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## MINI REVIEW

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# Treatment of cardiovascular diseases using nanoparticle mediated drug delivery

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### ABSTRACT

One of the main causes of high morbidity and death worldwide is cardiovascular disease (CVD). The lack of effectiveness of CVD prevention, diagnosis, and treatment options calls for innovative alternative approaches. In the field of CVDs, nanoscience and nanotechnology open up new doors for effective treatment, improved prognosis, and reduced side effects on tissues outside the target area. Due to the properties such as passive and active

targeting to the cardiac tissues, improved target specificity, and sensitivity, the use of nanoparticles and nanocarriers in the field of cardiology has attracted significant attention.

According to reports, nanotechnology can be used to successfully treat more than 50% of CVDs.

This review summarizes the difficulties associated with the conventional treatment modalities in comparison to the nanomedicine for CVDs.

**Key Words:** Cardiovascular diseases; Nanoscience; Nanoparticles; Nanomedicine; Nanocarriers

### INTRODUCTION

In the entire world, cardiovascular diseases (CVDs) rank among the main causes of death. According to the World Heart Federation, 17.3 million people worldwide die each year as a result of CVDs. The expense of diagnosing and treating CVDs was increasing more quickly and was expected to continue to rise over the next 10 years. Due to the rise in CVD risk factors like diabetes, obesity, and the ageing population, there is a significant economic burden associated with CVDs. According to recent data, cardiovascular diseases are expected to be the leading cause of death worldwide. By 2030, there will be more than 23.3 million CVD-related deaths, primarily from heart disease and stroke [1].

#### Cause of cardiovascular diseases

##### Hypertension

The high mortality ratio from CVDs in the world is caused by hypertension. Regardless of age or sex, hypertension has been seen in all population groups. Significant body organs like the heart, brain, blood vessels, eyes, and kidneys are frequently harmed by excessive blood pressure. Additionally, ischemia, atherosclerosis, congestive heart failure, and cardiac arrest are all caused by hypertension [2].

Adopting a healthy, preventative lifestyle and early identification of the diseases are the only ways to lower the incidence and mortality rate of CVDs. Annually, the early diagnosis could prevent millions of deaths and enhance quality of life. Patients' responses to the available therapy approaches are insufficient and impractical. According to reports, diabetes mellitus and cardiovascular diseases are closely related. The most frequent cause of morbidity and mortality in diabetic populations, both in male and female populations, is

cardiovascular disease (CVD) [3].

#### Types of cardiovascular diseases

Atherosclerosis is a key contributor to CVDs like stroke. Atherosclerotic plaques are brought on by lipoprotein retention on the sub-endothelial extracellular matrix. Plaques develop as a result of the interaction between lipid buildup and the inflammatory response. In most cases, inflammation, proteases, and oxidative stress have eliminated plaques. The collagen network is obliterated by proteases, which also cause the plaque to dissolve. Myocardial infarction and stroke may result from the plaque's rupture. One of the most severe forms of atherosclerotic cardiovascular disease is acute myocardial infarction, which results in the ischemic death of cardiomyocytes [4]. Another major killer in the world is coronary artery disease, which can be fatal if it results in an acute myocardial infarction.

Coronary artery diseases are caused by coronary atherosclerosis due to the coronary artery stenosis or occlusion. Heart failure, a complex pathophysiological disease that results from the heart's decreased ability to fill or empty the blood, is also a type of CVD.

Heart failure has been linked to many clinical symptoms as well as myocardial insults like hereditary factors, hypertension, hypertrophy, and coronary artery disease. Age-related increases in the prevalence of symptomatic heart failure are observed, and heart failure is listed as the leading cause of more than 55,000 fatalities annually.

The increase in the size of the cardiomyocytes causes hypertrophied hearts, also known as myocardial hypertrophy [5]. Aneurysm and restenosis are other CVDs. Restenosis, which causes an unnatural constriction of the blood vessel, develops as

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a severe complication of vascular interventional operations. It's because vascular interventional procedures frequently concentrate on opening blocked arteries to blood flow. Restenosis develops after angioplasty and stent implants remove the occlusion and expand the inner diameter of the artery with an increased hemodynamic flow rate.

In a nutshell, abnormalities in muscle development, repair, heart function, and rhythm are referred to as cardiac disorders. An alternate and efficient treatment for these illnesses entails administering cardioprotective medications directly to the cardiovascular system. Different techniques for targeted drug delivery have been developed as a result of the necessity to deliver these medications to specified targets. Along with a healthy lifestyle, methods for reducing CVDs have been suggested. These include not smoking, eating a nutritious diet, getting regular exercise, losing weight, doing aerobic exercise, regulating blood pressure, and lowering blood lipids [6].

However, a number of therapeutic approaches and medications on the market rely on synthetic substances. The body may experience various bouts of negative effects as a result of this illness. This subject encourages researchers to concentrate on more effective and safe therapeutic approaches.

When it comes to the controlled and precise delivery of medications to treat lipid disorders, thrombosis, inflammation, and angiogenesis in atherosclerotic plaques, nanoparticles have proven to be an efficient and dependable platform.

Nanoparticles of size 1 nm to 100 nm hold unique properties compared to their larger counterparts.

They can move between cells, tissues, and biological membranes. Nanosize, their particular quantum scale, a high surface to volume ratio, and shape are the distinguishing characteristics. To emphasise the physical characteristics of nanoparticles, their surfaces can be altered. By manipulating the particle's size, shape, and aggregation, monodispersed nanoparticles have been created that can be internalised by cells [7].

Due to their distinctive properties, nanomaterials have been used in a variety of biomedical applications as theranostic, diagnostic, drug carrier, and therapeutic agents. For instance, nanoparticles with a high surface to volume ratio can bind, absorb, or encapsulate molecules to deliver them to the target site.

**TABLE 1**  
**Advantages and disadvantages of nanoparticle-mediated drug delivery in cardiovascular diseases**

S.no	Advantages	Disadvantages
1	Targeted delivery to the site of cardiovascular injury	Lack of data about clinical trials and safety
2	No adverse effects and systemic toxicity	Tedious methods for characterization and purity analysis
3	Enhanced efficiency of drugs/dose	Cost of scale up production
4	Combined for treatment, diagnosis and imaging	Long term stability of drugs

**NANOPARTICLES FOR THE TREATMENT OF CORONARY ARTERY DISEASE (CAD)**

There are just a few clinical trials using nanomedicine in the treatment of cardiovascular disorders. The development of atherosclerotic plaque on the inner wall of the coronary artery has led to coronary artery disease. It manifests in the stenosis of the cavity, which lowers the vascular wall's compliance. As a result, there has

been some disruption in the myocardium's blood supply. Atherosclerosis is a chronic disease that causes plaque inflammation and arterial wall thickening. When coronary arteries become blocked due to atherosclerosis, a heart attack occurs.

Nanoparticles can be used to treat atherosclerosis by increasing drug circulation throughout the body, improving drug solubility, lowering dosage requirements, reducing cytotoxicity, improving targeted drug delivery at specific concentrations, and combining diagnostic and therapeutic approaches to create a bettertheranostics. Targeting macrophages, preventing plaque neovascularization, modifying lipid metabolism, inhibiting neointimal development, and treating thrombosis are the main goals of nanoparticle-mediated medication delivery and treatment for atherosclerosis and associated problems. In rabbits with iliac artery stenting, a liposomal formulation of the bisphosphonate alendronate reduced neointimal formation before suppressing the circulating monocytes. Early clinical trials have shown that liposomal alendronate is safer to inject during percutaneous coronary intervention. Statins are often prescribed medications to treat coronary artery disorders. Since its high dose therapy is linked to systemic side effects, statin use has generally been restricted. Pravastatin-loaded nanometer-sized vesicles were created after being functionalized by oligonucleotides to specifically target macrophages.

**NANOPARTICLES FOR THE TREATMENT OF HEART DISEASES**

Myocardial infarction is one of the severe ischemic heart illnesses that results in heart failure and, ultimately, death. The use of cardioprotective medications in therapy has been shown to stimulate angiogenesis, promote cardiomyocyte survival, enhance heart function, reduce inflammation and myocyte activation, and ultimately avoid fibrosis. In essence, heart function is safeguarded and preserved by all therapeutic and therapy agents. Successful and well-known methods of improving cardiomyocyte survival and cardiovascular function in mice include virus-mediated gene transfer and treatment. A promising alternative in the field is gene delivery using nanoparticles to enhance heart function. Due to their small size, which makes it possible for them to enter cells smoothly and effectively, nanoparticles have been employed for gene transfer.

For better absorption by the target cells, specific tags can be covalently bonded to nanoparticles.

Nanoparticles have an additional benefit over viruses in that they can cluster receptors to activate signalling pathways more quickly during synthesis. Nanoparticles can be employed as carriers for the transfer of DNA or RNA through surface binding or entrapping methods. The entrapping system, which shields the target gene from deterioration, is a nanosphere reservoir system. The anionic nucleic acid and cationic polymer's ionic interaction is supported by the surface binding system. PEGylation can be used for the delivery of a gene to vascular tissues [8]. PEG-POD/DNA was created by researchers by joining a peptide to the PEG for ocular delivery. A twenty-one-fold increase in transgenic expression is induced when PEG-POD/DNA is reduced. When evaluated in vivo, it ultimately causes a reduction (50%) in choroidal neovascularization. Chitosan nanoparticles that have been mannosylated make good carriers for delivering siRNA and DNA, but macrophages are more likely to take them up. Further research is needed to determine the use and potential of mannosylated chitosan nanoparticles in preventing myocardial infarction and lowering inflammation.

## NANOPARTICLE AS A DRUG DELIVERY AGENTS IN THE TREATMENT OF CVDS

### Gold Nanoparticles

One of the most often employed nanocarriers for the delivery of cardioprotective medications is gold. The use of gold nanoparticles in combination with already available clinical medications has been proposed as a novel strategy with increased promise for the treatment of heart disorders. Due to their simplicity in production, low toxicity, low immunogenicity, and stability, metal nanoparticles have been widely used in gold nanocarriers. Clinical medications have reportedly been shown to improve in accuracy and efficacy when they are conjugated. A medication for the treatment of heart disease is called Simdax. In doxorubicin-induced heart failure rats, simdax conjugated on gold nanoparticles (AuNPs) has cardioprotective properties. Due to the improved targeting of gold nanoconjugates to the wounded tissue, their cardioprotective capabilities are greater to those of their counterparts [9]. The sympathetic nervous system hyperactivity of the volume-loaded heart failure is alleviated by the blockers. One of the commonly used  $\beta$ -blockers, metoprolol has been conjugated with AuNPs for better distribution to the cardiac tissues. (Table 1). The receptors are the ones that metoprolol preferentially targets, and the conjugates target the volume-loaded heart failure tissue twice as effectively. These conjugates can be used in therapeutic settings as they have minimal negative effects on other organs. miR155-AuNPs have the potential to treat diabetic cardiomyopathy. It is a disease that usually affects women after menopause, and oestrogen insufficiency makes the disease symptoms worse. Typically, the hearts of diabetic mice had an excess of pro-inflammatory type 1 macrophages compared to anti-inflammatory type 2 macrophages. The hearts of ovariectomized diabetic mice also showed an increase in cell apoptosis, fibrosis, reactive oxygen species generation, and cardiac hypertrophy. Type 2 macrophages that are anti-inflammatory are greatly increased and inflammation is reduced when miR155-AuNPs conjugates are delivered in vivo. It ultimately results in the restoration of heart function by reducing cell death [10]. Gold nanoparticles have been demonstrated to be potential nanomaterials for medication delivery without harming healthy tissues. Although clinical studies and further research have need to be investigated, gold nanoparticles have been utilised in the lab to treat AMI. AMI may result in additional side effects include cardiac enlargement, fibroblast proliferation, cardiomyocyte necrosis and apoptosis, myofibroblast conversion, collagen deposition in the myocytes, and cardiomyocyte necrosis.

### CONCLUSIONS

It has become clear that one of the main causes of morbidity and mortality worldwide is cardiovascular disease and the disorders that are associated with it. With the rapid changes in human lifestyle, coronary artery diseases continue to be a threat to biomedical researchers even though some of the disorders are treatable. For the treatment and prevention of cardiovascular disorders, a variety of cardio-protective medications are available, and interest in newer therapeutic approaches is growing among the medical community. Natural substances, herbal remedies, and TCM were among the most effective accessible treatment techniques. These methods and drugs because they have fewer substances are chosen

over synthetic negative side effects.

However, because they were not backed by scientific research, these drugs frequently did not make it to clinical settings. However,

experts continue to call for new developments in the field of CVD diagnosis and therapy that are more effective and efficient than more traditional approaches.

The disadvantages of conventional treatment modalities that target various pathways, including lipid metabolism, blood volume, the coagulation cascade, and arterial constriction, include ineffective treatment of CVDs and adverse effects like thrombosis in stents, unusual immune system activation, and systemic toxicity.

Nano-drug delivery devices have been used as a substitute method for the effective and regulated administration of medications into damaged heart tissue. Similar to this, nanoparticles have several uses in the imaging and diagnosis of CVDs since they enable quick diagnosis of CVDs and real-time monitoring throughout therapy.

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