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Nanoformulation-Based Medicines for the Treatment of Reactive Oxygen Species-Induced Diseases: A Review

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Abstract: Reactive oxygen species (ROS), are highly reactive molecules formed as a natural by-product during cellular metabolism primarily within the mitochondrial matrix. Excessive production of ROS may cause serious illnesses like cardiovascular disease, diabetes, cancer, Alzheimer's and Parkinson's disease. The therapeutic drugs currently available in the market for the treatment of these illnesses have larger systemic effects and a variety of adverse effects. Therefore, it is important to identify an alternative way of delivering drugs in the form of nanomedicine, which has low cost, great efficacy, fewer side effects, and narrower systemic effects. Nanoparticles have the potential to deliver drugs at specific targeted sites and can be used as new therapy methods for the treatment of various diseases and can also be used in diagnostic methods. This review paper aims to examine the synthesis of nanomedicine, its delivery methods within the body and its mechanism of action against ROS-induced diseases. The findings of our study suggest that nanomedicine-based therapy may be a very effective method in the treatment of cancer, diabetes mellitus, cardiovascular diseases, and Alzheimer's and Parkinson's disease. However, nanomedicine raises a variety of safety concerns, including the risk of toxicity and persistence in human tissues.

Keywords: Free radicals, Nanoparticles, Nanomedicines, Nanotherapy, Nanodiagnosis, Nanotubes

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1. INTRODUCTION

The human body is a complex system that performs various metabolic and physiological activities for its survival. During these activities, the body produces free radicals like reactive oxygen species (ROS)// reactive nitrogen species (RNS) (Gupta et al., 2023). A free radical is an atom or molecule that contains one or more unpaired electrons, making it unstable and more reactive. Reactive oxygen species are free radicals that originate from molecular oxygen by the process of the electron transport chain (Pizzino et al., 2017). ROS/RNS is important for many biological functions, but overproduction of ROS can cause oxidative stress in animals as well as in plants (Nathan and Cunningham-Bussel, 2013; Zhou et al., 2016). It can damage several macromolecules such as proteins, carbohydrates, lipids and DNA (Singh et al., 2013). Several external factors, such as cigarette smoking, pollutants, radiation, unhealthy food, and industrial chemicals and internal factors like the electron transport system in mitochondria, peroxisomes, exercise, and phagocytosis can promote the over-expression of ROS and cause oxidative damage to biologically important molecules (Gonzalez et al., 2005). From the literature, it has been found that mitochondria itself

produces 45% of total ROS during the electron transport chain (Wong et al., 2019). The overproduction of ROS disturbs the balance between antioxidant and free radicals which leads to the development of various diseases like respiratory disease, cardiovascular disease, primarily atherosclerosis, diabetes, cancer, neurodegenerative disorders such as Parkinson's disease, Alzheimer's and amyotrophic lateral sclerosis (ALS), Huntington's disease (HD), and various disorder like stroke, heart failure, hypertension (Benjamin et al., 2017; Erkkinen et al., 2018).

Nanomedicine is an emerging innovation in healthcare that utilizes the principles of nanotechnology. The synthesis of nanomedicines is based on materials like polysaccharides, proteins, synthetic polymers, ascorbate, citrate, and borohydride that are roughly 1 to 100 nanometres. In the medical industry, nanotechnology provides a significant contribution to targeted drug delivery, regenerative medicine, diagnosis, developing vaccines, and monitoring for specific diseases by synthesizing the nanoparticles (NPs) (quantum dots, polymeric nanoparticles, carbonnanodots, gold NPs, alloy or bimetallic NPs, metal oxide and liposome NPs (Dang et al., 2020). Nanomedicines are not limited to only disease treatments but it is widely used for other purposes such as imaging, monitoring, repair, and diagnosis of serious diseases (Tinkle et al., 2014).

Nanomedicines may be both hydrophilic and hydrophobic, which, as compared to conventional small-molecule medications, delays quick blood clearance and supports sustained drug release through extending circulation half-life, enhancing bioavailability, and reducing adverse effects (Xu et al., 2023). Antioxidant-based nanodrug delivery strategies showed significant improvement in counteracting ROS overproduction (Huang et al., 2021; Repellin et al., 2023). In 1995, clinical approval of doxorubicin encapsulation (DOX) as nanomedicine was a recent success in the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Ahmad et al., 2021; Jia et al., 2023). NPs-based nanomedicines have been experimentally shown to improve the therapeutic efficacy of therapy for a variety of diseases (Xu et al., 2023). In this review, we will explore the synthesis of nanoparticle-based nanomedicines and different nanomedicine-based approaches to reduce and prevent oxidative stress-induced diseases like cancer, diabetes mellitus, cardiovascular diseases Alzheimer's and Parkinson's disease. This review paper will also explore the strategies for targeted and controlled drug delivery, toxicity concerns, enhancing carrier stability and controlled release of nanomedicines.

2. MECHANISM OF ROS-DEPENDENT MACROMOLECULE OXIDATION

Macromolecules refer to large molecules such as carbohydrates, lipids, nucleic acids, proteins, enzymes, and hormones that are found in living organisms. The function of macromolecules includes storage for energy and genetic information, transportation, insulation, catalyzing reactions, cell signaling, defense and other various cellular processes and biosynthesis pathways (Mena-García et al., 2019; Famakinwa et al., 2023). Literature shows that reactive oxygen species have the potential to damage macromolecules (DNA, protein, lipid, etc) and that causes serious diseases (Gupta et al., 2015). It can break double strands of DNA and destroy genetic information and also cause protein and lipid oxidation (Shrinivas et al., 2019). The detailed mechanism for the oxidation of macromolecules by the ROS is described as follows:

2.1 Oxidative Stress-Induced DNA Damage

Excessive production of reactive oxygen species can damage DNA and break their phosphodiester bond. The hydroxyl radical (.OH) reacts with DNA bases and hydrogen atoms of the methyl group and the C-H bond of 2-deoxyribose. Various endogenous sources, exogenous sources and xenobiotics such as aromatic amines, polycyclic hydrocarbons, and nitrosamine can cause double and single-strand breaks, leading to mutation and also causing base lesions, sugar lesions, and DNA cross-link. DNA bases react with hydroxyl radicals and produce more than twenty different products. One of the most important oxidized DNA products is 8-hydroxydeoxyguanosine (8-OHdG), which is widely used in the evaluation of oxidative damage DNA. The consequences of oxidative DNA damage lead to the development of various cellular dysfunctions and diseases such as heart disease, multiple sclerosis, cardiovascular disease, cancer, Alzheimer's disease, cataracts, diabetes and age-related functional disorders (Singh et al., 2016).

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2.1.1 DNA Damage Through Nitrogenous Base

Ionizing radiation generates ROS, especially hydroxyl radicals that directly react with the purine and pyrimidine base (Steenken 1989). Pyrimidine, purine bases, and deoxyribose react with hydroxyl radical generating base and sugar by-products. Oxygen can rapidly attach to the radical site in thymine and form corresponding hydroperoxyl radicals that are subsequently converted into 8-trans and cis diastereomers of 5-hydroxy–6hydroperoxy-5,6 dihydrothymidine and 6-hydroxyl–5-hydroperoxy-5,6-dihydrothymidine. The oxidation of adenine forms 8-oxo-7, 8-dihydroadenine (8-oxoadenine) and 4, 6-diamino-5-formamidopyrimidine. These modified nucleotides are detected by the HPLC-ESI-MS/MS in the DNA of human monocytes exposed to gamma rays (Pouget et al., 2002).

2.1.2 Pentose Sugar Oxidation

Hydroxyl radical react with the sugar moiety of the DNA and form 2,3 dideoxypentose -4 ulose; 2,5 – dideoxypentose -4- ulose; 2- deoxytetro–dialdose and 2- deoxypentos -4 ulose (Fig. 1).

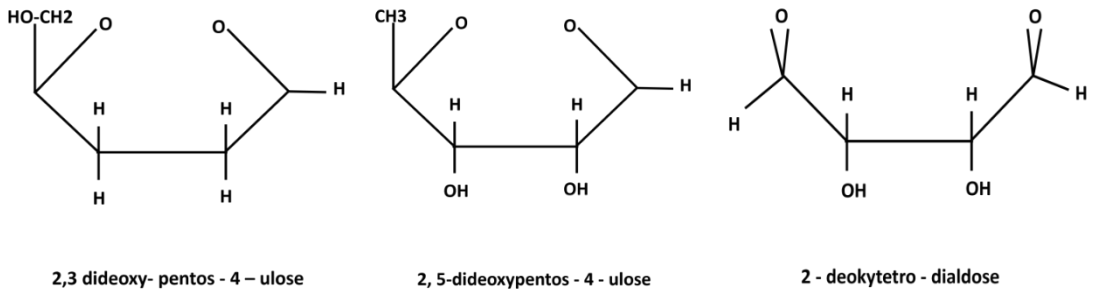

Figure 1. Alteration in DNA sugar by ROS results in diverse DNA damage

2.2 Oxidative Damage to Proteins and Enzymes

Proteins are an essential biomolecule for living organisms and it has an important role in physiological and cellular processes. It contains primary, secondary, tertiary and quaternary structures. However, various physical factors such as pH and temperature can disturb their structure and break bonds and become less functional (Qing et al., 2022). Reactive oxygen species can also act on proteins and cause protein oxidation (Murphy et al., 2022). The free radical directly cleaves the peptide bond and causes 50–75% of protein damage. Free radicals are more reactive and can attack protein molecules by coupling, oxygenation, abstraction, and cleavage and develop several severe diseases (Grune et al., 2004). Furthermore, they can directly disrupt cell signaling, cell structure and enzymatic processes (Cecarini et al., 2007). Some of the amino acids, such as lysine, arginine, proline and threonine are oxidized and converted into carbonyl derivatives. Sulfur containing the amino acid methionine under an oxidative environment converts into methionine sulfoxide in the presence of the enzyme methionine sulfoxide reductase (Sreekumar et al., 2011). Furthermore, the phenolic side chain of the aromatic amino acid (tyrosine, tryptophan, and phenylalanine) can rapidly oxidize, resulting in cellular dysfunction. The major diseases due to protein oxidation include muscular dystrophy, rheumatoid arthritis, Werner's and respiratory syndrome, Alzheimer's, progeria, amyotrophic lateral sclerosis, diabetes, hypertension, Parkinson's disease, cystic fibrosis, colon cancer, coeliac disease, eye disease (cataracts), uremia (kidney disease).

2.3 Lipid Peroxidation (LPO)

Lipids are organic compounds that are essential for cell structure integrity, cell signaling, and energy storage. The overproduction of ROS causes lipid peroxidation via nonenzymatic (iron-dependent) and enzymatic (LOX-catalyzed) processes. In lipid peroxidation, phospholipids present in the cell membrane get oxidized and can act as cell death signals that regulate programmed cell death. These oxidized phospholipids can cause several diseases like

ischemia-reperfusion, heart failure, Alzheimer's, cancer, arthritis, and various immunological disorders (Que et al., 2018; Su et al., 2019).

In lipid peroxidation, malondialdehyde (MDA) is one of the major products generated during polyunsaturated fatty acid peroxidation in the cells and used for the quantitative assay of lipid peroxidation. Free radicals attack the carbon-carbon double bond of polyunsaturated fatty acids (PUFAs) and produce a variety of oxidation products. The main primary product of lipid peroxidation is lipid hydroperoxide (LOOH) and secondary products *i.e.*, malondialdehyde (MDA), propanol, hexenal and 4-hydroxy-2-nonenal (4-HNE). 4-HNE is more harmful than MDA. During LPO, MDA is produced in high amounts, so it is commonly used as a measure of oxidative stress. MDA has been used as a convenient biomarker for the oxidation of Omega 3 and Omega 6 fatty acids because it rapidly reacts with thiobarbituric acid (TBA) (Rizzo, 2024). In the TBA test, MDA, the by-products of lipid peroxidation, react with TBA and form pink chromagen or fluorescent red MDA-TBA2 adducts, which are known as thiobarbituric acid-reactive substances (TBARS). Various bio-instrumentation techniques such as a spectrophotometer, gas chromatography, and liquid chromatography-mass spectrometry (LC-MS) are used to determine the concentration of free and total MDA. The higher concentration of MDA indicates oxidative stress in clinical situations (Giera et al., 2012).

3. NANOMEDICINE

The term Nanomedicine is used for the applications of nanotechnologies in medicine and healthcare by the use of nanomaterials. The area of nanotechnology is advancing and making great progress in the field of nanomedicines and their applications. Nanomedicine involves the restoration, maintenance, enhancement, construction, and control of the human biological system at the molecular level. Nowadays, nanomedicines are not only used in the treatment of disease but also play a crucial role in monitoring, diagnosis, imaging, tissue repair, and regeneration. Nanoparticles are small particles ranging from 1 to 100 nm that may be of different shapes, such as discs, cylindrical, cones, tubes, hemispheres, wire spheres, or spherical (Seigneuric et al., 2010). In the biomedical field, it can safeguard the human body from multiple diseases. Nanoparticles are widely used as antimicrobial agents, biosensors, and *in vitro* anticancer therapy (Joseph et al., 2023). Several types of nanoparticles (NPs), such as carbon-based nanoparticles, organic-based NPs, and inorganic-based nanoparticles are popularly used for the synthesis of nanomedicines (Ren et al., 2021).

In recent years, enhanced progress in the drug delivery system by the use of liposomes as carrier molecules for targeted drug delivery in the treatment of various diseases has been quite satisfactory (Liu et al., 2021; Zhao et al., 2023). Furthermore, various nanoparticles are also utilized in targeted drug delivery, including magnetic nanoparticles, nanotubes, and virus nanoparticles. It has the potential to transport the nanomedicines without any disruption of healthy cells (Seigheuric et al., 2010).

3.1 Approaches for the Nanoparticle's Synthesis

There are several ways to synthesize nanoparticles, including physical, chemical, and biological approaches. The method used for nanoparticle synthesis will depend on the desired properties and applications of the nanoparticles (Fig. 2).

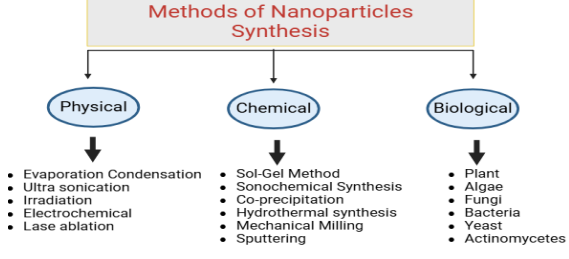

Figure 2. Physical, chemical and biological approaches for the synthesis of nanoparticles

3.2 Types of Nanoparticles and Their Applications in the Medical Field

Currently, we are using several nanoparticles like liposome-mediated nanoparticles, metal oxide nanoparticles, alloy nanoparticles or bimetallic nanoparticles, polymer-based nanoparticles, gold nanoparticles (AuNPs), nanodiamonds, nanorobots, virus-like nanoparticles, quantum dots, dendrimers and micelles for the treatment of diseases, diagnosis, drug delivery, and imaging (Fig. 3; Table 1).

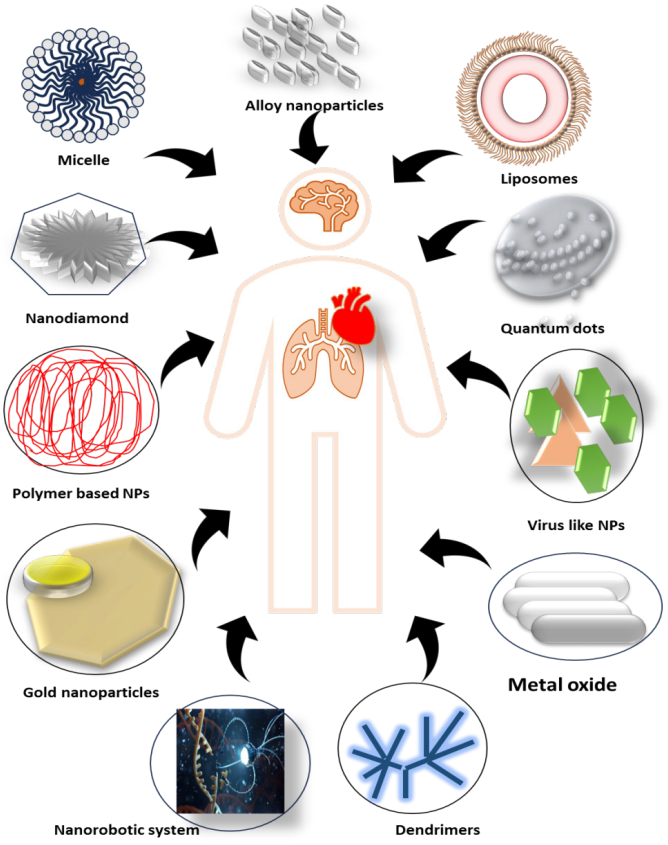

Figure 3. Different types of nanoparticles are used in treatment, diagnosis, drug delivery, and imaging.

Table 1. Different types of nanoparticles and their applications in disease treatment

Nanoparticles	Target/Action	References
PEGylated colloidal gold Nanoparticle	Solid cancer	Hofmeister et al., 2008
Gold monoshell	Head and neck cancer	Dobrovolskaia and McNeil, 2007
Liposomal cytarabine	Malignant lymphomatous meningitis	Zhang et al., 2008
Liposomal amphotericin B	Fungal infection	Zhang et al., 2008
Aerosol OT (AOT) alginate nanoparticle	Breast cancer	Chavanpatil et al., 2007
Pegfilgrastimis -granulocyte colony-stimulating factor (PEG-GCSF)	Neutropenia associated with cancer chemotherapy	Zhang et al., 2008
PEG-L- asparinase	Acute lymphoblastic leukemia	Zhang et al., 2008
Antibody-enzyme conjugated NPs (Polymeric micelles)	Enzyme prodrug therapy (Ovarian cancer)	Fonseca et al., 2003
Poly (Lactic- CO- glycolic acid) block–poly ethylene glycol	Prostate cancer	Farokhzad et al., 2006
Folic acid-conjugated polyamidoamine (PAMAM) dendrimers	Epithelial cancer	Kukowska et al., 2005

Polypropylene mine dendrimers	HIV infection	Dutta et al., 2007
Ligand conjugated PEG-Poly-L- Lysine Dendrimers	Malaria	Bhadra et al., 2006
SPIONS (Metallic NPs)	Cancer-associated fibroblast	Ferraz et al., 2020
Cur-loaded PMMA NPs (polymeric nanoparticles)	Human lung cancer lines	Pulingam et al., 2022
Quantum dots	Imaging of lymphnodes tumours and lung blood vessel	Akerman et al., 2002; Gao et al., 2004; Kim et al., 2004
Superparamagnetic iron oxide nanoparticles	Cancer detection	Huh et al., 2005
Nano ceria	Inflammatory effect (Human aortic endothelial cell)	Gojova et al., 2009
Polymer and liposome-based NPs	Neurodegenerative disease therapy and HIV/AIDS therapy	Joseph et al., 2023

3.2.1 Liposome-Mediated Nanoparticles

Liposome-mediated nanoparticles are a type of nanoparticles that consist of a lipid bilayer. It is an amphiphilic molecule that has both hydrophilic and hydrophobic properties that are similar to biological membranes and can be used in drug delivery systems and diagnosis. Liposome-mediated nanoparticles are popularly used in targeted drug delivery of chemotherapeutic drugs in cancer treatment (Malam et al., 2009; Panahi et al., 2017).

3.2.2 Metal Oxide Nanoparticles

Metal oxide nanoparticles are mainly used in pharmaceuticals and environmental remediation. Metal oxide nanoparticles include titanium oxide (TiO_2), zinc oxide (ZnO), iron oxide (Fe_3O_4), and recently ceria (CeO_2) or nanoceria. The nanoceria has been used as an anticancer agent and biosensor, whereas TiO_2 nanoparticles are used in photo ablation therapy and bio-imaging (Wu et al., 2011; Lee et al., 2015; Alpaslan et al., 2015). Due to chemical stability, biocompatibility, and high surface area, metal oxide nanoparticles have high antioxidant and catalytic activity (Andreescu et al., 2012). Superparamagnetic nanoparticles have low toxicity and are specific for tumor treatment.

3.2.3 Alloy Nanoparticles or Bimetallic Nanoparticles

Iron platinum (Fe-Pt), Iron cobalt (Fe-Co), Iron-nickel (Fe-Ni) and Copper-nickel (Cu-Ni) are bimetallic nanoparticles that are composed of two different metals. Fe-Co nanoparticles are used in MRI (An et al., 2014). Fe-Pt NPs contain specific magnetic properties and they get oxidized smoothly and are primarily used as a contrast agent. Ferromagnetic nanoparticles showed supra paramagnetism which absorbs more X-rays and has high chemical stability and is most commonly used for the treatment of hyperthermia (Seehra et al., 2010; An et al., 2014).

3.2.4 Polymer-Based Nanoparticles

Polymeric nanoparticles are more extensively used in nanomedicine research (Galvin et al., 2012). It is used mainly in the drug delivery system that has more biological safety and better biodegradability, and it can protect the drugs or antigens from degradation. Polylactic acid, chitosan, polyglutamic acid (PGA), and polylactic glycolic acid (PLGA) are examples of polymer-based nanoparticles (Han et al., 2018). Biosynthesized nanoparticles are acquired by using microbial enzymes. These compounds contain microbial polysaccharides and polyesters such as poly-β-hydroxybutyrate (PHB), bio fiber bundle, polyamine acid, poly (3-hydroxybutyrate CO-3-hydroxylvalerate) (Wang et al., 2013). These nanoparticles are not only in drug delivery as carriers but are also utilized in tissue engineering and surgical treatment as bone repair material (Chaturvedi et al., 2015). PHB is mainly used in soft tissue repair such as skin tissue and palatal tissue repair (Zhang et al., 2014).

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3.2.5 Gold Nanoparticles (AuNPs)

Gold nanoparticles are used in disease diagnostics and therapeutic methods and precise drug delivery (Al-Thani et al., 2024). Reports suggest that the administration of gold nanoparticles derived from apple polysaccharides can be used in the treatment of type 1 diabetes mellitus. Gold nanoparticles are able to covalently bind with biological molecules and regulate targeted cancer therapy. Drugs conjugated with AuNPs are widely used vehicles for drug delivery at targeted sites and selective distribution (Huang et al., 2023; Dykman et al., 2025). AuNPs also showed broad antimicrobial activity, such as fungicidal, bactericidal, and virucidal effects against specific pathogenic microorganisms (Fadak et al., 2021).

3.2.6 Nanodiamonds

Nanodiamonds (NDs) are carbon-based nanomaterials, approximately 2 to 8 nm in diameter (Lam et al., 2009). Applications of nanodiamonds are in imaging, therapy and the detection of infectious diseases. In 2007, NDs proposed the newest detection method for bio-labelling using a detection probe (Chao et al., 2007). Nanodiamonds have a small size, less cytotoxicity, high binding properties, and can be used successfully in infectious diseases. It contains bactericidal and anticancer properties (Jira et al., 2018; Chipaux et al., 2018).

3.2.7 Nanorobots

Nanorobots are nanodevices or machines that are made up of molecular components at the nanoscale level. Nanorobots are applied by utilizing many constituents such as sensors, control and power actuators. It can perform specific functions like diagnosis, surgery, drug delivery and tissue repair at the molecular level (Xie et al., 2019). Nowadays, this technology is also used in cancer treatment, the removal of kidney stones and gene therapy.

3.2.8 Virus-Like Nanoparticles (VLNPs)

Virus-like NPs are natural polymer-based nanomaterials that mimic viral structures. Numerous viruses are used as a carrier platform in cancer therapy and diagnosis. Particles of some viruses like bacteriophage, Qubevirus durum and Emesvirus Zindagi (MS2), tobacco mosaic virus (TMV), human papilloma virus (HPV), hepatitis B virus (HBV) and cowpea chlorotic mottle virus (CCMV) have been used as carrier platform in cancer research (Cai et al., 2020). VLNPs are utilized for other medical purposes that are vaccine-based immunotherapy, gene therapy, drug delivery, bioimaging, MRI, and fluorescence imaging (Kim et al., 2023).

3.2.9 Quantum Dots

Quantum dots are tiny fluorescent semiconductor particles and they have unique optical and electronic properties due to quantum mechanics. It is used in drug delivery and cellular imaging (Probst et al., 2013).

3.2.10 Dendrimers

Dendrimers are highly branched tree-like structures that are used for drug delivery, bacterial cell killing, and gene transfer agents, imaging and diagnosis (De Jong et al., 2008). The dendrimers can be tagged with an imaging agent in MRI contrast agent or fluorescent dye that helps to visualize diseases like cancer.

3.2.11 Micelles

It is a very specific and sensitive spherical nanoparticle. They contain hydrophilic outer shells and hydrophobic cores that are used in drug delivery, gene delivery, cancer therapy and antimicrobial agents.

3.3 Mechanism of Targeted Drug Delivery

Currently, we are using different types of nanoparticle-based delivery systems for the delivery of drugs at specific sites, which may be of organic and inorganic nature. Organic nano carrier includes liposomes, dendrimers, polymeric nanoparticle, virus-mediated NPs, etc., whereas inorganic nanocarriers include mesoporous silica NPs, carbon nanotubes and quantum dots. These nanoparticle-based delivery systems have successfully delivered specific drugs at targeted sites without any side effects (Sahoo et al., 2021; Sultana et al., 2022). In the drug delivery system, targeted drugs are liberated in multiple-step processes. The growth of the nanotechnology field can enhance the solution of multiple problems in terms of efficacy and targeted drug action. The nanoparticles are used in drug delivery as a therapeutic agent or genetic

material at specific sites (Ould-Ouali et al., 2005). Multiple anti-cancer drugs such as doxorubicin, paclitaxel and dexamethasone were successfully delivered at specific sites by the use of nanoparticles (Table 2) (Panyam et al., 2004; Koziara et al., 2006). Liposomal doxorubicin is an anthracycline-type chemotherapy drug that is used in the treatment of various cancers (such as ovarian cancer, AIDS-related Kaposi's sarcoma, and multiple myeloma). Polymeric nanoparticles and micelles are utilized in the chemotherapeutic treatment of breast cancer (Fig. 4) (Lombardo et al., 2019; Pathak et al., 2022).

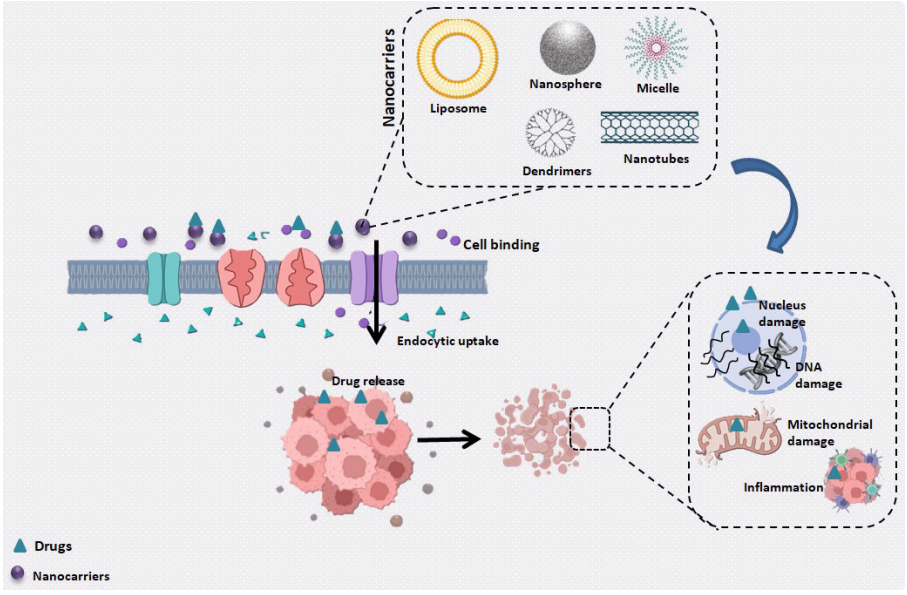

Figure 4. Mechanism of specific drug delivery at the targeted site through the nanocarrier

Table 2. List of the drugs incorporated in various types of nanoparticles for drug delivery and their action/target site

Drugs	Nanoparticles	Action/Targeted Site	References
Human epidermal growth factor receptor-2 (HER)	Polyamidoamine (Dendrimers)	Selective cancer killer gene therapy	Moradian et al., 2021
Doxorubicin	CXCR4 targeted dendrimers	It binds to breast cancer cells, suggesting an effective way for cancer therapy	Chittasupho et al., 2017
Paclitaxel	Chitosan oligosaccharide conjugated pluronic polymers (Liposome type)	Inhibit 86.4% tumour	Miao et al., 2021
Hydrophobic curcumin	Chitosan polymeric nanoparticles	Highest inhibition zone of *Pseudomonas aeruginosa*	Samrot et al., 2018
Streptokinase	Tobacco mosaic virus (virus like NPs)	It enhances thrombolysis	Pitek et al., 2017
Leukosomes	Rapamycin	Antherosclerosis plaques	Boada et al., 2020
Folic acid modified poly(ethylene glycol)-poly(ε-caprolactone) (FA-PEG-PCL) (FDMCA)	MIP-3β Plasmid	Immune cell in tumour	He et al., 2020

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PMCS	Cisplatin and sodium nitroprusside	Induce tumor cell apoptosis	Chen et al., 2021
p-hydroxybenzoic acid (pHA)- anti-programmed death ligand 1 antibody (αPDL1)	αpdl1	Brain and glioma	Guo et al., 2020

3.4 Role of nanoparticles in disease diagnosis

Nanoparticles are very small particles that are smaller than the blood cell and nearly the same size as DNA. Nano diagnosis is the newest imaging technique that gives the physical and chemical information of the disease by the use of nanoparticles (Fig. 5; Table 3). The nanoparticles can be applied in both conditions *i.e.*, in vitro and in vivo. Quantum dots are most commonly used in diagnosis because they strongly absorb light. Nanotubes, nanoshells, and gold nanoparticles are also used to diagnose diseases (Alharbi et al., 2014). This technique is sensitive, specific, robust, user-friendly and cost-effective. In infectious diseases, it can detect (in vitro diagnosis) the pathogenic microorganisms (bacteria, fungi, parasites, and viruses) by using pathogen-specific biomarkers. A new approach has been used for the diagnosis and screening of cancers by the use of paper-based sensors.

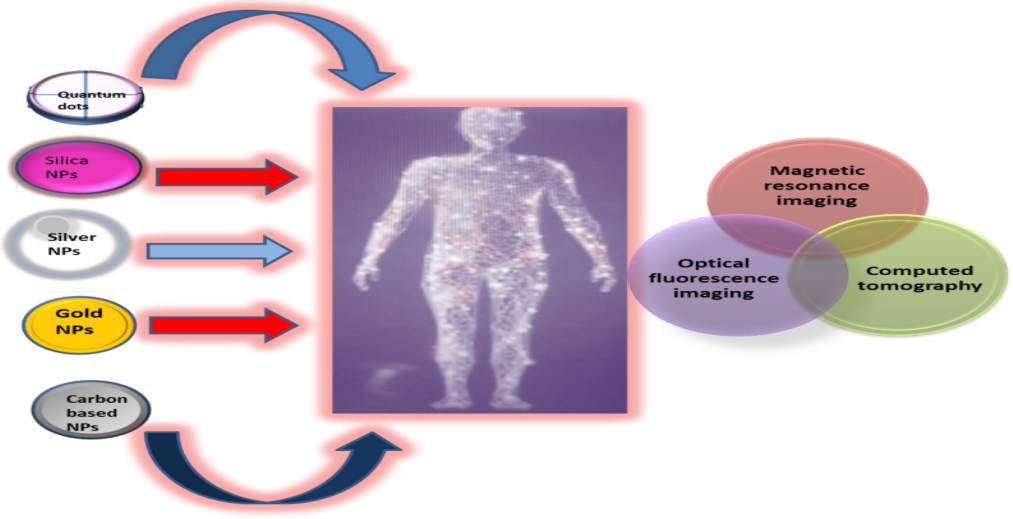

Figure 5. Different types of nanoparticles used in disease diagnosis

Table 3. Applications of NPs in disease diagnosis

Types of Nanoparticles	Detection Technique	Target Disease	References
Silica nanoparticles	Photochemical	HIV/AIDS	Chunduri et al., 2017
Gold nanoparticles	Electrochemical	Tuberculosis	Ng et al., 2015
Gold nanoparticles	Colorimetric	COVID-19	Moitra et al., 2020
Carbon nanoparticles	Amperometric	Diabetes	Zhu et al., 2012
Graphene oxide	Fluorescence	Prostate cancer	Feng et al., 2012

Gold nanoparticles	Colorimetric	COVID-19	Pramanik et al., 2021
Silver nanoparticles	Fluorescence	Typhoid	Leng et al., 2018
Superparamagnetic iron oxide nanoparticles	MRI	Pancreatic cancer cell	Pan et al., 2021
Magnetic gold nanoparticles	ELISA based detection	Breast cancer check	Shamsipur et al., 2018

3.5 Applications of Nanomedicines in the Treatment of ROS-Induced Diseases

3.5.1 Cancer

According to the GLOBOCAN, 2018 report, cancer is one of the most serious diseases in both developed and developing countries. It has been estimated that by 2030, 13 million people will die from numerous cancers each year (Lancet, 2018). Exogenous and endogenous ROS can cause DNA mutation and disrupt the genetic information, resulting in the deactivation of the tumor suppressor gene and activation of an oncogene (Jiang et al., 2019; Kontomanolis et al., 2020). ROS also causes the mutation in p53 and the oncogene rat sarcoma (Ras) gene. Mutation in p53 gene has been reported in liver cancer and breast cancer (Brancato et al., 2016). The findings on the Ras gene mutation suggest that it causes skin cancer and colorectal cancer (Margetis et al., 2017). ROS can inhibit the immune cells' (T cells, NK cells and macrophages) maturation, activation and differentiation and function. It can block the antitumor activity of T-cell macrophage. The different types of cancers induced by ROS are summarized in Table 4.

Table 4. The mechanism by which ROS contributes to the development of several types of cancer

Types of Cancer	Reactive Oxygen Species Involved in Cancer Development	References
Pancreatic cancer	Hydrogen peroxide	Liedtke et al., 2017
Head and neck cancer	DNA damaged by ROS	Kang et al., 2014
Gastric cancer	ROS and RNS	Chen et al., 2016
Cervical cancer	Hydrogen peroxide	Li et al., 2017
Breast cancer	Hydrogen peroxide	Liu et al., 2017
Triple-negative breast cancer	ROS and RNS	Nguyen et al., 2016
Lung cancer	ROS and RNS	Karki et al., 2017
Colon cancer	DNA damaged by ROS	Choi et al., 2017
Brain cancer	ROS	Kaushik et al., 2013
Thyroid cancer and oral cancer	ROS-induced DNA damage and apoptosis	Kaushik et al., 2014
Blood cancer	ROS	Schmidt et al., 2016

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3.5.1.1 Cancer Nanomedicine: Cancer is the second biggest cause of mortality due to available less efficient treatment and side effects, but the treatment based on nanotechnology through nanomedicines is more efficient than the traditional treatment methods and has fewer side effects. It involved nanotherapy, targeted drug delivery, diagnosis, and imaging by the use of nanocarriers and nanoparticles (Giri et al., 2023). According to Matsumura and Maeda in 1986, they first observed that it is a very effective therapy for cancer by the use of nanocarriers. The other researcher also reported that radiation-induced tumors can also be treated with the use of nanoparticles. Numerous types of nanoparticles are utilized in anticancer therapy. Liposome nanoparticle dendrimers, inorganic nanoparticles, organic nanoparticles, and solid lipid nanoparticles are used. In cancer therapy, doxorubicin-loaded liposome nanoparticles are used in the treatment of breast cancer (Senapati et al., 2018). Furthermore, mainly in bioimaging use the nanobots, gold NPs and quantum dots in future expectations (Alshehri et al., 2020).

3.5.1.2 Nanoparticles-Based Drug Delivery System in Cancer Treatment: The tiny size of NPs can be majorly used in oncology. Nanoparticle-based drug delivery systems have shown very specific and selective properties. It can successfully deliver drugs at specific sites to cancer cells without interacting with any healthy cells and tissue. It is possible to design nanoparticles that can deliver drugs in a regulated way. This holds great promise for the development of more personalized and effective cancer treatments in the future (Benoit et al., 2016). Nanoparticle-based chemotherapy drugs can be encapsulated for targeted cancer cell treatment. Therapeutic agents can be entrapped covalently in encapsulated bags or adsorbed into the NPs (Praetorius et al., 2007). It is a promising method for specific receptor targeting (luteinizing hormone, releasing hormone receptor, transferrin receptor, folate receptor, etc), and antibody-mediated targeting (Sutradhar et al., 2014).

3.5.2 Parkinson's Disease

Parkinson's disease (PD) is the second most neurodegenerative disease (Tieu et al., 2003). Epidemiological data suggest that recently about 1 million people have been influenced by PD in North America and 50,000 new cases are recorded every year. It has been estimated that the number of PD patients will be approx. 13 million in 2040 (Fahn et al., 2000). Of total respiratory oxygen, 20% of oxygen goes to the brain and a major part of this oxygen can change in the ROS that can disrupt the dopaminergic neurons of the substantia nigra. The oxidation of dopamine can form dopamine quinones and cause neurodegeneration. The gene products DJ-1, PINK1, Parkin, α-Synuclein and LRRK2 are involved in PD onset. Symptoms of PD included slowness of movement, tremors and rigidity in striated muscles, and posture disorder (Kucukoglu et al., 2022).

3.5.2.1 Nanomedicine for Parkinson's Disease: Nanomedicines provide a better way to treat Parkinson's disease due to targeted drug delivery, lesser side effects and also the possible use of nanoparticles in diagnosis, monitoring, control and therapy.

3.5.2.2 Drug Delivery System in PD: PD utilizes several types of nanoparticle drug delivery systems, mostly polymeric NPs because it is biodegradable, non-toxic, biocompatible, and releases drugs at targeted sites (Jesus et al., 2019). Poly (lactic –CO- glycolic acid) (PLGA), polylactic acid (PLA) and polyethylene glycol (PEG) are the most common drug delivery systems in PD (Bobo et al., 2016). Lipid-based NPs, inorganic NPs, gold NPs, and magnetic iron NPs are also used for the targeted delivery of drugs (Niu et al., 2017). The small nano and lipophilic molecules can cross the blood-brain barrier.

3.5.2.3 Nanoparticle-Based Gene Therapy in Parkinson's Disease: Nanoparticle-based gene therapy provides a new technology for the treatment of PD. In this technology, nanomaterials loaded DNA transferred into the brain by transduction technique to express specific genes in the cell. The cell expresses this gene and forms gene products. It is applicable to dopamine secretion in PD patients and has fewer side effects. This therapy is also very useful in the treatment of other neurodegenerative disorders. Numerous types of nanoparticles are used in this therapy which pass via the blood-brain barrier. Surface-modified dendrimers easily penetrate the CNS (Central Nervous System), resulting in decreased dopaminergic neuronal loss and progressed locomotors' activity compared to non-modified nanoparticles (Huang et al., 2010).

3.5.3 Diabetes

Diabetes is a metabolic disorder that may be of two types *i.e*. type 1 and type 2 diabetes. In type 1 diabetes, the pancreatic β-cell is unable to produce insulin hormone due to an autoimmune disorder when immune cells attack the insulin-producing cells, whereas in type 2 diabetes, either β-cell does not produce enough insulin or the body's cell receptors do not interact with insulin. The consequences of these conditions lead to the development of chronic kidney disease, stroke, foot ulcers, and damage to the nerve cells, diabetic retinopathy, cataracts, and cardiovascular disease and these all serious diseases have increased the death rate worldwide (Nickerson et al., 2012). A recent study published in 2019 indicated that around 9.3% of the adult population is suffering from diabetes and predicted that by 2045, it will reach approximately 11% of the total adult population. Mostly, 90% of diabetes cases are due to unhealthy lifestyles, high carbohydrate and fat diet, genetics, and hormonal diseases (Burrack et al., 2017; Saeedi et al., 2019). Excessive production of ROS in the body due to external and internal factors plays a very important role in the onset of diabetes disorders. The overproduction of ROS can reduce insulin hormone gene expression and secretion. Insulin resistance and β-cell dysfunction are also caused by the reduction of insulin hormone receptor expression in type 2 diabetes. Studies on oxidative stress showed that it can enhance diabetes-associated cardiovascular disease (Kayama et al., 2015). Diabetes patients are increasing day by day and their treatment includes conventional insulin injections, a therapeutic option for type 1 diabetes, whereas type 2 diabetes treatment includes a mix combination of lifestyle changes and medication. The available drugs such as metformin (Fortamet, Riomet, Glucophage and Glumetza), sulfonylureas, thiazolidinedione, GLP-1 receptor inhibitor, meglitinides, sodium-dependent glucose transporters (SGLT-2) and α-glycosidase inhibitors, doctors are using to treat diabetes patients but these drugs treatment do not provide satisfactory results and show high side effects and less effective. The nanotechnology field has solved these problems and provided better treatment options as compared to available methods. The nanoparticle-based cures include disease diagnosis and oral insulin delivery of drugs with fewer side effects and high efficacy (Sen et al., 2015).

3.5.3.1 Application of Nanoparticles in the Diagnosis of Diabetes Mellitus: Multiple types of nanoparticles are utilized in the diagnosis of diabetes mellitus, such as metallic nanoparticles, quantum dots, polymeric nanoparticles and biomolecule-based nanoparticles for bioimaging and biosensing (Lemmerman et al., 2020). Currently, quantum dots are nanoparticles most utilized in quantum dots-driven breath sensors that can detect metabolic variation in patients. Magnetic nanoparticles can be used as a contrast agent for β-cell monitoring. MRI of the pancreas, dextran-coated iron oxide nanoparticles i.e. ferumoxtran-10 is used to observe pancreatitis (Gaglia et al., 2011). Ferromagnetic iron oxide nanocubes are highly reliable and are capable of enhancing the MRI resolution (Lee et al., 2011).

3.5.3.2 Nanomedicines for the Treatment of Diabetes Mellitus: Several nanoparticles, such as natural polymeric nanoparticles, alginate-based nanoparticles, dextran-based nanoparticles, PLGA-based nanoparticles, polyallylamine nanoparticles, niosomes, polymeric micelles, liposomes, and chitosan-coated NPs can be used for the delivery of the insulin hormone at the targeted site (Souto et al., 2019). These nanoparticles are utilized to secure the insulin from deterioration and direct delivery of insulin at the target site by effective routes like pulmonary, oral, nasal and subcutaneous. Oral insulin delivery is the most successful delivery system for diabetes mellitus. Insulin loaded in polymeric biodegradable nanoparticles (polymethacrylic acid, polyethylenimine) in the form of pellets is used in oral insulin delivery in animal studies. Insulin is a hydrophilic drug, thus it cannot diffuse the intestinal epithelium (Harsoliya et al., 2012). So, different approaches like the use of permeation enhancers, modifications in chemical nature, and enteric coatings have been exploited for the oral delivery of insulin. Superior outcomes were reported under in vivo experiments with antidiabetic drugs loaded with nanoparticles.

3.5.4 Cardiovascular Disease

Cardiovascular disease (CVD) has become a dangerous disease in today's time and is responsible for high mortality in the world (He et al., 2015).

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Overproduction of ROS can damage the cardiovascular system resulting in blocked blood flow, and several other diseases such as atherosclerosis, hypertension, heart failure, cardiac arrhythmia, and aortic aneurysms and ischemic heart disease, cerebrovascular disease (stroke), peripheral arterial disease, heart valve disease, and hypercholesterolemia (Fig. 6) (Wang et al., 2016; Lepedda et al., 2020). It has been found that an increase in mtROS (Mitochondrial stress) can also enhance cardiac dysfunction, ventricular remodeling finally heart failure (Bertero et al., 2018).

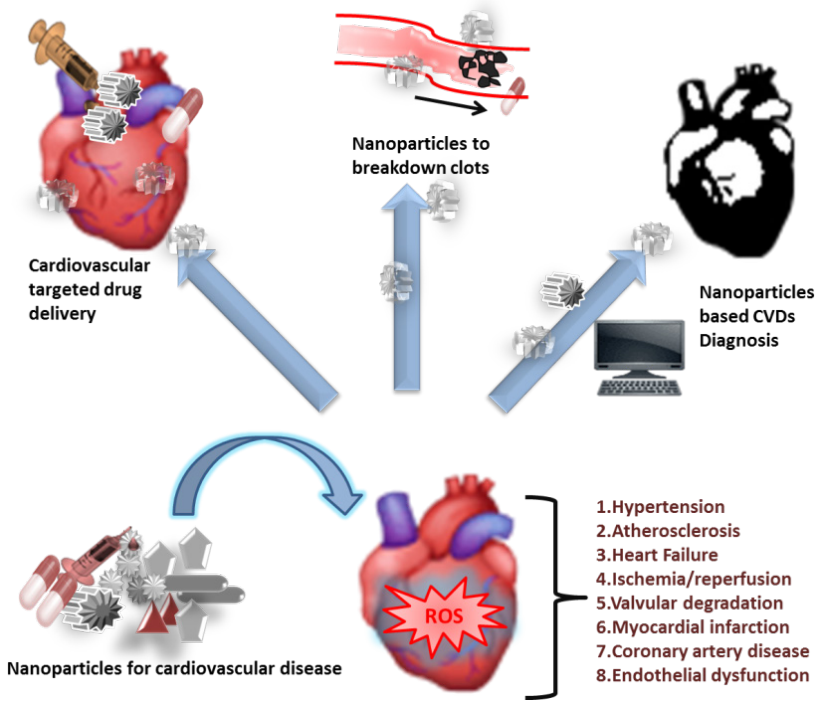

Figure 6. Nanoparticles used in cardiovascular disease (CVDs) treatment

3.5.4.1 Nanomedicines for Cardiovascular Disease: Medicines for CVD treatment are available but still show challenging issues like delivering a therapeutic drug to a specific location in a blood vessel and their efficacy. Currently, we are using various NPs based nanomedicines like lipid-based NPs, dendrimers, carbon-based NPs, metal NPs, polyglycolic acid, polylactic-co-glycolic acid (PLGA) and FDA-permitted polymers for the treatment of cardiovascular disease. PLGA has been broadly tested as a drug carrier for CVD treatment (Oduk et al., 2018). Furthermore, carbon nanotubes are also suitable for the drug carrier in case of CVDs. Several studies showed that carbon nanotubes are capable of cardiac tissue engineering and can enhance the growth and function of cardiomyocytes (Ahadian et al., 2017). Polymeric NPs such as PLGA, cyclodextrin, chitosan, and gold NPs are widely used as nanocarriers for the cardioprotective drugs in atherosclerosis treatment (Psarros et al., 2012). Delivery of PLGA NPs significantly inhibited the plaque developed in blood vessels, whereas superparamagnetic iron oxide NPs are popularly used in the treatment of myocardial infarction. It has good magnetic properties and biocompatibility that can be utilized to monitor and treat myocardial infarction. Tissue plasminogen activator (t-PA) i.e. thrombolytic drugs also delivered at targeted sites and it played a significant role in the fast recovery of blood vessels and decreased bleeding and other complications (Torchilin 2014).

4. FUTURE PERSPECTIVES AND CHALLENGES

The development of the nanotechnology field has contributed significantly roles in nanodiagnosis, regenerative medicine monotherapy, and imaging, etc. The National Institute of Health (NIH) has reported that in recent decades, the synthesis of nanomedicines has been an important invention in pharmaceutical and biomedical fields. In regenerative medicine, nanoparticles can be used for tissue engineering and promote tissue repair and regeneration. The nanorobotic system will be applied in the treatment of many serious illnesses within the body. It is cost-effective and has fewer side effects and is toxic. Numerous engineers, scientists, clinicians, and regulatory agencies are working to enhance the effects and functions of nanomedicine with clinical and preclinical trials. In the future, it may prove to be a very effective treatment for the pandemic (infectious disease). Nanomedicines have many potential benefits over other available medicines, but it has also had many challenges like synthesis and the use of nanomedicines, the complexity of nanomedicines, surface modification, nanomedicine properties, no specific regulatory guidelines for nanomedicines, still need more research to understand the impact of nanomedicines on biological systems and environmental (Table 5).

Table 5. Advantages and disadvantages of different nanoparticles for ROS-induced disease treatment

S.No.	NPs in ROS-Induced-Disease Treatment	Advantages	Disadvantages	References
1.	Carbon-based nanoparticles (fullerenes, graphene, carbon dots)	Strong antioxidant activity, high stability, versatile functionalization	Potential toxicity, challenges in large-scale production	Liu et al., 2020
2.	Metal oxide nanoparticles (cerium oxide, manganese oxide NPs)	Enzyme-mimicking antioxidant properties, long-term ROS regulation, high redox activity	Stability issues, possible adverse cellular effects, complex synthesis	Lord et al., 2021
3.	Polymeric nanoparticles (e.g., PLGA, chitosan-based NPs)	Biocompatible, controlled drug release, reduced systemic toxicity	Limited ROS-scavenging ability alone, degradation concerns	Li et al., 2020
4.	Nanozymes (Cerium oxide, iron oxide NPs)	Mimic natural antioxidant enzymes, high catalytic efficiency, potential for ROS regulation.	Potential immunogenicity, stability under physiological conditions	Liang et al., 2022
5.	Lipid-based nanoparticles (liposomes, solid lipid NPs, nanoemulsions)	High biocompatibility, efficient drug delivery, improved solubility	Short circulation time, potential drug leakage	Dai et al., 2024
6.	Protein nanocages (e.g., DPS)	Natural protein structure, excellent antioxidant properties, blocks Fenton reaction	Complex synthesis process, potential immunogenicity	Zhu et al., 2021
7.	Biomaterials	Anti-inflammatory effects, ROS scavenging capability, supports neural regeneration	Limited long-term efficacy, potential toxicity	Liu et al., 2023
8.	Nanozymes	Mimics natural enzymes, high stability, cost-effective production	Potential toxicity, biocompatibility concerns	Gorgzadeh et al., 2024
9.	Cerium oxide nanoparticle-integrated poly-ε-caprolactone fibers	Enhanced biocompatibility, antioxidant properties, tissue regeneration potential	Mechanical properties need optimization for clinical applications	Jahan et al., 2024

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10.	Cerium oxide nanoparticles stabilized with functional copolymers	Improved stability and biocompatibility, effective ROS scavenging	Long-term toxicity and clearance mechanisms still under investigation	Goujon et al., 2021
11.	Co-Mn complex oxide nanoparticles for pulmonary fibrosis	Multifunctional ROS scavenging inhibits fibroblast activation	Requires further clinical testing	Yang et al., 2024
12.	Gold nanoparticles for radiotherapy	Enhances ROS generation, improves radiotherapy effectiveness	Possible accumulation in organs, toxicity concerns	Nguyen et al., 2025
13.	Nanozymes for redox-related diseases	Versatile, mimics natural enzymes, effective ROS scavenger	Long-term effects and bioavailability need evaluation	Sun et al., 2023
14.	Mackinawite nanozymes (FeS)	Mimic antioxidant enzymes to scavenge ROS	Long-term effects need further study	Xu et al., 2023

Nanotoxicity represents a significant health concern associated with the use of nanomaterials in drug delivery systems, diagnostics, prognostics, vaccines, and gene therapy (Thu et al., 2023). Moreover, research has demonstrated that NPs can penetrate the human body via inhalation, ingestion, and dermal exposure, leading to potential damage at the cellular, tissue, and organ levels. Recent investigations have primarily aimed at elucidating the mechanisms underlying NPs-induced toxicity and identifying key factors responsible for their harmful effects (Ali et al., 2023). It has been found that factors such as size, shape, surface area, and chemical composition, along with their interactions with biological molecules like proteins, enzymes, and DNA are responsible for their toxicity (Xuan et al., 2023). In biomedicine, metal and metal oxide nanoparticles (Ag, Au, ZnO, CuO, and CeO_2) are extensively utilized in drug delivery, diagnostics, therapy, and imaging due to their distinctive physicochemical properties. However, their interactions with immune cells have raised significant safety concerns related to immunotoxicity. Research has demonstrated that these nanoparticles can trigger various immune responses, potentially posing risks to human health by activating the body's defense mechanisms (Mohammapdour et al., 2022). The effective bioavailability of nanomedicines, which refers to the fraction of a drug that successfully reaches systemic circulation to produce the intended therapeutic effect, remains a significant challenge. Moreover, nanomedicines need to overcome several biological barriers, including the gastrointestinal tract and the blood-brain barrier, to effectively reach their target sites. These barriers can restrict the absorption and distribution of nanoparticles, ultimately reducing their bioavailability and clinical translation remains a challenge due to formulation, toxicity, and regulatory barriers (Liu et al., 2024). Continued interdisciplinary collaboration is essential to overcoming translational challenges and ensuring nanomedicines reach clinical use effectively (Peng et al., 2024)

CONCLUSIONS

Nanotechnology has made historical achievements in the treatment of serious diseases by synthesizing nanomedicine. It can treat human disease at the molecular level. The findings of our manuscript showed that nanomedicines have the potential to treat ROS-induced acute as well as chronic diseases with high efficacy. The nanomedicine utilized different types of NPs to enhance the drug efficacy with fewer side effects. Nanoformulation-based medicines include PEGylated polymeric nanodrugs, nanocrystals, metal-based nanoparticles, protein-based nanoparticles, liposomes and lipid nanoparticles that are popularly used for the treatment of diseases like cancer, diabetes, cardiovascular diseases, Parkinson's and Alzheimer's diseases, etc. Nanomedicines provide a promising technology for the delivery of drugs at targeted sites with less toxicity. Our review paper also suggests that among different nanoparticles, quantum dots and polymeric nanoparticles are

widely used due to their biodegradability and lower toxicity.

LIST OF ABBREVIATIONS

.OH: Hydroxyl radical; 4-HNE: 4-hydroxy-2-nonenal; 8-OHdG: 8-hydroxydeoxyguanosine; AD: Alzheimer's disease; ALS: Amyotrophic lateral sclerosis; AuNPs: Gold nanoparticles; CCMV: Cowpea chlorotic mottle virus; CeO2: Ceria; CNS: Central nervous system; CuNi: Copper–nickel; CVD: Cardiovascular disease; Fe3O4: Iron oxide; Fe-Co: Iron cobalt; Fe-Ni: Iron-nickel; Fe-Pt: Iron platinum; HBV: Hepatitis B; HD: Huntington's disease; HPV: Human papillomavirus ; LC-MS: Liquid chromatography mass spectrometry; LOOH: Lipid hydro peroxide; LPO: Lipid peroxidation; MDA: Malondialdehyde; NDs: Nanodiamonds; NIH: National institute of health; NPs: Nanoparticles; PD: Parkinson's disease; PEG: Polyethylene glycol; PGA: Polyglutamic acid; PHB: Poly-β-hydroxybutyrate; PLA: Polylactic acid; PLGA: Poly lactic glycolic acid; PLGA: Polylactic-co-glycolic acid; PUFA: Polyunsaturated fatty acid; RNS: Reactive nitrogen species; ROS: Reactive oxygen species; SGLT-2: Sodium dependent glucose transporters; TBA: Thiobarbituric acid; TBARS: Thiobarbituric acid-reactive substances; TiO2: Titanium oxide; TMV: Tobacco mosaic virus; t-PA: Tissue plasminogen activator; VLNPs: Virus Like Nanoparticles; ZnO: Zinc oxide

Ethics Approval and Consent to Participate

There is no requirement for ethical approval and consent of participants.

Human and Animal Rights

No humans and animals are involved in this designed study.

Consent for Publication

There is no requirement of consent for personal details, audio-video material, etc.

Availability of Data and Materials

The sources of data and materials have been mentioned in the manuscript in support of the findings.

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Authors' Contributions

Pankaj Singh and Manikant Tripathi: Conceptualization, writing, reviewing, supervision, and editing; Aditi Mishra, Rajat Pratap Singh and Pankaj Kumar Tripathi: Conceptualization, writing, reviewing and editing.

Conflict of interest

The authors declare that there are no conflicts of interest.

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