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Review Article

Enhancement of Bioavailability of Some Cardiovascular Drugs by Novel Nano-carrier Delivery System

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Abstract

Cardiovascular diseases (CVDs) have emerged as a major danger to human life and health. Despite the fact that numerous medicines working through various mechanisms of action are available in the market as traditional formulations for the treatment of CVDs, they are still far from adequate due to poor water solubility, limited biological activity, non-targeting, and drug resistance. With the advancement of nanotechnology, nano-drug delivery systems (NDDSs) provide a novel drug delivery mechanism for the treatment of CVDs, displaying significant advantages in tackling the aforementioned difficulties. Nonetheless, several issues with NDDSs, such as cytotoxicity, must be addressed. The kinds and targeting techniques of NDDSs were covered in this study, as well as recent research advancements in the diagnosis and management of CVDs. In order to give new ideas for the enhancement of cardiovascular medications, future prospects for nano-carriers in drug delivery for CVDs include gene therapy. Furthermore, its safety was addressed in the evaluation.

Keywords: Nano-drug Delivery System; Cardiovascular Disease; Targeting Strategy; Application Progress; Safety

Introduction

Cardiovascular diseases (CVDs) have become a severe global public health burden, with morbidity and death rates much exceeding those of other illnesses [1]. With such a dire scenario, researching medications for the treatment of CVDs has risen to the top of the priority list. Because of the rapid growth of nano-science and the exceptional performance of nanomaterials, nanotechnology has emerged as a novel solution to the bottleneck in cardiovascular disease therapy. Nano-drug delivery systems (Nano DDSs) are a type of nano-material that has the capacity to enhance drug stability and water solubility, lengthen cycle duration, and boost target cell or tissue absorption rate and reduce enzyme degradation to increase medication safety and efficacy [2]. Nano DDSs can be delivered via a variety of methods, including inhalation, oral administration, or intravenous injection, while maintaining high bioavailability. More researchers have begun to develop nano-drug carrier systems for the detection and treatment of CVDs in recent years. Furthermore, as the application of nano-materials grows, so does the exposure danger of nano-materials in clinical applications, resulting in more chances for nano-materials

to interact with blood vessels, blood, and its components, which will have a significant influence on human health. Therefore, this article mainly introduced the different types of NDDSs, their targeting strategies and application in CVDs, and the safety of nano-materials was discussed as well.

Types of the nano DDSs

NDDSs are materials that have at least one dimension at the nano-scale scale (1-100 nm) or are made up of them as fundamental units in three-dimensional space [3]. Nano DDSs have become a research hotspot in the fields of pharmacy and contemporary biomedicine as an effective technique of optimizing medication delivery [4]. The study of NDDSs has lasted more than 40 years, yielding a plethora of nano-drug carriers. The nano-materials utilized in Nano DDSs are classified as organic, inorganic, or composite materials based on their composition. The following is a description of several common Nano DDSs and their characteristics.

Liposomes

Liposomes are lipid vesicles composed of an organized phospholipids bilayer with a cell-like structure [5]. Liposomes have several benefits as a form of drug carrier, including non-toxicity, non-immunogenicity, sustained-release medicines, extending drug action time, modifying drug distribution *in vivo*, enhancing drug treatment index, minimizing medication adverse effects, and so on [6]. Liposomes are not only simple to create for the trapping of hydrophilic and ionic compounds, but they are also compatible with hydrophobic drugs [7]. Hydrophobic medications can be encased in the bimolecular structure of phospholipids, whereas hydrophilic drugs, particularly those encoding genes, can be linked to the hydrophilic portion of liposomes. Different lipid materials may be modified to alter particle size, potential, and surface chemistry. Cationic liposomes are positively charged, implying that they may cause dose-dependent cytotoxicity and inflammatory reactions, and as a form of complex, they may interact non-specifically with negatively charged serum proteins. Neutral lipids and pH sensitive liposomes [8] are two approaches to addressing the aforementioned issues. Micellar Polymer Co-delivery System Polymer nanoparticles, another kind of drug carrier, may be divided into non-biodegradable and biodegradable compounds [9]. Poly (lactic-co-glycolic acid) (PLGA), polyvinyl imine (PEI), polycaprolactone (PCL), polyvinyl alcohol (PVA), and other synthetic polymer materials are often used. These polymers are biocompatible, non-toxic, and teratogenic. Its breakdown products, including oligomerization and end products, are not harmful to cells and may coexist peacefully with the majority of medications. Polysaccharides, peptides, Chol and cyclodextrin inclusion complexes are the most common types of natural polymers. Polymer nanoparticles are stable in the core and can be employed to intercept insoluble medicines [10]. They are typically generated by self-assembly of Amphiphilic block copolymers. The stable structure of polymer nanoparticles is favorable to particle size uniformity and drug release control, and it can successfully withstand the effects of the gastrointestinal environment during oral delivery. Their nano-scale and vast surface area facilitate medication absorption in cells and improve bioavailability. Unfortunately, certain polymer nanoparticles have downsides. Chitosan, a natural polymer, for example, is incompatible with biologic fluids, which might cause particle disintegration and lower operating efficiency. Its shortcoming can be remedied by structural adjustments. The compound, which combines chitosan and polyethylene glycol, exhibits a distinct endocytosis and macrophage phagocytosis mechanism. Furthermore, modifying chitosan with a polypeptide can boost its working efficiency [11].

Macromolecules in dendritic networks

Macromolecules are synthetic, come in a variety of shapes, and are frequently branching. Macromolecules in the shape of spheres can be organized in mono-disperse space and are commonly utilized as nano-carriers for the delivery and dissolving of insoluble targeted medicines. Dendritic macromolecules with distinct branch structures are also mono-dispersed and have a controllable molecular weight. Furthermore, the package has a significant number of ready-made surface functional groups and a hydrophobic environment, making it an ideal drug delivery medium. Dendritic macromolecules are widely employed in biomedical and pharmaceutical industries due to their good biological characteristics, although the presence of surface cationic charge restricts their clinical utility [12].

Nano-materials made of metal

Gold and silver nano-materials are the most often utilized metal nano-materials, and they come in a variety of shapes such as nanoparticles, nanorods, nano-capsules, nanocuboids, and nanowires [13]. Aside from being employed as a nano-contrast agent for CT and surface enhancement, Raman spectroscopy, gold

nano-materials are also used in photo thermal treatment of tumors and rheumatoid arthritis. According to several research, the primary application sectors of silver nanoparticles were antibacterial, anti-infection, and anti-tumor [14]. Furthermore, to facilitate targeted medication delivery, certain therapeutic medicines can be physically inserted into hollow gold or silver nanostructures or chemically attached to the surface of nanoparticles. However, the clearance of gold nanoparticles in the human body is too slow, and the toxicity of silver ions *in vivo* restricts their use in the treatment of chronic disorders [15].

Inorganic Nano-materials which is not metallic

Quantum dots, iron oxide, silicon, grapheme, and other inorganic non-metallic nano-materials are examples [16]. Because of their distinctive luminous features, quantum dots (QDs), or semiconductor nanocrystals, are mainly focused on fluorescence imaging, whereas iron oxide nanoparticles are primarily focused on the investigation of novel MRI contrast agents [17]. Because of their enormous surface area and porous structure, mesoporous silicon nanoparticles have gotten a lot of interest in disease therapy in recent years. Through the incorporation of various functional groups, these inorganic nanomaterials can be employed to increase the transport efficiency of medicines and genes in mammalian cells. In the meanwhile, they are proposed as a type of shared carrier with development potential. However, the bio-safety of inorganic non-metallic nanoparticles would be a significant barrier to their clinical use [18,19].

Nanomaterials composites

In addition to the nanoparticles mentioned above, the fabrication of composite nanomaterials with varying characteristics is being investigated in a number of research. Metal or inorganic non-metallic nanoparticles, for example, are mixed with polymer or lipid nanomaterials to create multifunctional NDDSs that contain both medicinal medicines and contrast agents. Organic materials are used to decorate or modify metal and inorganic nanomaterials in order to increase their physical and chemical characteristics, *in vivo* kinetic behavior, and biocompatibility. Some NDDSs with unique structures and functionalities may be created by combining various metals and inorganic elements [20].

The NDDSs' targeting strategy

The targeted design of Nano DDSs focuses on the early identification and management of cancer, but new research has claimed that lesion cells or tissues of CVDs may also be targeted, even more easily than tumor tissues with many physiological barriers.

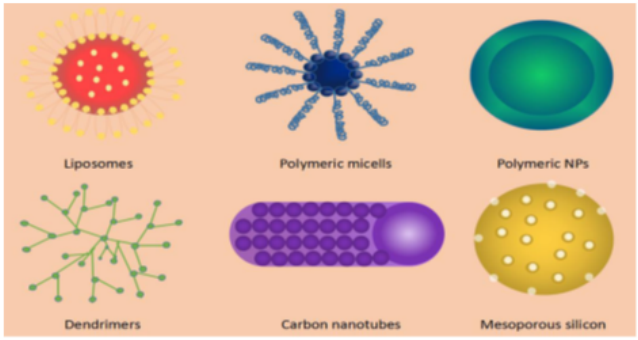

Figure 1: Common types of nano-drug carriers.

Because of these preparations, the metabolic duration of nano-transporter medications in the bloodstream may be extended. The rate of such targeted nano-transporter medications may be managed to operate longer by altering pH value [21], temperature, light, ultrasound, or biological enzyme. Passive targeted transport is mostly based on the effects of high permeability and high retention (EPR). EPR refers to the tendency of certain chemicals or particles to collect in tumor tissues [22]. In normal tissue, the microvascular endothelial cell space is thick and unbroken, and NDDSs loaded with medication, often of large molecular weight, are difficult to move through the vascular wall. The tumor tissue is densely packed with blood vessels but lacks structural integrity [23]. Those drug-loaded NDDSs in high molecular weight can selectively pass through the vascular wall and remain in the tumor tissue. A large number of studies have shown that nano-drug carriers with particle size <100 nm can be located and targeted to solid tumor tissues by EPR. When compared to the direct injection approach, the nano-drug carrier can enhance drug accumulation in tumor tissue by more than tenfold, considerably boosting bioavailability [24]. However, it has been revealed that the EPR effect may be exploited in a variety of CVDs other than malignancies. For example, in various CVD courses, the onset and progression of AS is a chronic inflammatory process in which vascular permeability is frequently enhanced, which is quite similar to that of solid tumors. Vascular endothelial permeability allows Nano DDSs to be delivered from the lumen side to the inside of the plaque. In addition, the nano-drug carriers that enter the blood are swallowed by inflammatory

cells (monocytes or macrophages), and these drug-carrying cells travel to plaque inflammation, allowing medications to be given in a different method [25].

Because of the size and surface properties of certain nanomaterials, they are rapidly removed in the blood upon intravenous administration, making nanomaterials unsuitable for medications with lengthy cycle durations. In this scenario, nano-coating technology may be used to disguise the nano-system, and the rate of administration of the coating agent can also be regulated and altered. This method is well suited to the treatment of Nano DDSs. Developers on Nano DDSs have employed poly (ethylene glycol) (PEG) in particle design. In fact, PEG is a flexible hydrophilic polymer that can form a hydrated layer when grafted onto the surface, effectively reducing the adsorption of proteins on the surface [26]. The tissue plasminogen activator is encased in the nanoparticles, which conceals the nano-system to some extent, shielding it from inactivation by plasma inhibitors and extending the half-life [27]. Shear-Induced Targeting Studies have shown that as the intima grows outward (toward the lumen) in CVDs such as advanced atherosclerosis or myocardial infarction, thrombosis or micro thrombus occurs, stenosis of the blood vessels occurs, and blood flow rate through the plaque increases, and thus the fluid shear force increases. The normal vasculature has a mean blood fluid shear force of 70 dynecm2, whereas AS plaque stenosis has a blood fluid shear value of up to 1,000 dyne/cm [28]. As a result, by using the differential in blood fluid shear force between AS plaque and normal blood arteries, the design of blood fluid shear-sensitive nanoparticles can enable physicochemical targeting. The drug-loaded nano-scale can retain structural stability in normal blood vessels, and the configuration change may be used to release the medicine through the blood circulation to the AS plaque under the effect of strong blood fluid shear force. Inspired by platelet activation and adherence to plaque blood vessels caused by local high blood fluid shear stresses in AS plaques, the researchers created a nanoparticle aggregate that can be produced locally in plaques [9. The scientist's first synthesized PLGA nanoparticles with a particle size of around 180 nm and entrapped tissue plasminogen activator, then spray dried them to generate a PLGA nanoparticle aggregate with a particle size of 3.8 nm. When the nanoparticles were subjected to the AS plaque's local high fluid shear stress, they dissolved into 180 nm PLGA nanoparticles and relied on the strong penetrability of the tiny particle size nanoparticles to penetrate the plaque's local thrombus. The thrombolytic effect increased effectiveness, considerably lowered the dosage necessary for thrombolysis, and minimized thrombolytic adverse effects. The endothelial gap in ischemic myocardium expanded, affecting blood flow shear, and the concentration of polysaccharide from Ophiopogon japonicus in ischemic myocardium was twice as high as in normal rats [30].

Magnetically guided

Magnetically guided nanoparticle targeting is an intriguing "pseudo passive" approach. The introduction of an external magnetic field can theoretically drive magnetic nanoparticles to the illness location. This technique appears to be favorable for CVDs, according to recent research [31]. Iron oxide particles, super paramagnetic iron oxide nanoparticles, ultra-small super paramagnetic iron oxide nano-carriers, and extremely tiny super paramagnetic iron oxide nanoparticles are all examples of nanoparticles. The ultra-small super paramagnetic iron oxide nanoparticles outperformed the other groups in terms of vascular wall penetration and plaque retention. According to some studies, the external magnetic field aids in the movement of particles from the cell-free layer, which lacks red blood cells, to the artery wall. Active Vascular Endothelial Cell Targeting Vascular endothelial cells are activated in an inflammatory state at various phases of CVD. When compared to normal vascular endothelial cells, certain small molecules such as intercellular adhesion molecule-1 (ICAM-1), vascular adhesion molecule-1 (VCAM-1), integrins, selections, and others are frequently over expressed, providing an active target for Nano DDSs [32,33].

It has been demonstrated that conjugating a lung-targeted single-stranded variable fragment/liposome with a platelet endothelial cell adhesion molecule-1 (PECAM- 1) antibody improves liposome transport to the pulmonary circulatory system and strengthens its anti-inflammatory effects. Before being taken up by endothelial cells, the nanoparticles were able to bind to areas of inflammation [34]. Based on the pathogenic characteristics of elevated ICAM-1 expression in AS early vascular endothelial cells. Through the particular activity of anti-ICAM-1 and ICAM-1, studies have revealed that the liposome might accomplish active targeting of vascular endothelial cells and AS plaques. However, competing binding of circulating white blood cells to the ICAM-1 site and blood flow shearing may limit liposome targeting to AS

plaques. The authors improved the active targeting efficacy of liposomes by assessing liposome particle size, antibody and lipid ratio. E-selecting is a surface glycoprotein of endothelial cells that can stimulate the attachment of monocytes/macrophages and lymphocytes, resulting in an inflammatory response and the onset and progression of CVDs. E-selectin is potentially a potential target for nano-transport medicines. Functional liposomes containing mouse H18/7 mAb (E-selectin-specific antibody) were employed to act on interleukin (IL)-1b-activated human umbilical vein endothelial cells and non-interleukin (IL)-1b-activated human umbilical vein endothelial cells (IL) Human umbilical cord vein endothelial cells stimulated by -1b It was shown that functional liposomes have a 275-fold greater capacity to target activated human umbilical vein endothelial cells than non-activated cells. When there is a myocardial infarction or heart failure, AT1 levels rise in the myocardium. The ligand on these liposomes is a string of amino chain sequenced Gly-Asp-Arg-Val-Tyr-Ile-His-Pro-Phe (AT1 receptor binding sequence), which might drive the nanoparticles to the infarction site [35].

Active targeting of macrophages or foam cells

Macrophages, also known as foam cells, play an important part in the development of AS. In the early stages of AS, mononuclear/macrophages were attracted to activate vascular endothelial cells, and several inflammation-related receptor molecules, such as CD44 and interleukin-4 (IL-4) receptors, were over expressed in an inflammatory milieu. The use of Nano DDSs for imaging and medication administration to macrophages or foam cells will aid in the monitoring of disease progression and pharmacological therapy in AS.

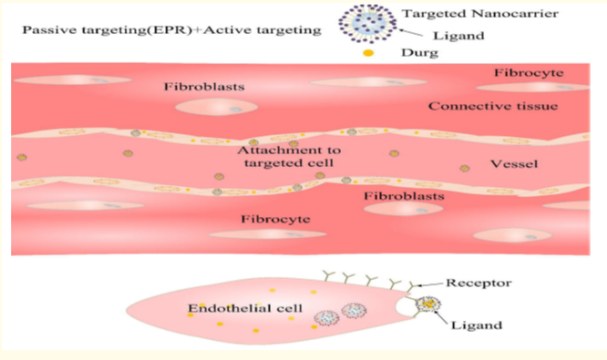

Figure 2: Diagrammatic sketch of active targeting. The surface of the nano-carrier is grafted with a targeting ligand, which is strongly bound to the selective cell surface by ligand-receptor binding.

Application of the NDDSs in the diagnosis of CVDs

- Early, quick, and precise identification is critical for successful CVD prevention and therapy. In recent years, there has been a growing interest in the use of molecular imaging in the diagnosis of CVDs. New contrast agents, in addition to the ongoing improvement of various imaging systems, are critical to real-time, quick, high sensitivity, and high resolution diagnostics. Nano-contrast agents provide the following benefits over traditional contrast agents:
- *In vivo* stability, controllable distribution, and prolongation of contrast agent or drug half-life;
- Controllable physical and chemical features (such as chemical composition, size, and imaging performance);
- Certain identification of specific biomolecules;
- Capability of multimodal imaging realization;
- Values in personalized diagnosis and therapy.
- The contrast agent can be directed to the lesion area in the early stage of the disease for magnetic resonance imaging (MRI), X-ray imaging, fluorescence imaging, and contrast-enhanced ultrasound (US) imaging by designing specific nano-probes with the unique chemical signal molecules of diseased tissues determined by pathological studies [36].

Magnetic resonance imaging (MRI)

Magnetic resonance imaging is a noninvasive, safe, and high resolution imaging technology that is useful for soft tissue imaging. However, the sensitivity of MRI is not high (10−3-10−9M). The complexes of gadolinium commonly used in clinical.

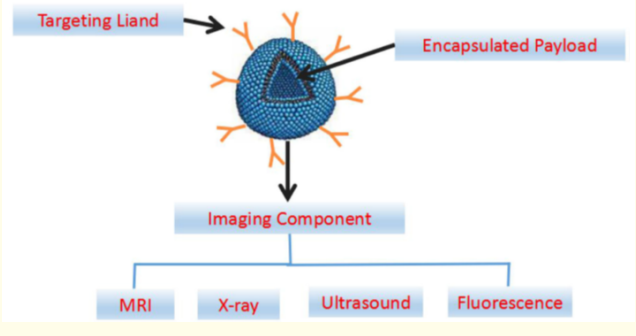

Figure 3: Abridged general view map of targeted nanoparticles engineered for imaging and drug delivery.

A multifunctional nano-carrier has a ligand for cellular targeting as well as an encapsulated payload for therapeutic drug delivery. The imaging components, which can be contained in the inner payload, on the targeting ligand, or connected with the nanoparticle shell, are utilized as T1-weighted imaging contrast agents, and gadolinium has some nephrotoxicity. T2-weighted imaging contrast agents using Fe_3O_4 nanoparticles are thought to be non-toxic [37]. They have excellent sensitivity, strong tissue compatibility, and super paramagnetism when compared to tinctures [38]. Targeted contrast chemicals are used to accumulate MRI probes in the target tissue at a high enough concentration (in micrograms to milligram's) to generate a high signal-to-noise ratio. After injecting magnetic nanoparticles into the body, it is revealed that vascular imaging may be conducted in the early stages of cardiovascular disease creation, and medications can be provided for therapy. As a result, its targeting to atherosclerotic plaque was improved, and it may now be utilized to identify thrombus early. Winter., *et al*. used paramagnetic nanoparticles targeting integrin avb3 to inject intravenously into high fat fed New Zealand white rabbits in order to identify neo vascularization in plaques [39].

X-Ray imaging

In the field of nuclear medicine, imaging using radionuclides is critical. Radio nuclides are not only sensitive, but they may also be quantified. The most frequent forms are positron emission tomography (PET) and single photon emission computed tomography (SPECT) [40]. To accomplish targeted imaging, radionuclide-labeled nanomaterials can already be employed to monitor the embolization process and the distribution of nano-medicine. The researchers, for example, employed 186Re-BMEDA and 99mTc-PEGylate-labeled doxorubicin liposomes to conduct SPECT, which can track drug distribution in the body as well as induce drug release. The nanoparticles may be employed by CT to detect the development of atherosclerotic plaques as well as to predict the prognosis. Galperin., *et al*. used a vein injection of iodine nanoparticles contrast agent (N1177) into mice. It was discovered that the contrast agent accumulated in macrophage rich tissue, as well as the signal of at heromatous plaques, could be greatly amplified, with the enhancement duration lasting more than 30 minutes. In 2016, 11-mercaptoundecanoic acid (11-MUDA) was used to encapsulate gold nanoparticles, and it was shown that gold nanoparticles may aggregate in foam cells of atherosclerotic plaques and boost imaging contrast [41].

Fluorescence imaging

Although optical imaging is a potent imaging modality with the benefits of no radiation, no invasion, excellent resolution, and superior controllability, its penetration is low. Fluorescence imaging is typically achieved by generating fluorescence signals with fluorescein. Because of their high penetrating power and safety, near-infrared fluorescence (NIRF) probes are frequently employed. They have been utilized in small animal life imaging systems as well as clinical tumor transformation. At the moment, a wide range of nano-drug carriers, such as liposomes, metal or non-metallic nanoparticles may contain NIRF and allow for optical imaging of blood arteries. Its use in cardiovascular disease imaging is becoming increasingly popular. McCarthy., *et al*. created a type of diagnostic and therapeutic nanoparticles by combining a group of near infrared light activated therapeutic (NILAT) with macrophage-targeted magnetic nanoparticles (MNP) [42].

Ultrasound imaging

When compared to fluorescence imaging, ultrasound imaging offers several inherent benefits in medical imaging, including safety, convenience, and real-time imaging. Nano-ultrasound imaging materials with vascular-related marker targeting have been created. For example, vascular ultrasound nanoparticles that can be targeted to high levels of vascular endothelial growth factor receptor expression. Not only does it enable clearer ultrasound imaging of tumor blood vessels, but it also promotes drug localization in blood vessels. Scientists created per fluorocarbon nanoparticles that target blood fibrin and include the thrombus medication streptokinase for thrombus diagnostics and treatment [43]. The drug-loaded particles, which have a diameter of around 250 nm and may be employed for ultrasonic imaging, are manufactured using an evaporation/dispersion process.

Multi-modal bioimaging

At the moment, multi-modal imaging technology that combines several types of imaging technologies can have synergistic effects, delivering more complete and accurate image information for accurate diagnosis and precise treatment of CVDs. It was discovered, for example, that 64Cu-labeled SPIO-loaded doxorubicin nanoparticles may be employed for MRI and PET. Cy5, sputum, and folic acid have been found to be able to be encapsulated in gold nanoparticles to produce trimodal optical

imaging, MRI, and CT imaging in mice [44]. This multimodal imaging and integration of diagnosis and treatment will be a new direction for the development of cardiovascular nano-medicine in the future.

Application of the NDDSs in the treatment of CVDs

In AS, the Nano DDSs the most prevalent kind of CVD is AS, which frequently leads to a stroke or heart attack. Endothelial dysfunction is the first step in the development of AS. Plaque-induced coronary artery narrowing can result in ischemic cardiomyopathy, whereas plaque rupture can result in an acute myocardial infarction. Increased vascular permeability, Platelet endothelial cell adhesion molecules (PECAM) expression, macrophage aggregation, and protease expression are all mechanisms of plaque instability that can be treated. The medication may be administered to atherosclerotic plaques via a nanodrug carrier, thereby extending the half-life of drug plasma, increasing the concentration of lesions, and lowering the risk of stroke. These nano-drug carriers' therapy tactics include controlling lipoprotein levels, lowering inflammation, blocking neovascularization, and preventing coagulation, among other things. These therapy techniques are employed as therapies to slow the progression of AS, decrease plaque area, and stabilize susceptible plaques [45]. In Hypertension, the NDDSs Angiotensin converting enzyme inhibitors, vascular angiotensin antagonists, central sympathetic nerve medicines, adrenergic receptor blockers, diuretics, and vasodilators are being used to treat hypertension. All of these antihypertensive therapeutic medicines, however, have evident flaws, such as short plasma half-life, limited bioavailability, toxic and side effects (upper respiratory tract abstraction, angioedema, reflex tachycardia, strong hypotensive impact, and so on). Olmesartan has been transformed into a nanoemulsion system by certain researchers. When compared to the standard dosage, the nanoemulsion group has a superior blood pressure lowering impact, longer maintenance duration, and can reduce the dose by nearly three times [46].

Safety of the nano DDSs

As nanomaterials research advances, a growing number of nanomaterials are created as NDDSs, but their future application is limited by their unknown toxicity and a lack of systematic analysis of the materials themselves. When particle size approaches the nano-scale scale, it exhibits a strong surface effect, a small scale effect, a quantum scale effect, and a macroscopic quantum tunneling effect [47]. Few research have been conducted on the toxicity of NDDSs, particularly on cardiovascular damage. However, the cardiovascular system is thought to be the primary location of NDDS-induced damage, with a significant influence on illness prognosis. Studies have revealed that nanomaterials could enter the blood circulation through respiratory tract, digestive tract, skin and other mucous membranes, and inevitably interacted with the blood system, immune system and other organs or tissues including plasma proteins and immune proteins, blood cells and immune cells, and so on.

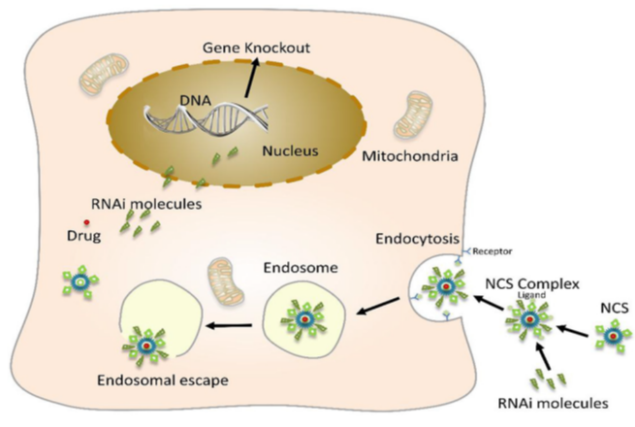

Figure 4: Schematic diagram of nanoparticles-mediated gene and drug delivery. Nano-carrier system (NCS) encapsulates or adsorbs a drug, therapeutic foreign gene molecule on its surface, and also couples a specific targeting molecule to the surface of the nano-carrier and then binds to a cells surface-specific receptor through a targeting molecule. This enables safe and effective targeted genes and drug treatment.

Conclusion and Future Perspective

In conclusion, the nano-carrier, as an effective, selective, and adjustable intracellular drug delivery technology, has demonstrated distinct benefits in the diagnosis and treatment of CVDs. It may successfully tackle the difficulties of targeting, local drug delivery, controlled release, sustained release, and toxicity while progressing toward a multifunctional and integrated direction of diagnostic and therapy. With the advancement of nanotechnology and the advancement of research into the molecular pathogenic mechanisms of CVDs, the use of Nano DDSs will be encouraged and new procedures and approaches for clinical diagnosis and

therapy will be developed. Furthermore, because research on these nano-carriers is still in its early stages, many questions remain unanswered. The primary problem in the field of nano-biomedicine in the future is how to address the biocompatibility of nano-drug-loaded particles themselves or their breakdown products.

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