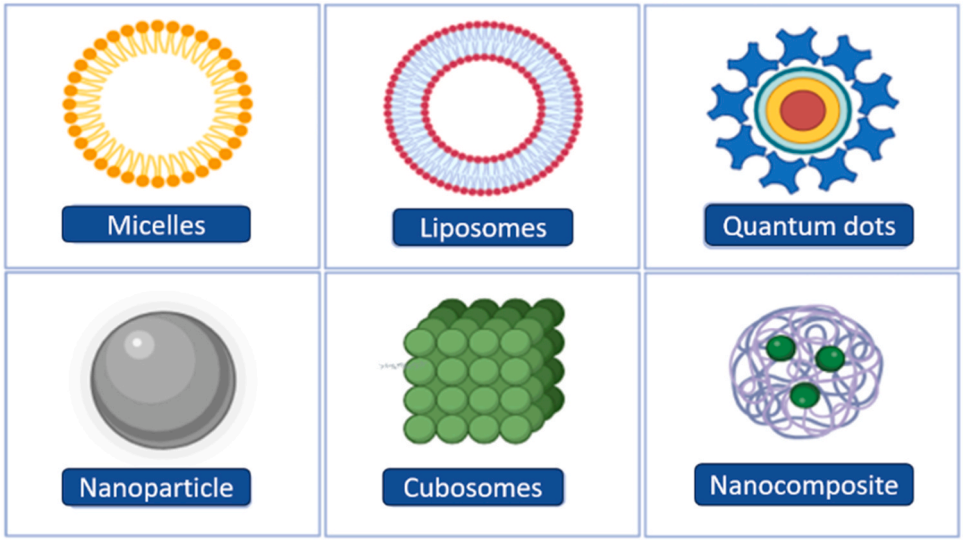

Fig. 1. Nano-based drug carrier.

2.3. Protein nanoparticles

NPs, a natural carrier based on genetic material, can serve as an effective nanocarrier system [18]. Researchers used self-assembled caged protein-type structures. These resemble virus morphology and act as nanocarriers to deliver cancer vaccines. They may also trigger Ag-specific IgM production against cancer cells [19]. Polymer-based protein nanoparticles offer significant advantages for therapeutic drug delivery through genetic engineering [20]. The neutral internal cavity surface of protein NPs forms non-covalent interactions with the drug. This non-specific physical interaction contributes to effective drug loading and release. Protein-based NPs provide flexibility in targeting drugs to desired sites. They offer rapid drug solvation into the bloodstream and help maintain drug levels in the blood. However, they can have reduced drug loading capacity, which decreases drug delivery effectiveness. The endocytosis process (Fig. 2) delivers protein-based NP drugs into the cell, protecting them from enzyme degradation. The non-antigenic property of this polymer-based protein NP enables its use in various therapeutic functions [21].

2.4. Carbon-based NPs

Carbon-based nanoparticles, especially those with unique morphologies, play a significant role in biomedical applications. One important type is the tube-shaped, non-polymeric nanoparticle, which measures approximately 1 nm in diameter and ranges from 1 to 100 nm in length. This structure is formed by encasing a layer of graphene, a form of graphite. Single-walled and multi-walled nanotube configurations are particularly attractive for therapeutics due to their stable morphology. Another variant, C60 fullerene, has an internal diameter of 1–2 nm, consisting of core structures with more conjugated double bonds [22]. This nanoparticle carrier system has improved the therapeutic efficiency of antiviral and anticancer agents. Both single-walled and multi-walled nanotubes can directly attach to cells and release drugs via endocytosis. Carbon nanotubes are widely used, making them appealing options for transporting chemotherapeutic medicines, DNA, and proteins. Nanohorns, a modified type of single-walled nanotube with a single carbon hexagonal ring, exhibit an increasing diameter with length, which facilitates drug delivery and targeting of malignant cancer [23]. Recently, three-dimensional mesoporous carbon nanoparticles (MCNs) have emerged in nanomedicine. They stand out for having well-defined nanoporous geometries, high pore volumes, and good biocompatibility. MCN-based smart multifunctional composite nanosystems are steadily gaining popularity, serving as smart theragnostic platforms for drug delivery and molecular imaging that respond to stimuli [24].

2.5. Metal-based NPs

LSPR characterization guides the design of metal-based nanoparticles using metal precursors with optoelectrical properties. In this study, we synthesized nanoparticles (NPs) from AI, Co, Au, Pb, Cu, and Zn. The unique optical properties of these metal-based NPs help researchers pursue more therapeutic applications. For example, gold-based nano-coating is used to enhance scanning electron microscope imaging, yielding high-quality images. Furthermore, AuNPs are commonly used for cancer treatment and diagnostic purposes [25]. Transitioning to semiconductor materials, quantum dots (QDs) are notable for their fluorescence and optical properties, which result in photo and chemical stability. QD-based nanoparticles, with nanocrystals less than 10 nm in diameter, are widely used as biosensors in drug delivery and diagnostic imaging applications [26]. In addition to these, material composites such as chitosan-cotton have demonstrated high reusability due to their ability to elute and simultaneously regenerate [27]. Adsorption, known for its cost-effectiveness, recovery, and ease of use, remains one of the most widely used techniques for removing metal ions [28]. To support this approach, a variety of compounds, including cellulose, chitosan, and activated carbon, have been developed to adsorb heavy metals from wastewater. However, the main drawbacks of most of these materials are their low mechanical resistance and high economic costs [29,30]. Our data further indicated that, under ideal experimental conditions, the developed CMA effectively eliminated over 99 % of the Pb(II) ions from an aqueous solution [31]. Importantly, due to the Ni(II) ion's high affinity for composite material under optimal experimental conditions, the presence of co-existing metal ions did not interfere with the detection and removal of Ni(II) ions. Moreover, the use of MpCA at pH 5.50 enabled Pb(II) capture, which was notable due to its distinct visual color change. Key experimental parameters, including contact time, limit detection, color optimization, concentration effects on adsorption equilibrium, and maximum adsorption capacity, were systematically evaluated [32,33]. For the Cd(II) ion, the detection and

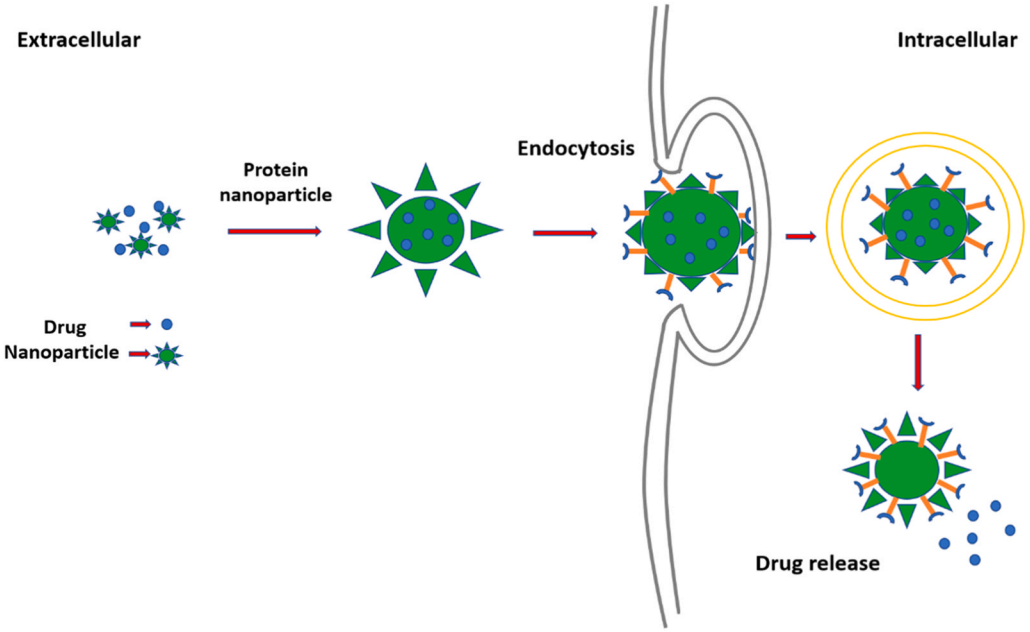

Fig. 2. Drug delivery system of protein nanoparticle.

adsorption processes were not negatively affected by competing ions. Only the Cd(II) ion generated a significant signal intensity, demonstrating high selectivity for Cd(II) under these experimental conditions [34]. In summary, under appropriate conditions, solid design conjugate nanomaterials show promise as effective and economical materials for the selective detection and removal of Pd(II) ions. After the extraction/elution process, the NCA demonstrated reversibility and maintained functionality for reuse across multiple cycles without significant degradation. Therefore, this NCA can be considered a viable approach for Pd(II) extraction from waste materials [35,36].

3. Designing of therapeutics-based nanoparticles

To achieve the goal of nano-based drugs, it is important to ensure safe collaboration between therapeutic nanoparticles and the carrier system. When nanoparticles (NPs) enter the bloodstream, protein components in the blood bind to the NP surface. This binding serves as a label for identifying the immune system. As a result, phagocytosis removes the NPs from the bloodstream. Non-specific filtration by the IgM system results in maximum bioavailability but shorter retention times. Surface-level modification of NPs with PEG, sugar groups, and acetyl groups can change their retention time [37]. Therefore, during the design process, we should focus on altering the biodistribution and accumulation of therapeutic NPs. The size of NPs significantly influences their distribution. NPs less than 10 nm are easily filtered by the kidney through physiological processes. NPs larger than 200 nm are filtered by the kidney using RES processes through phagocytosis. Most studies indicate that NPs in the 20–200 nm range accumulate more rapidly in the body because the kidneys cannot effectively excrete them. Choosing the right NP size is essential to reach target tissues [38,39]. NP surface charge also plays a vital role in targeted drug delivery. Researchers have reported that positively charged NPs create a stronger immune response than negatively or neutrally charged NPs. The surface charge of NPs strongly depends on pH [40]. To increase nanoparticle target stability, scientists are developing new surface modifications and employing sophisticated surface functionalization techniques for therapeutic nanoparticles. For example, thiolated DNA binds to gold nanoparticles, functionalizing and improving the stability of targeted drug delivery systems. Biodegradable nanoparticles are gaining popularity, but they also raise environmental and safety concerns. These nanoparticles are commonly used in regenerative medicine, especially in sustainable technologies for cardiac and neuroregenerative treatments. 3D printing in nanotherapy offers a novel approach for drug development in the pharmaceutical industry. With advanced drug delivery systems, 3D printing allows for the creation of nanoscale medication formulations and carriers.

4. Nano-based drug delivery system

Known as "smart drugs" or "theragnostics," nanoparticles are used in diagnostics and therapeutics. This creates a new strategy to treat or control diseases like cancer that are often untreatable. The primary benefits of nano-based drug delivery are targeted drug delivery, improved safety and biocompatibility, and reduced toxicity. Nano-based drugs can be given orally or by injection. However, some nano-based drugs break down before entering the bloodstream, and poor biodistribution remains a challenge [1]. The design of these drugs focuses on achieving a stable formulation, ensuring biocompatibility, optimizing biodistribution, targeting specific sites, and maintaining functionality. Most nano-based carriers are biodegradable and break down after releasing the drug [41]. Stimulus-responsive systems utilize factors such as pH, temperature, and redox conditions to facilitate improved nanoparticle design. These systems help inhibit tumour growth and enable focused drug therapy. New technologies, such as magnetic or ultrasound-triggered drug release and magnetic electrospun fiber-loaded drugs, aid in managing controlled drug delivery. DNA-based nanostructures represent a sophisticated application for tailored delivery in nanomedicine. Invasomes are the latest innovative nanocarriers designed for drug delivery. These vesicles advance dermatological research and improve transdermal drug administration (Fig. 3).

4.1. Nano-based passive drug targets

Passive targeted drug delivery refers to the transport of a drug to a target site through a highly enhanced permeability and retention effect. Tumor cells are surrounded by the highest number of blood vessels with less structural integrity. This results in high permeability. A nanobased drug can easily pass into the vascular wall of tumor tissue due to this high permeability. Nanoparticle drugs, those smaller than 100 nm, are said to target tumor tissues by making blood vessels more permeable. This allows the drug to accumulate and become bioavailable in the tumor tissue [42]. Enhanced vascular permeability increases the specificity of drug delivery to tumor tissues by 20–30 %. This enhances the drug's effectiveness. The effect depends on the degree of endothelial progenitor cells, lymphangiogenesis, perivascular tumor growth, and intra-tumor pressure. All of these are characterized by the use of physicochemical methods to create effective nano-based drug delivery systems.

4.2. Nano-based active drug targets

Transport of a drug molecule to a specific target site through an active transport system, utilizing ligand binding, is known as an active targeted drug delivery system. It delivers a certain quantity of therapeutic drug to a specific target area of the concerned organ. Researchers have developed a nano-based drug targeting system using antibody fragments, such as Fab and scFv. Direct antibodies synthesized against tumor cells detect specific tumor antigens [43]. Generally, a nano-based drug delivery system utilizes antibody-conjugated nanoparticles, such as anti-EGFR antibodies targeting cancer tumor cells [44] and anti-VEGF antibodies targeting endothelial vascular tumors, to suppress the growth of specific tumors. SELEX (Systematic Evolution of Ligands by Exponential Enrichment) is a method used to generate aptamers, which are short single-stranded nucleic acid or peptide sequences that can specifically bind to targets. These aptamers are either chemically or naturally synthesized, and compared to antibodies, they exhibit no natural immunogenicity. This enables the creation of targeting ligands that are stable, non-toxic, and easy to use in diagnostics, therapies, and drug delivery systems [45].

5. Targets of therapeutic nanoparticles

Most studies have reported that targeting drugs at the molecular level plays a key role in nanoparticle therapeutics. In recent years, the majority of therapeutic drugs employing this approach have demonstrated successful results, thereby reducing reliance on conventional therapies [46]. Researchers have observed that employing molecular nanoparticle targeting and biofunctionalized drug formulations produces excellent outcomes. However, only a few therapeutics using nanoparticle-targeted drug delivery systems have received clinical approval (Table 1). Combining nanoparticle and ligand targeting techniques is more effective because it enables better functionalization and increased uptake by target cells. In vitro studies have shown that cancer cells absorb aptamer nanoparticles and folate-targeted polymeric nanoparticles more efficiently than non-targeted nanoparticles [47]. Biofunctionalized targeted nanoparticles were also shown to accumulate at higher levels within target tissues compared to non-targeted nanoparticles [48]. The use of anti-HER2 immunoliposomes in human tissue grafts demonstrated significant efficiency [49]. Overall, biodistribution and bioaccumulation of targeted nanoparticles are more effective in delivering therapies directed at siRNA targets.

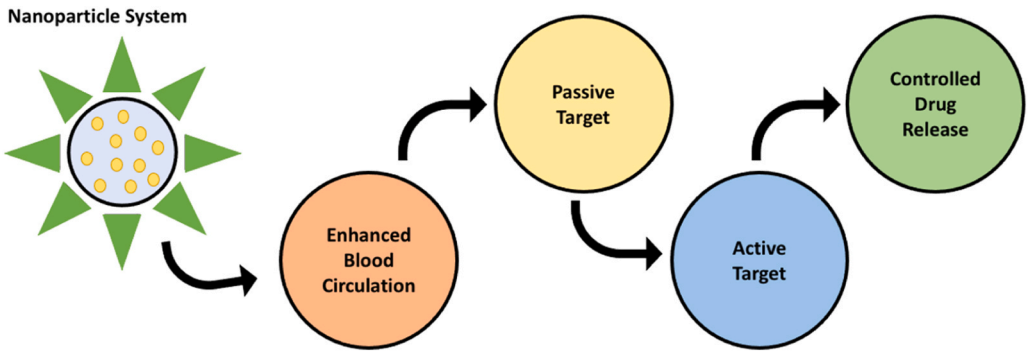

Fig. 3. Nano-based drug target delivery system.

Table 1
List of FDA approved nanomedicine since 2010.

S. No	Drug	Product	Material description	Indication	FDA approved year	References
1	Pegloticase	Krystexxa®	PEGylated Urease	Gouty arthritis	2010	[75]
2	Paclitaxel	Abraxane®	Albumin	Pancreatic cancer	2012	[76]
3	Trastuzumab	Kadcyla®	Trastuzumab	Breast cancer	2013	[77]
4	Ferumoxytol	Ferahema®	SPION with dextran	Anemia in kidney	2013	[78]
5	Dantrolene	Ryanodx®	Dantrolene sodium	Malignant hyperthermia	2014	[79]
6	Interferon β-1a	Plegridy®	PEGylated interferon	Multiple sclerosis	2014	[80]
7	Irinotecan	Onivyde®	Nanoliposomes	Colorectal cancer	2015	[81]
8	Factor VIII	Adynovate®	PEGylated factor VIII	Hemophilia	2015	[82]
9	Paliperidone	Sustenna®	Paliperidone palmitate	Schizophrenia	2015	[83]
10	Daunorubicin	Vyxeous®	Distearoylphosphati-dylcholrine	Myleoid leukemia	2017	[84]
11	Factor IX	Rebinyn®	Glycopegylated coagulation	Hemophilia	2017	[85]
12	Transthyretin targeted SiRNA	Non-liposoma®	Lipid nanoparticles	Transthyretin mediated	2018	[86]

6. Mechanism of nanomedicine

6.1. *Mechanism of nanoparticles in antimicrobial activity*

Researchers have reported effective anti-microbial activities of NPs. Nanomedicines kill microbes through oxidative stress induction, non-oxidative induction, and metal ion release, among other mechanisms. The nano-based drug is capable of altering bacterial metabolic activity, which in turn controls the growth of bacteria [3]. Oxidative stress is caused by reactive oxygen species like hydroxyl radicals, hydrogen peroxide, and superoxide radicals [4]. This stress is a key part of the antibacterial activity of NPs [4]. Most studies have shown that ROS initiates DNA damage and damage to the bacterial cell wall. Oxidative stress induces bacterial cell wall damage by altering the cell membrane's absorbency [50]. In the process of bacterial cell apoptosis, reactive oxygen species (ROS) elevate the expression level of oxidative protein genes [51]. Also, oxidative stress affects the activity of periplasmic enzymes, which changes the normal physiology and morphology of bacteria [52] (Fig. 4). A study that used proteomic tools, electronic microscopic techniques, and FTIR analysis to look at how magnesium oxide nanoparticles kill microbes found that they were effective against Escherichia coli. Researchers found that NPs' mode of antimicrobial activity has multiple targets in both gram-positive and gram-negative bacterial cell membranes [53]. NPs attach themselves to the

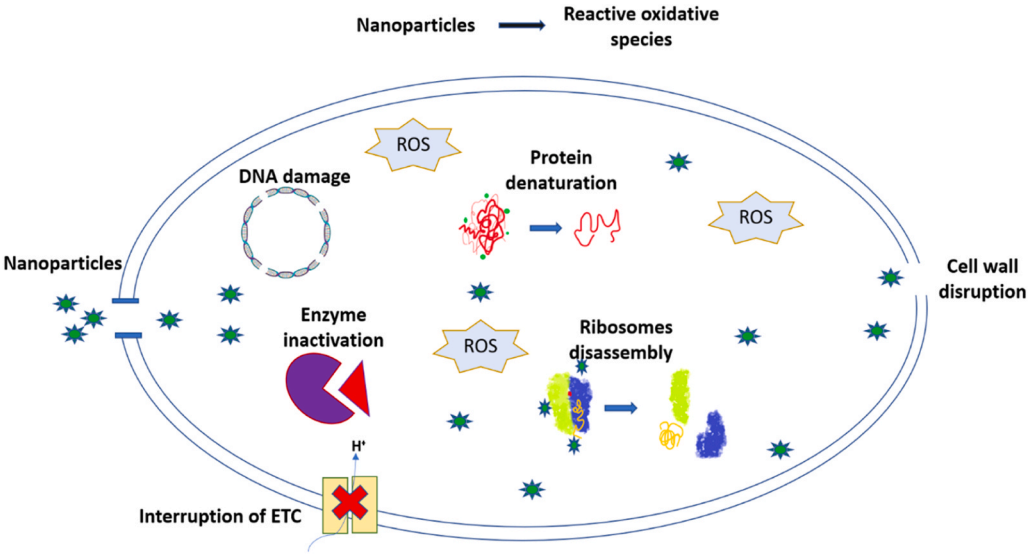

Fig. 4. Mechanism of antimicrobial activity using Therapeutic Nanoparticles.

negatively charged LPS region in Gram-negative bacterial cell membranes. In Gram-positive cell walls, NPs attack the teichoic acid. The current investigation supports the theory that the water-soluble, antioxidant-rich kefir fraction serves as an effective reducing agent for the environmentally friendly production of AgNPs. Furthermore, it was shown that AgNPs from the WSF and the < 10 kDa fractions improved the water-soluble fraction of kefir's antibacterial activity. These results highlight the potential of green-synthesized AgNPs made from various kefir fractions in clinical settings, such as topical antimicrobials, disinfectants, and medical device coatings. Additional toxicity assessments will be conducted in future studies, with a particular emphasis on possible morphological alterations in specific model organism organs. Additionally, attempts will be made to investigate wider applications in medication development and improve specificity through chemical conjugation [54]. Franciele Garcia Baveloni et al. have shown promise in using AgNPs to control germs in polluted wounds while encouraging tissue repair. The purpose of the study was to assess AgNPs' bactericidal activity in S. aureus-contaminated and non-contaminated wounds [55]. The nanocomposites demonstrated strong biocompatibility and antibacterial activity. The ability of halloysite/chitosan nanocomposites to maintain drug release was demonstrated by the in vitro release studies. Additionally, the nanocomposites were stable under different humidity levels. Thus, all of the results point to the possibility of the produced nanocomposites as a nano vehicle for sustained drug administration and as a means of enhancing therapeutic advantages [56]. Sheershwal et al. discuss the properties of various nanoparticles and their biosynthesis from different microbes. It also sheds light on the potential future directions and real-world applications of microbial-mediated nanoparticle biosynthesis in various industries, including food processing, medicine, agriculture, pharmaceuticals, and the environment [57] (Fig. 4).

6.2. Mechanism of nanoparticles in cancer

Therapeutic drugs based on nanotechnology enhance the effectiveness of cancer treatments. There are a number of approved nano-based oncology drugs that have better permeability and retention effects. These drugs were the basis for the development of tumor-targeting nano-based drug delivery systems [58]. The nano-based drug enters the solid tumor as a complex by extravasating through the endothelial lining gap [59]. Tumor microenvironmental immune cells play a key role in the nano-based drug intratumoral delivery system [60]. Targeted transcytosis facilitated the EPR-mediated accumulation of nanomedicine in stromal solid tumors [61]. Targeted monoclonal antibodies for tumor targets' ligands improve the therapeutic index in molecular imaging of cancer. The combination of different nano-based drugs improves the efficiency of oncology therapy [62]. Researchers found that NPs, when combined with chemotherapy and gene therapy, induce synergistic killing effects on tumors [63]. Researchers reported that catalase-loaded, nano-based drugs convert hydrogen peroxide to oxygen in the tumor, reducing tumor hypoxia, improving the ultrasound ablation effect, and increasing the efficacy of doxorubicin against cancer cells. Based on the tumor immune microenvironment, immunotherapy-based nanomedicine was developed [64].

The study by Shreya Chatterjee et al. [65] demonstrated that efficient magnetic nanoparticles were tested on both healthy and malignant cells, and it was determined that the co-precipitation approach produced magnetic nanoparticles with an ideal molar concentration of reagents. Additionally, the MTT assay demonstrates the need for covering uncoated magnetic nanoparticles. Synthesized magnetite nanoparticles have demonstrated possible apoptotic effects on cancer cell lines, according to cell apoptotic tests. Instrumental analysis demonstrated that the drug-loaded chitosan nanocomposite based on MNP efficiency of 85–90 %. The MTT investigation also demonstrated that it is harmful to breast cancer cells and that cell viability declines as the concentration percentage rises. According to the release study, the release of the drug from the MNP-based drug-loaded chitosan nanocomposite varied depending on the pH level. In light of this, a drug-loaded chitosan nanocomposite based on MNP may be used as a targeted drug delivery system to treat breast cancer cells [66]. The ability of nanoparticles to target particular regions and release medications in a regulated manner, increasing drug effectiveness, decreasing overall toxicity in the body, and creating new opportunities for cancer treatment. It also addresses issues with nanoparticle compatibility and potential side effects, highlighting the importance of ongoing research to advance nanotherapeutic techniques for medical intervention applications. The review concludes with a summary of possible future uses of nanotechnology in personalized medicine and predictive oncology [67]. Recent developments in the adaptation of batch bottom-up techniques to perpetual procedures, with an emphasis on the crucial material properties, critical process parameters, and important quality attributes for the production of nanoparticles; the integration of continuous methods; and the related implementation challenges in pharmaceutical manufacturing, such as scale-up, downstream processing, and regulatory considerations [68] (Fig. 5).

6.3. Mechanism of nanoparticles in diabetes treatment

The use of the nanomedicine approach has improved the therapeutic index of diabetes treatment [69]. The nano-based oral delivery of insulin uses both paracellular and transcellular routes for drug delivery. Oral medicine is effective at targeting tissues because the gut contains lymphoid tissues, such as Peyer's patches, with follicles arranged in single or cluster form, as well as epithelial M cells [70]. Nanoparticle-based drug ligands bind to receptors in the digestive tract. This prevents insulin from breaking down into proteins, protects the biological activity, and minimizes barriers from the digestive tract. Encapsulation in a nano-coated form shields the drug from low pH levels in the gastrointestinal tract. Hydrogen bonds with mucins and a mucoadhesive coating facilitate the absorption and release of insulin to the epithelial layer by the nano-based drug. The nano-based drug also interacts with the gastrointestinal mucus layer, as observed with PLGA [71]. Absorption of nano-based drugs is supported by phagocytosis and receptor-mediated endocytosis [72]. Microfold cells take up the nano-based insulin, which then passes through the capillaries of the intestinal villi, reaches the mesenteric lymph node, and finally enters the systemic circulation through the thoracic duct. Biodegradable diabetes treatments help the body safely break down and eliminate waste without accumulation. Both synthetic and natural polymers can serve as insulin agent nanocarriers. To achieve targeted release, various degradative enzymes will be designed. Reducing toxicity is crucial for diabetics to avoid inflammation and organ damage. Biocompatible materials will facilitate the biodegradation of nanocarriers and prevent the accumulation of heavy metals. The multifunctional nanostructures of insulin-release, anti-inflammatory, and glucose-responsive nanoparticles will help reduce adverse effects and serve as a cutting-edge anti-diabetic drug (Fig. 6).

6.4. Mechanism of nanoparticles in cardiovascular disease

Cardiovascular disease is one of the top causes of death around the world. The nano-based medication has the potential to aid in the detection and prevention of cardiovascular disease [73]. The nanoparticles, which are extremely small particles measured in nanometers, have unique biological qualities that allow them to connect with cardiac cells and control processes. They are also more effective in targeting a specific area of the heart and controlling the illness. For diagnostic purposes, such as computed tomography (CT) and magnetic resonance imaging (MRI), as well as biomarker detection for atherosclerosis diagnosis, nanoparticles offer unique features. Superparamagnetic oxide nanoparticles (NPs), a type of magnetic particle that becomes magnetized only in the presence of an external magnetic field, can enhance drug absorption and facilitate selective target engagement within

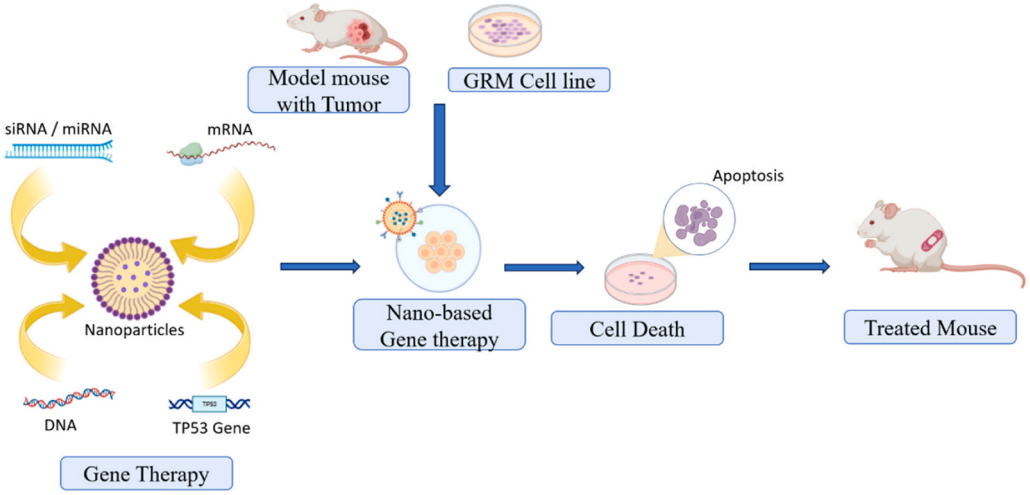

Fig. 5. Nanoparticles - gene therapy-based cancer treatment.

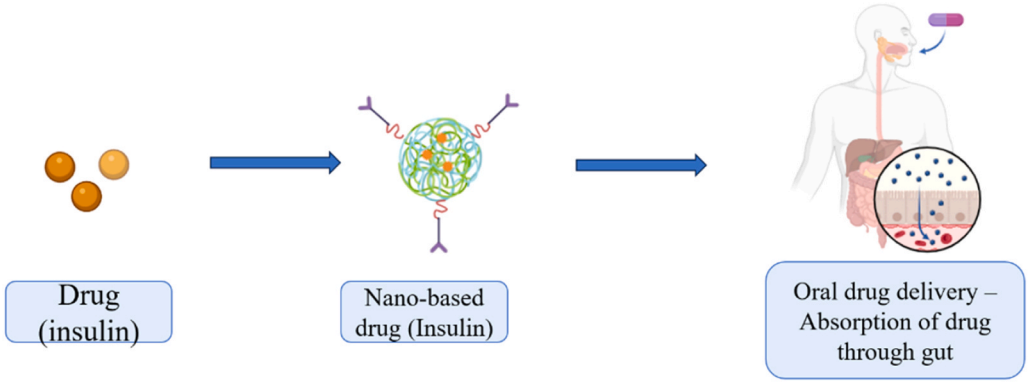

Fig. 6. Nano-based antidiabetic drug delivery system.

tissues. Magnetic resonance angiography, a type of MRI scan, increases the visibility of veins and arteries [7]. The angiogenic vasculature of integrin V3, a protein involved in cell adhesion, and ultrasmall superparamagnetic iron oxide (USPIO) nanoparticles acts as an active biomarker for angiogenesis [74]. Researchers have found that nano-coated CT agents improve the accuracy of arthritic plaque measurements, such as renal toxicity and clearance. Gold-coated CD163, which targets a specific macrophage receptor, targets asymptomatic atherosclerotic plaques [75]. Nano-based antibodies are helping to improve the treatment of cardiovascular disease in the next generation (Fig. 7).

6.5. *Mechanism of nanoparticles in neurological disease*

The blood-brain barrier (BBB) protects the brain from various diseases, such as Alzheimer's, Parkinson's, epilepsy, brain tumors, and multiple sclerosis. Additionally, it delivers nutrients to the brain, limits fluid flow, and optimizes the brain's environment [6]. By promoting

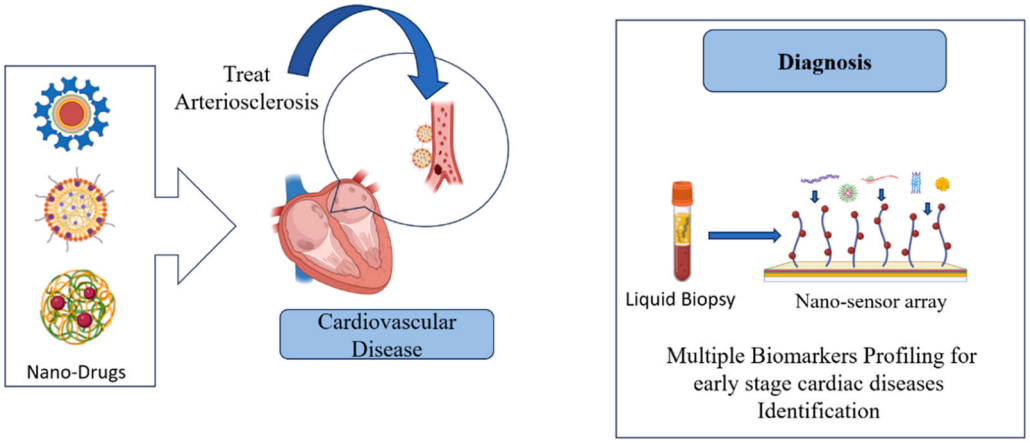

Fig. 7. Nanoparticles in cardiovascular disease.

cytokine fluid recruitment in the brain space, the BBB protects the brain from inflammation. To bypass the BBB for diagnostic and therapeutic purposes, intracranial or intraventricular administration can be used; however, there is an inherent risk associated with delivering agents directly into the brain [6,76]. As an alternative, the NP-mediated targeted drug delivery technique offers a safer method for BBB bypass and effective delivery to the brain (Fig. 8) [6]. In this approach, different antibodies, DNA ligands, and probes combine to form nanoparticles, which serve as targeted delivery systems. These nanoparticles range in size from 10 to 1000 nm [77]. Notably, both imaging and drug delivery can utilize this coupled system. For neurological disorders, polymeric-coated NP-based drug delivery is primarily used. More specifically, one common method to achieve stable drug release and prevent drug degradation is to have NPs adhere to the conjugated drug on their surface [78]. Furthermore, researchers have discovered that a crystalline, drug-filled polymeric nanosuspension containing non-ionic surfactants can enhance drug encapsulation, thereby aiding in the treatment of chronic neurological conditions. Lastly, carbon nanotubes, due to their unique structures and properties, are used to deliver drugs in in vitro neuronal circuit models [79].

6.6. *Nanoparticles in gene therapy*

Gene silencing and correction hold potential for treating many diseases. Gene-based nanoparticle drug delivery systems are more efficient and effective. They can treat cancer by targeting specific genes. NPs-linked gene therapy increases drug circulation time and improves targeting. Gene therapy induces apoptosis and reduces cell proliferation. NPs serve as single-gene delivery systems, enabling controlled delivery to the therapeutic site for safer, more precise cancer treatment [80]. Clinical development can use liquid nanoparticles for drug delivery. Polymeric nanoparticles support gene therapy, offering long-term stability, low cost, reduced immune response, and adaptability [81].

7. Impacts of therapeutic nanoparticles

Although nano-based therapeutic drugs have the potential to treat a wide range of diseases, their development faces key challenges related to nanoparticle toxicity and delivery. Reports indicate that toxicity occurs when nanoparticles escape the phagocytic system and are not physiologically blocked, triggering immune responses [82]. Researchers have found correlations between nanoparticle size and toxicity, both in vitro and in vivo. Smaller nanoparticles tend to accumulate more in the nucleus, resulting in intrinsic toxicity at both cellular and systemic levels [83]. Heterogeneities in vascular permeability also lead to lower concentrations of NP-based drugs reaching tumor tissues. To address this, in vitro experiments have utilized drug-loaded liposomes with constrained delivery to minimize that variability [84]. Quantum dot-based NPs, important in medical imaging due to fluorescent emission, have been shown to cause toxicity in hepatocyte cultures when cadmium-based QDs are used [85,86]. Nanoparticle composition, morphology, size, shape, and charge all impact physicochemical properties and toxicity. For example, particles larger than 100 nm show certain cellular uptake but may cross the blood-brain barrier and cause neurotoxicity, similar to needle-like shapes. Studies such as Yb(III) ion detection highlight the development of non-toxic and stable optical sensors [87]. Additionally, interactions between nanoparticles of differing charges can result in poisoning, and non-target cell exposure may cause systemic side effects. Regulatory guidelines for assessing nanomaterial risks are still being developed by the FDA and EMA (Fig. 9).

8. Conclusion and future perspectives

Nano-based therapeutic drugs, particularly polymer-based nanoparticles (NPs), offer a promising approach for delivering drugs specifically to targeted disease sites. While lipid-based nanoparticles also offer advantages over other treatment methods, the primary challenge remains in optimizing nanoparticle formulations, evaluating their toxicity, and facilitating their commercialization. Addressing the interaction of NPs with biological processes and understanding their costs are essential steps to designing new strategies for treating more diseases. Further studies in these areas are critical to realizing the full potential of nano-based therapeutics in disease treatment.

The primary argument is that nanotechnology in therapeutics has enormous potential to shape the future of medical treatments. Ongoing advancements are likely to redefine drug delivery, diagnostics, and therapies, making interventions more precise, efficient, and minimally invasive. In particular, future applications are expected to include targeted drug delivery, vaccine development, and regenerative therapies such as tissue engineering and stem cell therapy. Enhanced diagnostic

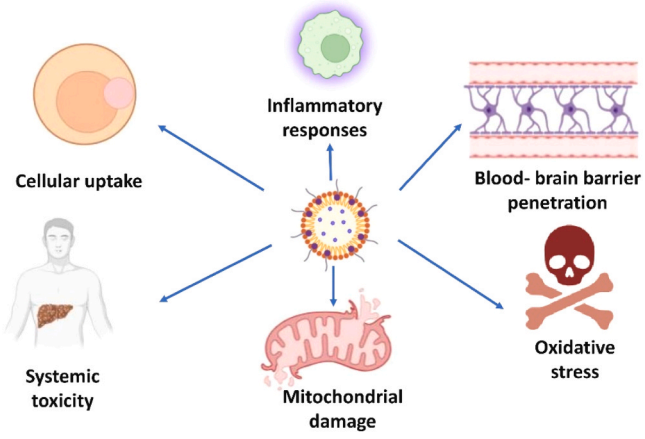

Fig. 9. Toxicology impacts and mechanism of nanoparticles.

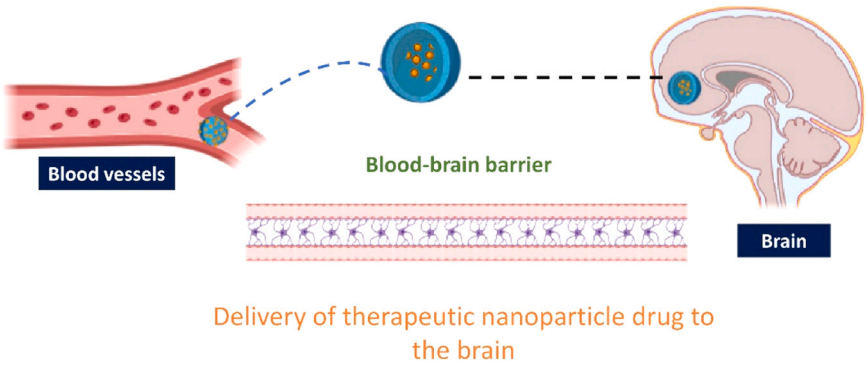

Fig. 8. Mechanism of nanoparticle transport across the BBB.

techniques, including nanotechnology-based biosensors and nano-devices, will improve early detection of diseases. Furthermore, innovations such as nano-based robotics and computational modeling by AI will support microsurgeries, cancer treatments, and large-scale pharmaceutical manufacturing. Overall, further research and development in nano-based therapeutics will lead to safer and more effective healthcare solutions.

8.1. Limitations

This evaluation is primarily descriptive and solely concentrates on the medicine delivery method based on nanotechnology. It excludes pharmacokinetics and a meta-analysis, and emphasizes the role of nanomedicine in developing therapeutic domains. Numerous therapeutic and clinical trials are highlighted. This review covers toxicity, immunological response, biocompatibility, and regulatory issues. Although the synthesis of nanoscale metals holds significant promise, it faces obstacles related to product quality control, application, toxicity conditions, and material selection. These factors hamper the adoption of drug manufacturing and the widespread use of therapeutic nanoscale metals. Future research will concentrate on in-depth nanotoxicology, approval processes, and integrated limitations.

Credit authorship contribution statement

PK & MJ collected the literature and wrote the manuscript. PR is created the idea, revised the manuscript several times and responsible for the correspondence. MA & KKY formatted the manuscript according to the journal guidelines. PR is responsible for the correspondence of the article.

Ethical approval

Not applicable.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

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Data availability

Data will be available on request.

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