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Review Article

Cardiovascular Nanomedicines: A Review of Nanoparticle-Mediated Strategies for Disease Treatment

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ABSTRACT

Worldwide, cardiovascular diseases (CVDs) are the leading cause of mortality, demanding innovative therapeutic strategies. Nanomedicine offers promising solutions through nanoparticle-mediated drug delivery, enhancing precision, efficacy, and safety. This review examines nanocarriers, including liposomes, polymeric nanoparticles, and dendrimers, for targeted CVD treatment, encompassing coronary artery disease, atherosclerosis, and myocardial infarction. This review highlights advances in theranostics, gene therapy, and stimuli-responsive systems while addressing challenges related to biocompatibility and clinical translation. Nanotechnology holds transformative potential for CVD management, enabling personalized and least invasive treatments.

Key words: Cardiovascular diseases, targeted drug delivery, nanoparticles, ischemic heart diseases, myocardial infarction

INTRODUCTION

Globally, cardiovascular diseases (CVDs) are the main reason for mortality; the annual mortality figure reaches 17.3 million, and based on the estimates, there will be 23.6 million deaths by 2030, reported by the World Heart Federation. [1] Treatment and diagnostic costs of CVDs are increasing at a higher rate. Along with the aging population, the Growing incidence rates of obesity, diabetes, and other CVD risk factors have led to a significant financial burden. [2] WHO estimates that stroke and coronary heart disease cause 6.7 and 7.4 million deaths, respectively. With the established adverse consequences of existing treatments, new therapeutic approaches are beginning to emerge. The promising platform for enhancing cardiovascular health is provided by nanotechnology. It allows for the development of novel therapies and preventative measures that can increase effectiveness while lowering adverse effects. [3] A variety of disease management techniques can be applied to reduce morbidity and mortality.

Various approaches can be used to mitigate the effects of a disease. Primary prevention strategies focus on promoting healthy habits, such as a balanced diet and physical activity, to prevent disease onset. The objective of secondary prevention is early detection, which

aims at recognizing diseases before they significantly affect people's lives and result in permanent disabilities. Once long-term impacts start to manifest, tertiary prevention methods are used to help patients manage their pain, enhance their life expectancy, and further improve their quality of life.

TYPES OF CVDs AND RISK FACTORS

CVDs include multiple conditions, which include cerebrovascular disease, coronary artery disease, peripheral arterial disease, and venous thromboembolism, that can negatively impact lifestyle and health if not treated in a timely and effective manner.

Coronary artery diseases

Coronary artery disease has emerged as the predominant and escalating cause of death worldwide. According to estimates, almost one in every five deaths in the developed world is due to coronary artery disease. Plaque formation serves as the defining pathological process in atherosclerosis. Plaque is composed of various substances, such as cholesterol and calcium, on the inner walls of arteries. Vascular elasticity is reduced, and coronary arteries become constricted or obstructed as a result of atherosclerosis, which has a major impact on heart function. These plaques can cause angina pectoris by limiting the supply of blood to the heart muscle. [4] The primary symptom of coronary artery disease is angina pectoris, which includes chest pain, discomfort, or a burning sensation resulting from coronary artery narrowing or spasm. This can lead to a life-threatening myocardial infarction (MI). Furthermore, shear stress can result in the rupture of the atherosclerotic plaque, triggering coagulation and subsequent thrombus formation that can significantly reduce or completely block blood flow, possibly inducing MI or stroke. [5]

Peripheral arterial disease

Peripheral arterial disease is characterized by partial or total occlusion of peripheral arteries, resulting in reduced perfusion and ischemic conditions. While various diseases can impair blood flow. Atherosclerosis represents the primary pathological basis for these conditions. Risk factors like metabolic abnormalities, hypertension, renal dysfunction, ethnic predisposition, and elevated C-reactive protein levels contribute to the development of peripheral arterial disease. [6]

Cerebrovascular disease

Cerebrovascular disease, primarily caused by hypertension, damages the inner lining of arteries. This damage promotes platelet aggregation and collagen is exposed, potentially resulting in conditions such as Cerebral ischemia and tissue damage that occur when a thrombus obstructs arterial blood supply to the brain, defining the pathophysiology of stroke. A stroke occurs when oxygen-rich blood flow to the brain is restricted due to a blood clot, leading to brain damage. A transient ischemic attack represents a temporary interruption of cerebral or spinal cord perfusion, producing transient neurological deficits resembling a stroke. Subarachnoid hemorrhage includes blood leakage onto the brain's surface or out of arteries, damaging brain tissue and neural structures. [7] Vascular dementia, often an outcome of stroke, involves cognitive decline and memory impairment. However, estimating its onset is complicated by inconsistent diagnostic criteria. Lifestyle factors such as obesity, diabetes, and smoking substantially lead to the progression of cerebrovascular diseases, increasing the risk of vascular dementia. [8]

Venous thromboembolism

Venous thromboembolism exhibits two interrelated conditions: deep vein thrombosis (DVT) and pulmonary embolism (PE). DVT involves the formation of thrombi within the deep venous system, typically in the lower extremities or pelvic veins. PE occurs when a thrombus dislodges from its original site, embolizes the pulmonary circulation, and obstructs one or more pulmonary arteries. This obstruction increases right ventricular afterload, leading to hemodynamic compromise. Thrombosis refers to the pathological process of intravascular clot formation that disrupts normal circulation. As a critical complication of DVT, PE represents a medical emergency characterized by nonspecific clinical presentations that often challenge timely diagnosis. [9,10]

DEVELOPMENT OF NANOMEDICINE IN CVDs

Nanotechnology is the investigation of controlling the issue on a particle and sub-atomic scale. It deals with structures measured between 1 and 100 nm, and it can also be used to create or modify the material that falls within that range. It increases the material's lightness and durability. The interaction of nanotechnology and medicine contributed to the development of a new field known as nanomedicine. Nanomedicine utilizes nanotechnology to diagnose, treat, and prevent diseases, enhancing quality of life and health. Applications range from utilizing nanomaterials for targeted drug delivery and bio-imaging to developing and improving diagnostic and therapeutic technologies incorporating advanced sensing techniques. Nanomedicine includes strategies for evaluating nanomaterials' safety and potential toxicity and verifying their responsible use. [11]

Nanoparticles have been recognized as a vital tool in medicine because of their distinctive physicochemical characteristics, which increase biological efficacy. Using nanocarriers for targeted drug delivery, achieved through active or passive targeting mechanisms, holds great promise as a cutting-edge therapeutic approach. [12] Nanoparticles, typically measuring 1 to 100 nm, exhibit unique characteristics that set them apart from their larger analogs. Their small size enables them to penetrate biological barriers, including membranes, cells, and tissues. Important features of nanoparticles include their nanoscale dimensions, quantum effects, high surface area-to-volume ratio, and customizable shape. Furthermore, surface modification can enhance and tailor their physical properties. The size and shape of nanoparticles used for drug delivery are critical factors that influence their actions and efficiency in targeting CVDs. [13] Compared to conventional and contemporary medical procedures, nanoparticles in medicine offer numerous advantages (**Figure 1**).

TARGETING CVDs WITH NANOPARTICLES

Superior molecular imaging, targeted drug delivery, and selective nanoparticle-mediated cell destruction for improved disease treatment are the major applications of nanoparticles. Nanoparticles efficiently eliminate drugs by delivering them through the blood and tissue.

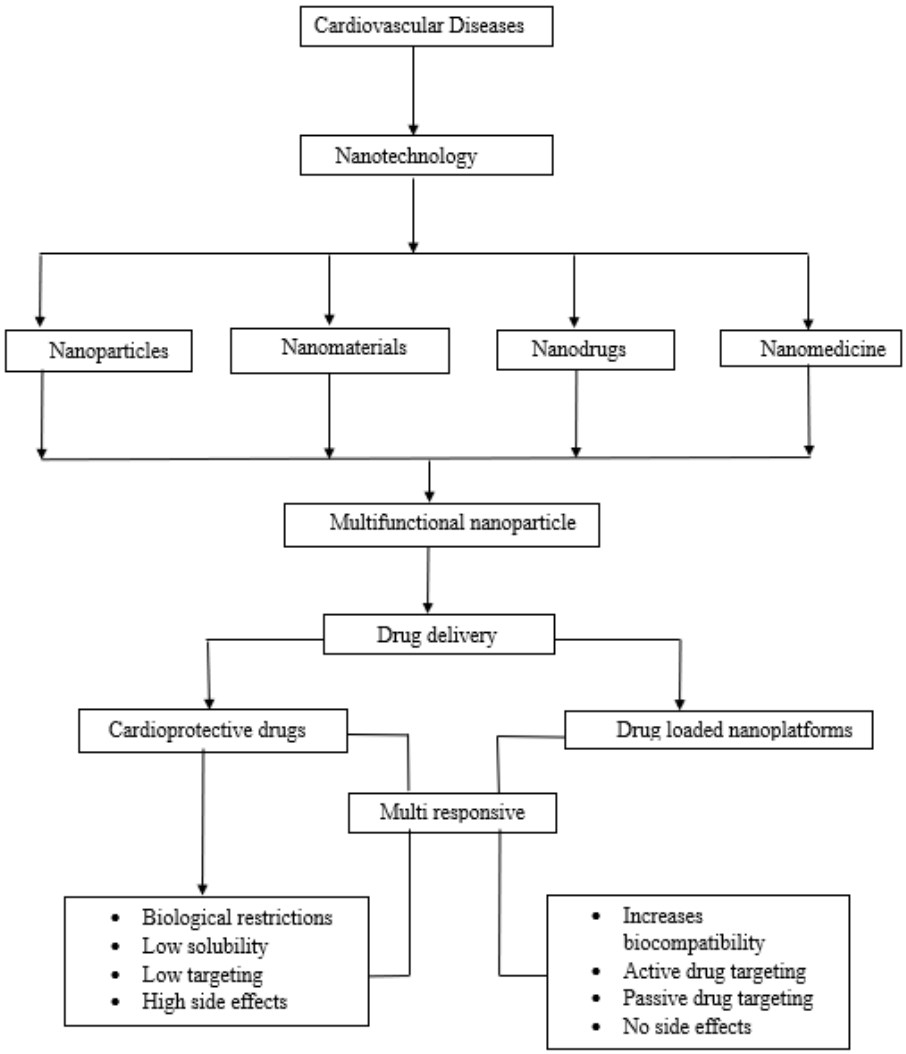

Figure 1: Nanomedicine for cardiovascular disease and its advantages. [14]

Superior molecular imaging

Morphological and functional imaging in cardiovascular disease is now achievable through the combination of cardiovascular molecular imaging technologies with cutting-edge scientific instruments. The field of nanotechnology has developed rapidly, which has helped to improve the imaging of CVDs by creating effective nanotechnology-based cardiac molecular imaging probes. Cardiovascular molecular imaging offers exact visualization at a molecular and cellular level, facilitating early detection and cutting-edge treatment approaches. This will also allow for an improved understanding of the basic biological processes of CVDs. Molecular imaging probes are useful for characterizing, measuring, and visualizing biological processes in living systems. [15] The characteristics of cardiovascular imaging using nanotechnologies are shown in **Figure 2**, and imaging and assessment of CVDs using nanoparticles are shown in **Figure 3**.

The complications, rationalizing future research should promote the advancement of cardiovascular drugs and the shift to personalized, preventative measures and therapy.

Theranostics can bridge the gap between large-scale trials and experimental evidence. Theranostics nanoparticles hold both therapeutic drugs and diagnostic labels. Theranostics use Imaging-based therapeutic delivery systems to combine imaging and therapeutic functions. Current imaging limitations could be almost addressed by theranostics. Numerous nano-theranostic approaches are established, but some limitations need to be addressed for future perspectives. [17]

Targeted delivery of the drug

Targeted drug delivery enables medication to selectively accumulate at the site of action, resulting in improved treatment response and minimizing unwanted effects. Nanoparticles' small dimensions promote their passage through cellular membranes and the cerebrovascular barrier. Targeted delivery of the drugs has been accomplished by improving various factors like temperature, pH, ultrasound, and magnetic field, which are determined using infrared and enzyme activity. The differences between active and passive targets are summarized in **Table 1**.

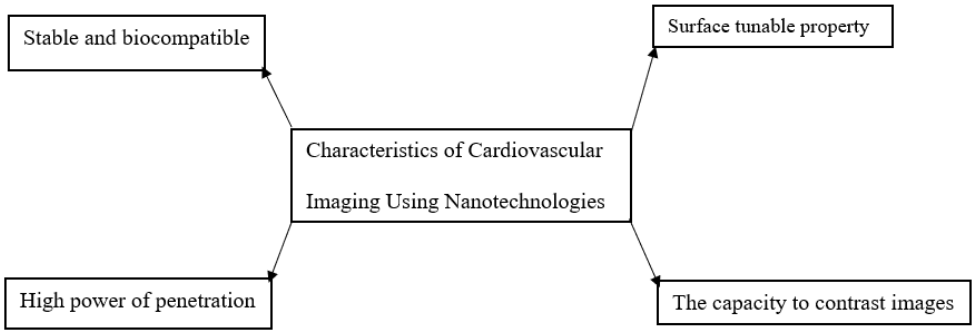

Figure 2: Characteristics of cardiovascular imaging using nanotechnologies.

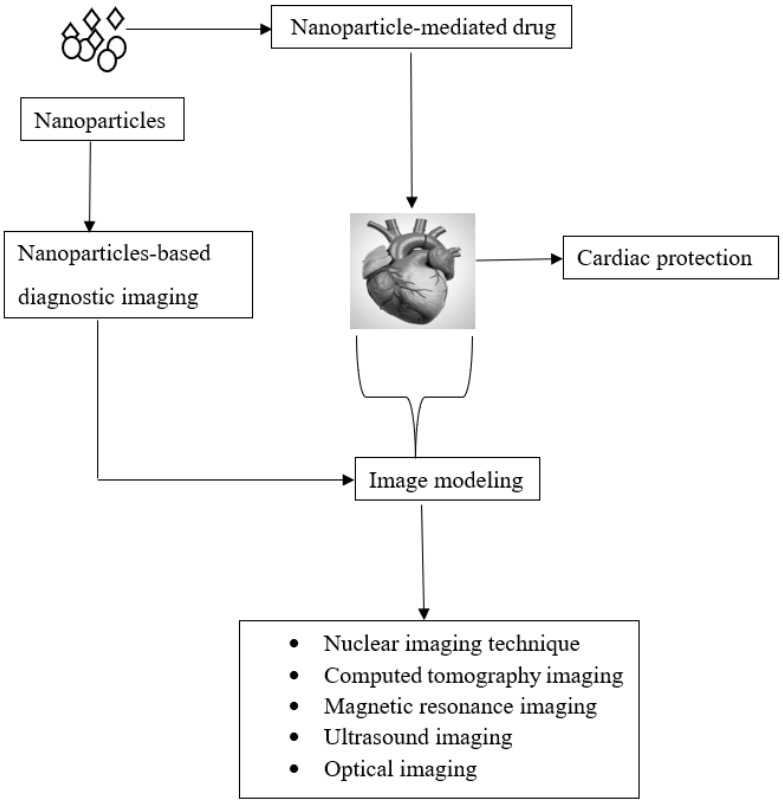

Figure 3: Imaging and assessment of CVDs using nanoparticles. [16]

NANOCARRIER FOR MANAGEMENT OF CVDs

Different types of drug delivery systems can help manage cardiovascular disease. The specifications for the planning and improvement development of nanocarriers include their nontoxic nature, biocompatibility, biodegradability, efficacy, non-inflammatory properties, targeted therapeutic action, and clinical acceptability. Various nanocarriers used for the study of CVDs are elaborated in **Figure 4**.

Liposomes

Liposomes are spheroidal structures consisting of lipid dual-layer shells that enclose an inner aqueous core (**Figure 5**). They are regarded as one of the most effective and versatile nanoparticle delivery technologies for medications to particular tissues and cells. The effectiveness of liposomes as drug-delivery vehicles has driven the development of innovative liposome-like nanostructures that utilize current developments in nanotechnology to enhance pharmacokinetics and pharmacodynamics. [20]

AT1 receptor-targeted nano-liposomes are functionalized with a specific peptide to bind AT1 receptors, which are overexpressed in the heart after MI or heart failure. In vitro, hypoxic cardiac cells showed 3-fold higher AT1 receptor expression, with 83% of nanoparticles accumulating in these cells. In vivo, fluorescent liposomes injected into mice post-MI predominantly accumulated in the infarcted left ventricle. This system targets injured heart tissue, offering the potential for targeted drug delivery in heart disease. [22]

To improve medication delivery to the heart, Wang and other scientists created a dual-targeted liposome device. The liposomes, composed of 1,2-Distearoyl-sn-glycero-3-

Table 1: Passive targeting versus active targeting. [18]

Passive targeting	Active targeting
• Utilize the abnormal physiological response predominant in the disease region of the body. • Restricted use • High chance of leading to side effects • Less selective method	• It relies on the species that is hyperexpressed during disease. • Versatile • Minimal side effects • Highly selective method

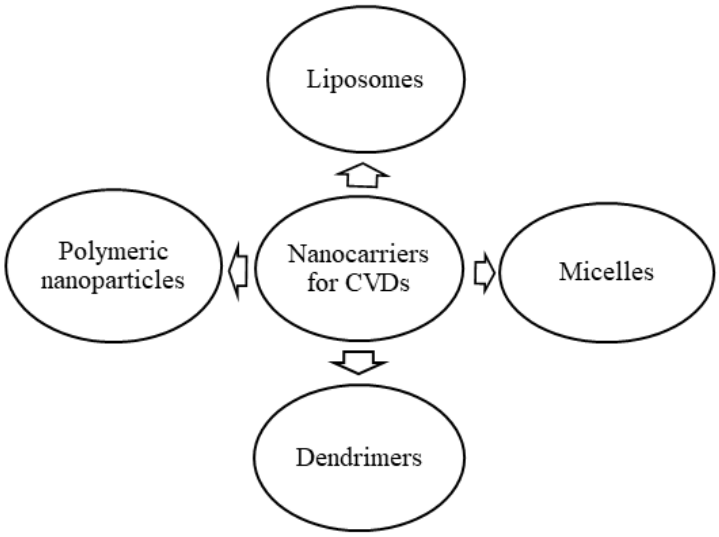

Figure 4: Nanocarriers for cardiovascular diseases. [19]

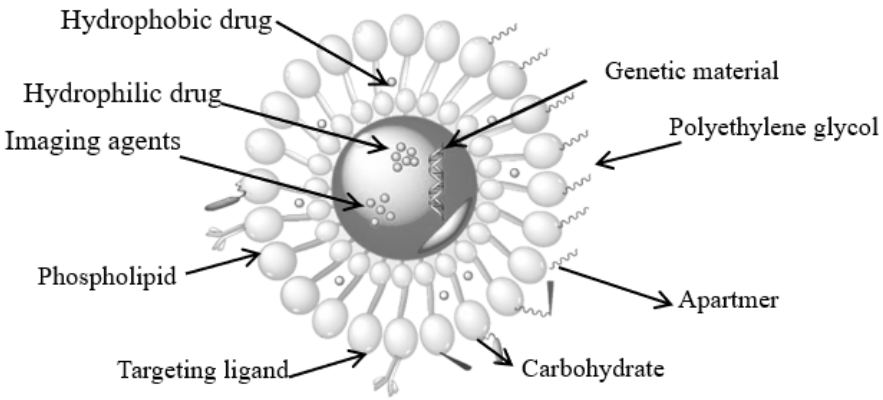

Figure 5: Functionalized liposomes with target ligand. [21]

phosphoethanolamine-polyethylene glycol (DSPE-PEG), cholesterol, and soybean phospholipids, were slightly >100 nm, had a zeta potential of −10 mV, and remained stable for more than 30 days. Two peptides were added to them: TAT, an 11-amino acid peptide that promotes cellular uptake via nonspecific endocytosis, and Primary Cardiomyocyte-targeting Peptide (PCM), a 20-amino acid peptide that particularly targets cardiomyocytes. Fluorescent coumarin-6 labeling indicated that the liposomes were effective in cellular uptake in both in vitro and in vivo trials, and they were not hazardous at doses <0.8 mM. [23] Myosin-targeting liposomes significantly improve cardiac function by restoring both diastolic and systolic function, bringing left ventricular pressure to a level greater than 80% and significantly reducing left ventricular end-diastolic pressure after reperfusion. [24]

Polymeric nanoparticles

Polymers are the predominant material utilized in the fabrication of nanoparticles, owing to their relatively low toxicity and the feasibility of a catalytic site for functionalization. Polymers can be categorized into two primary groups: Natural Polymers, which are derived from

natural sources, including starch, cellulose, proteins, and gelatin, and synthetic polymers, which include polylactic acid and polycaprolactone, which are extensively employed in the improvement of biodegradable nano-drug delivery systems. [25] Research has been conducted to immobilize poly(lactide-co-glycolide) on polytetrafluoroethylene film for the development of vascular grafts, facilitating the targeted delivery of antithrombotic agents. Furthermore, research has focused on the utilization of polymeric nanomaterials for cardiovascular disease applications. Electrically conductive polyester-carbon nanotube matrices have been developed to enhance cell-cell coupling. [26] The poly(lactide-co-glycolide) (PLGA) nanoparticles are a potential delivery system for targeting monocytes and macrophages during atherosclerosis. Fluorescein isothiocyanate-loaded PLGA nanoparticles demonstrated targeted delivery to peripheral monocytes and aortic macrophages. [27]

Dendrimers

Dendrimers stand out from traditional polymers due to their unique features, such as precise control over molecular structure, nanoscale size, numerous surface functional groups, and low polydispersity (**Figure 6**). Their ability to load various bioactive compounds through both covalent and non-covalent interactions makes them highly effective for binding. A major benefit of using dendrimers in drug delivery is their capacity for sustained release of bioactive agents, enabled by hydrophobic cavities that trap drug molecules. These properties have made dendrimers a promising and versatile option for targeted drug delivery systems. [28] Dendrimers are developed using either convergent or divergent techniques and have a characteristic tree-like structure. The most common polyamidoamine dendrimers are gaining a lot of interest for cardiovascular disease applications since they have their conjugation with nitric oxide, which has strong vasodilatory effects and relaxes vascular smooth muscle. [29] Lysine-based dendrimer structures have been utilized to combat atherosclerosis, where their assembly in the arterial lining facilitates the site-specific delivery of nitric oxide. Additionally, biologically compatible and optimized dendritic systems incorporating cyclic arginylglycylaspartic acid (RGD) peptides, along with entrapped 76Be, have distinctly targeted Positron Emission Tomography (PET) imaging applications in mice. Furthermore, streptokinase-modified dendrimers, synthesized using various polymers such as PLGA, chitosan, PEG, or glycol chitosan, have demonstrated the ability to provide sustained delivery of anti-thrombotic agents within the circulatory system. [30]

Micelles are highly efficient, specialized nanocarriers designed to transport poorly soluble drugs. They are nanoscale colloidal particles featuring a hydrophobic domain surrounded by a hydrophilic shell. Surface-modified polymeric micelles made up of amphiphilic macromolecules find extensive use in drug delivery systems and theranostics. The PEG polycationic block copolymeric micellar system was developed to target vascular injury in the rabbit carotid artery for gene transfer. The PEG-based lipid micelle system, co-loaded with a fluorophore as an imaging agent, could effectively deliver an antithrombotic agent to the identical target site. [32] Several promising micelle-based strategies have been explored to target endothelial dysfunction, which plays a critical role in thrombotic or atherosclerotic tissues. The insights highlight the significant capability of micellar systems for targeted delivery, demonstrating their utility in the treatment and management of CVDs. [33]

TARGETED NANO THERAPY FOR CORONARY ARTERY DISEASE

An atherosclerotic plaque gathers on the inner walls of the coronary artery, resulting in constriction, reducing the compliance of the vascular wall, and also causing impaired blood circulation to the myocardium, leading to coronary artery disease. Atherosclerosis is described by the thickening of the vascular walls and atherosclerotic plaque inflammation. A cardiac arrest occurs when the coronary arteries are blocked by atherosclerosis. Cardiomyocyte hypoxia is a complex, interconnected process involving extracellular matrix, cells, and cytokines. This ultimately leads to cardiac failure and myocardium replacement. [34] The breaking down or rupture of atherosclerotic plaques results in coronary thrombosis. Stress echocardiography, coronary computed tomography, electrocardiography, coronary angiography, and magnetic resonance imaging are commonly used to diagnose coronary artery disease, but these techniques cannot detect these plaques. Improvement in diagnostic requirements and technologies helps to detect certain targets like macrophages, oxidized Low-Density Lipoprotein (LDL), and small blood vessels. [35]

Atherosclerosis can be treated with nanotechnology by increasing the body's total circulation time, decreasing the systemic cytotoxicity of the medications, reducing the necessary dosage, increasing the medication solubility, integrating the diagnostic and pharmacological therapy to create theranostics, and raising the drug's cumulative effect at the location. The immune system irreversibly influences

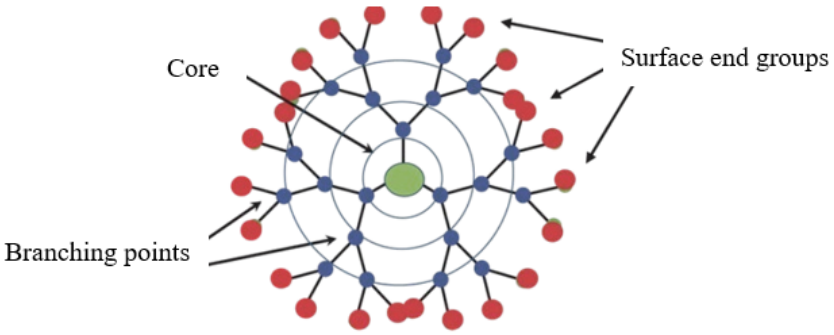

Figure 6: Schematic representation of dendrimer Micelles. [31]

atherosclerosis development, and immune cells have distinct properties. A few studies have integrated the various chemical and physical characteristics of the nanoparticles and immune cells to create a library of nanoparticles. In atherosclerotic diseases, the High-Density Lipoprotein (HDL)-based nanoparticle platform can selectively target macrophages, reduce off-target effects, and improve therapeutic effectiveness. [36] The reported lower risk of complications and death in coronary artery disease caused by high-dose statins is limited because of off-target adverse effects. However, oligonucleotide functionalized nano-meter-sized vesicles filled with pravastatin that targets macrophages can allow high-dose treatment to reduce the toxicity of other tissues and increase effectiveness. [37] It has been demonstrated that fumagillin, an efficient antiangiogenic medication, has the potential to be delivered via paramagnetic nanoparticles that are integrin-targeted to reduce side effects. [38] ox-LDL and apoptosis are the key factors in both initiating and encouraging plaque rupture. Different strategies, including the use of agents tagged with radioisotopes (123I, 124I, 99mTc, and 18F). Superparamagnetic particles have gained acceptance in PET, MRI, and single-photon emission computed tomography for imaging certain targets related to apoptosis and ox-LDL to identify plaques at risk of rupture. [39] An arginine-glycine-aspartic acid peptidomimetic derivatized gadolinium-coated perfluorocarbon nanomaterial has been used to target Integrin av3, a crucial mediator of angiogenesis. An increasing quantity of research will combine diagnosis and therapeutic partners to gradually create diagnostic therapies and evaluate treatment outcomes in several different ways. [40] Nanoparticles (NP) plaque accumulation across the vascular wall was found to be strongly correlated with the permeability determined by in vivo dynamic contrast-enhanced MRI. This implies that the buildup of NPs may help us determine the extent of inflammation and damage to the blood vessel wall. Thus, early detection and distinction of fragile plaque is made possible by nanotechnology-based cardiovascular imaging techniques, which also serve as the foundation for early atherosclerotic plaque prevention and treatment. To determine the inflammatory response in atherosclerotic lesion-imaged macrophages simultaneously using cross-linked iron oxide fluorescent Nanoparticles. [41] The co-localization of active macrophages in plaques using intravascular ultrasound and photoacoustic imaging in conjunction with gold nanoparticles as a contrast agent. The infiltration and proliferation of macrophages can be used to assess the fragility and the development of atherosclerotic plaques. [42]

TARGETED NANO THERAPY FOR ISCHEMIC HEART DISEASES

MI is a type of intense ischemic heart disease that causes cardiac arrest and eventually death. [43] Various therapeutic agents and treatments are available for the maintenance and safeguarding of cardiac performance. Multiple signaling pathways are modulated by cardioprotective drugs, which ultimately prevent fibrotic changes by promoting angiogenesis, improving cardiomyocyte survival, enhancing cardiac function, reducing inflammation, and suppressing myofibroblast activation. [44] Nanoparticles' unique physicochemical characteristics allow them to pass through cellular membranes effectively, and their targeted distribution can be enhanced when particular ligands are attached through covalent bonding. The advantageous characteristics of nanoparticles include receptor clustering and faster production, which help in effectively activating cellular signaling pathways. Nanoparticle-facilitated gene delivery for cardiac function improvement emerges as a promising therapeutic strategy, providing novel alternatives in the field. [45] In the context of acute MI, placental growth factor (PIGF) has become a potentially effective treatment for increasing heart function and encouraging angiogenesis. Chitosan-alginate nanoparticles, which are biocompatible, non-toxic, and biodegradable, have been created to improve PIGF delivery. These nanoparticles have shown remarkable effectiveness in preserving the growth factor from enzymatic degradation while delivering PIGF intramyocardially to the damage site. [46] A pH-sensitive Rapamycin (Sirolimus) (RAPA)-loaded nanoparticle system has been investigated for targeted delivery to ischemic tissues. With their rapid release in acidic environments and improved stability, biocompatibility, and RAPA loading efficiency, the nanoparticles enhanced therapeutic precision. [47] Small non-coding RNAs, or microRNAs, have a major post-transcriptional regulatory impact on the development of MI. Their potential for inhibiting apoptosis has been proven by research, making them a potential therapeutic approach in preclinical MI therapy trials. [48]

The therapeutic potential of microRNAs is hindered by their poor pharmacokinetic and pharmacodynamic properties. To overcome these barriers, scientists have concentrated on creating delivery systems based on nanoparticles that may enhance the stability, potency, and specificity of microRNA. To avoid cardiomyocyte apoptosis, miR-499 has been administered to the infarct site using new heparin NPs. It has been found that overexpression of MiR-499 may either promote cardiomyocyte proliferation or inhibit apoptosis. During MI, mitochondrial dysfunction leads to the mitochondrial permeability transition pore opening continuously, resulting in mitochondrial outer membrane permeabilization (MOMP) and triggering necrosis and apoptosis. To address this problem, researchers have created poly (lactic-co-glycolic acid) nanoparticles loaded with mitochondrial division inhibitor 1 (Mdivi-1) to prevent mitochondria-mediated cell death in the heart by blocking MOMP. [49] Nanomaterial-based therapeutic approaches for the treatment of ischemic heart diseases are summarized in **Figure 7**.

FUTURE PERSPECTIVE AND CONCLUSION

The application of nanomaterials has the potential to greatly expand the range of tools available to healthcare professionals in combating life-threatening diseases like CVDs. Innovations involving nanomaterials such as liposomes, carbon nanotubes, and polymeric nanoparticles are seen as groundbreaking advancements compared to traditional materials. As nanoscience continues to progress, new strategies and techniques are expected to emerge. The predictability and effectiveness of CVD treatments can be further enhanced and revolutionized as the promising potential of nanomaterials increasingly becomes a reality. Nanotechnology is revolutionizing cardiovascular care by

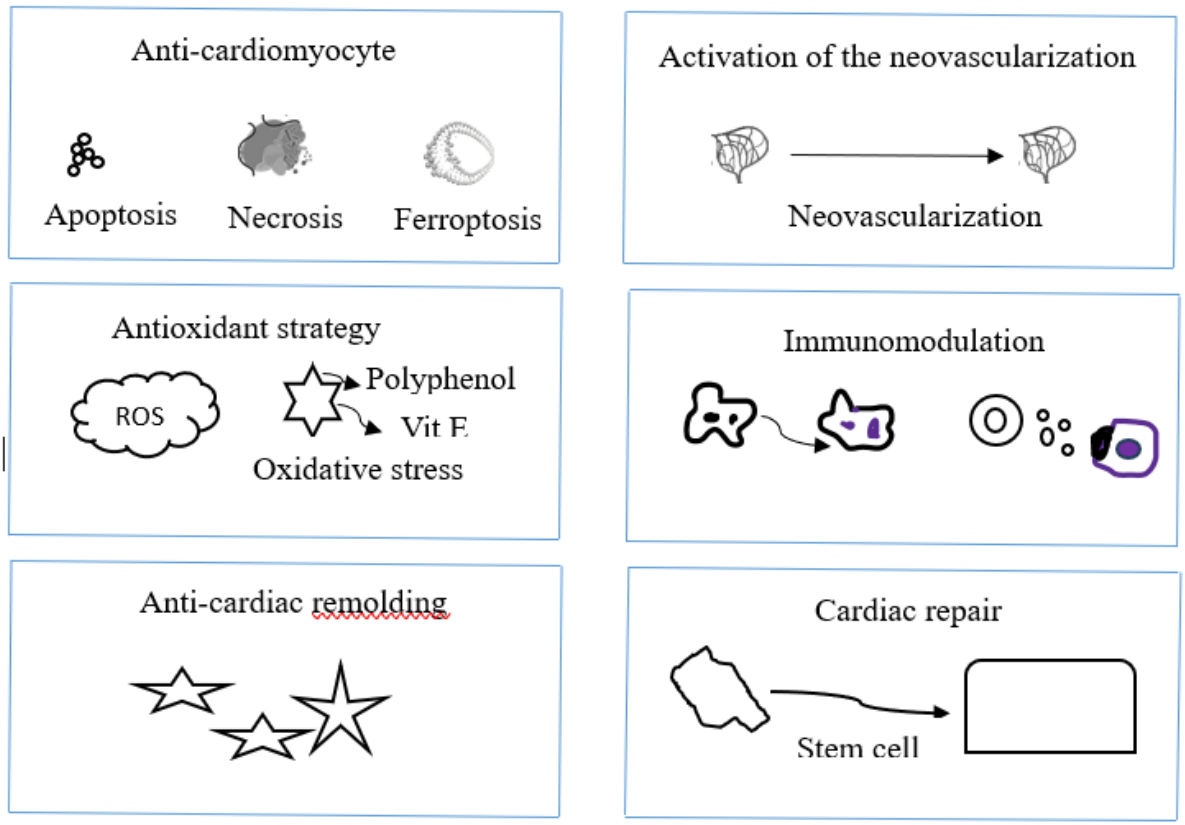

Figure 7: Schematic representation of nanomaterial-based therapeutic approaches for the treatment of ischemic heart diseases. [50]

enabling ultra-precise diagnostics and treatments. Tiny engineered particles act as dual-purpose tools—simultaneously detecting problems and delivering therapy exactly where needed. These microscopic carriers transport drugs with unprecedented accuracy, boosting effectiveness while reducing unwanted side effects. A key breakthrough involves smart nanoparticle delivery systems that solve long-standing drug challenges. By bypassing issues like poor absorption and rapid breakdown, these advanced carriers ensure medications work precisely where and when they're needed most in the heart and blood vessels. This targeted approach marks a major leap forward in treating complex heart conditions.

AUTHORS' CONTRIBUTION

All authors have significantly contributed to the work, whether by conducting literature searches, drafting, revising, or critically reviewing the article. They have given their final approval of the version to be published, have agreed with the journal to which the article has been submitted, and agree to be accountable for all aspects of the work.

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CONFLICT OF INTEREST

None.

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