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Decoding Nanomedicine in Tackling Cardiovascular Diseases; Reaching the Unreached

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Abstract

Cardiovascular diseases (CVDs) pose a serious global threat as they are a significant cause of morbidity and mortality claiming a large number of lives. Increased incidences of cardiovascular events are often associated with an increased uptake of unbalanced dietary high-saturated lipids, salt and sugar. A sedentary lifestyle as well as obesity contribute to other potential factors leading to cardiovascular diseases. Demerits of limited applications in the diagnosis and treatment strategy of CVDs have led to the further exploration of nanoparticles in medicine. The field of Nanomedicine based on employing nanoparticles has revolutionized the diagnostic and therapeutic landscape by playing an important role in identifying their targets, signaling process and efficient drug delivery. These nanotechnology-driven methods can serve as efficient biomarkers in the early detection of CVDs thereby helping in their therapeutic and future prevention of cardiovascular events.

Keywords: Nanomedicine; Cardiovascular Diseases; Drug delivery; Biomarker

Introduction

Cardiovascular disorders (CVDs) are the major cause of death worldwide. According to a World Health Organization report, about 17.9 million individuals died from cardiovascular diseases, accounting for 32% of all global deaths. Heart attacks and strokes were responsible for 85% of these deaths [1], more than 75% of deaths occur in low- and middle-income nations, where high blood pressure is one of the most prominent risk factors. In India, it accounted for 63% of the total deaths due to non-communicable diseases in 2016 [2]. The underlying pathology is atherosclerotic vascular disease, resulting in coronary artery disease (CAD), cerebral disease, and subsequent development of

congestive heart failure and cardiac arrhythmias [3].

A healthy heart at the incident of myocardial infarction may lose 25% of cardiomyocytes (CMs) [4]. Regeneration of new cardiomyocytes deteriorates due to their deprived proliferation leading to the failure of ventricular remodeling. This results in fatal congestive heart failure as a consequence of decreased cardiac contractility and muscular dystrophy [5]. Over the years, the key risk factors for these disorders have been identified, and they include high levels of low-density lipoprotein (LDL), cholesterol, obesity, hypertension, diabetes, smoking and excessive intake of alcohol, etc. [3].

Atherosclerosis is a prime risk factor that is characterized by the deposition of lipids, fibrous elements, and calcification in the arteries. This process is initiated by endothelial activation, which is followed by a series of events that refer to the vessel narrowing and activation of inflammatory pathways, that lead to atherosclerotic plaque formation [6]. Numerous studies have reported that elevated serum cholesterol and LDL were associated with the highest risk of CVD, but HDL was linked to decreased CVD mortality [7].

Hypertension is another strong risk factor for cardiovascular, cerebral, and renal failure. Many observational studies have reported the relationship between blood pressure and cardiovascular diseases [8]. Individuals with both Diabetes mellitus and hypertension have a higher risk of cardio-cerebrovascular disease than people with only one condition [9].

Myocardial infarction can be efficiently managed with the recovery of the affected myocardial region with either pharmacological reperfusion or by mechanical approaches including percutaneous coronary intervention (PCI) as well as coronary artery bypass graft (CABG) [10]. Recent advancements in treating cardiovascular diseases mostly target the restoration of normal blood flow and reducing the frequency of recurring cardiovascular damage [11]. Despite various strategic treatment measures like Statin therapy [12] and dual anticoagulant and antiplatelet therapy being available [13], decreased response to clopidogrel is documented with an increased risk of recurring events of cardiovascular diseases [14]. This condition creates an inevitable exploration of nanoparticles in tackling cardiovascular diseases [11].

Nanotechnology refers to the areas of science and engineering in which nano-scale phenomena are used in the design, characteristics, formation, and applications of materials, structures and devices [15]. Nanotechnology has emerged as the most promising technology of the twenty-first century, with experts investigating it as a breakthrough tool in medical research. Nanomedicine is the application of nanotechnology for medical purposes, and it is described as the use of nanoparticles for the diagnosis, monitoring, prevention, and treatment of diseases [16].

Nanoparticles are ultrafine units measured in nanometers. Due to their submicroscopic size, they are used in various fields such as medicine, engineering, material science, and environmental remediation [17]. They are recognized broadly owing to their physicochemical attributes of possessing high surface energy contributed by their larger surface area to reactivity, wettability, roughness and volume ratio, in turn, expanding the scope of their biological function [18].

Commonly encountered nanomaterials in our everyday lives include titanium dioxide nanoparticles (TiO2NPs), silver nanoparticles (Ag-NPs), zinc oxide nanoparticles (ZnONPs), silica nanoparticles (SiO2NPs), and polymeric nanoparticles (PNPs). The size, functional groups, and dosage of nanoparticles can contribute to their potential action on healthy human cells, tissues, and organs [19].

Employing nanoparticles in medicine carries numerous merits such as i) Extended half-life span of the drugs in circulation, ii) Decreased toxicity, iii) Greater biocompatibility and iv) Decreased side effects [20]. Various mechanisms can be attributed to the biological impacts of nanoparticles at specific sites. Commercial applications have been using gold nanoparticles as probes to detect specific nucleic acid sequences, while clinical studies are investigating their ability to treat cancer and other disorders. Advancements in nanotechnology facilitate earlier diagnoses, personalized treatment options, and improved treatment outcomes [21].

Nanotechnology-driven methods for identifying biomarkers of coronary artery disease (CAD)

Efficient and precise disease diagnosis is of paramount significance in healthcare, aiming for rapid, accurate, and specific detection to minimize instances of "false negative" results [22]. The cardiac markers such as Brain natriuretic peptide (BNP), Creatinine kinase-MB (CK-MB), Cardiac Troponins (C-Tns), Myoglobin, C-Reactive protein (CRP) along with various micro RNAs are discharged into the blood stream when the heart is damaged or severely stressed. The release of cardiac biomarkers into the bloodstream is caused by heart diseases, and their increase is primarily based on the condition of the diseases. These biomarkers serve as powerful indicators that enable healthcare professionals to identify high-risk individuals, quickly diagnose medical conditions, and accurately guide patients' treatment strategies for optimal care [23].

Identification of potential biomarkers of CVDs by mass spectrometry is not reliable as they are present at lower levels in the human plasma. A combination of nanotechnology-derived biosensors can serve as a promising strategy for the earliest CVD diagnosis. Nanotechnology enables specific binding to target molecules while biosensors enable them in target recognition and conversion of data into electrical signals [23].

Nano Formulation and Cardiovascular Drug Delivery

Nano formulation represent a promising approach to drug delivery for cardiovascular disease (CVD), which encapsulate therapeutic agents within the nanoparticles. It provides the best treatment strategy to minimize potential side effects and improve the efficiency of drug delivery [24]. Nano-based drug delivery systems overcome physical and biological barriers to ensure improved stability, solubility, and drug absorption [20]. The nano structured carriers fall into two primary categories such as organic and inorganic nanoparticles, which play a key role in the drug delivery for CVD. Polymeric nanoparticles are highly effective nano carriers for targeted drug delivery because of this diminutive particle exhibit greater uptake within artery walls, facilitating sustained drug release at the target site [25].

Herbal remedies have long been widely employed in addressing serious illnesses. Furthermore, many pharmaceutical products are made from plants. Natural compounds are valuable for use in the search for novel therapeutic agents due to their enormous chemical diversity, less toxicity, therapeutic efficiency, and affordability [26, 27]. Advances in nanomedicine and drug delivery systems have improved the safety and efficacy of nano formulation derived from medicinal plants for heart disease. Plant derived nanoparticle used for the treatment of cardiovascular diseases are listed in Table 1.

S. No	*Green Synthesized Nanoparticle*	*Plants*	*Size*	*Characterization*	*Inducing Agent*	*Parameters*	*Pharmacological Activity*	*Reference*
1	Iron oxide Nanoparticles (FeONPs)	Spinacia oleracea leaf	20-80 nm	XRD SEM FTIR	5% Triton X-100 (100 mg/kg body weight) for 14 days	Total cholesterol [TC] Triglycerides [TG] high-density lipoprotein [HDL] low-density lipoprotein [LDL] AST, ALT, ALP, Superoxide dismutase [SOD], Glutathione peroxidase [GPx], Catalase [CAT], Cardiac troponin CKMB and Histopathological studies.	The administration of FeONPs raised HDL levels and markedly reduced all biomarkers. Tissue architecture was also recovered.	[28]

2.	Gold Nanoparticles (AuNPs)	Silybum marianum	22.6 to 59.1 nm	FT-IR, FE-SEM, UV–Vis, and TEM	Isoproterenol (40 Mg/Kg) In C57BL/6 Mice	In vitro DPPH MI gene markers (IL-1β, TNF-α and IL-6)	Inhibits the expression of inflammatory cytokines. PPAR-Ɣ and PPAR-Ɣ/ NF-κB/IκB-α/ IK^α/β phosphorylation gene expression and normalization.	[29]
3	Silver Nanoparticles (AgNPs)	Syzygium cumini seeds	43.02 nm	UV, SEM, XRD XRD	Embryonic rat heart-derived H9C2 cells	DPPH, ABTS MTT assay 4′,6-Diamidino-2-Phenylindole Staining, Propidium Iodide Staining, Lipid Peroxidation Assay	Significantly suppress the glucose-induced cardiac stress in vitro, .	[30]
4	Zinc oxide Nanoparticles (ZnO-NPs)	Artemisia herba alba leaves' extract	25 ± 5 nm	UVD X-Ray diffraction	isoproterenol (100 mg/kg) adult Wistar male Rat	cTnT , CKMB,LDH, ALT, AST, TC, TG, HDL TBARS, GST, GRx, and GPx , Gene Expression - qRT-PCR (PPAR-α, ADD1, FASN, and ACC genes)	High antioxidant and hypolipidemic activities.	[31]
5	Silver Nanoparticles (AgNPs)	Rumex alpinus L	12–55 nm	UV–Vis, SEM, FT-IR	isoproterenol	GSH, SOD, GPx, GST, Keap1/ Nrf2 pathway), inflammation (IL-1β, IL-6, TNF-α, and NF-κB), apoptosis (caspase-3, caspase-9, Bcl2, and Bax), and autophagy (PI3K/Akt/mTOR pathway).	Increased antioxidant enzyme activities, modulated the PI3K/Akt/mTOR pathway, and ameliorated myocardial autophagy, inflammation, and apoptosis.	[32]
6	Chitosan	Pinus merkusii	201.8±14.6 nm	Scanning Electron Microscope (SEM) and Dynamic Light Scattering (DLS)	Lead acetate (15 mg/kg body weight i.p)	LDH, CKMB, MDA, SOD, GPx	Significantly decreased LDH, CK-MB, MDA, and increased SOD, GPx levels and potent antioxidant activity	[33]
7	Copper oxide Nanoparticles (CuO NPs)	Cistus incanus leaf extract	15–25 nm	TEM and SEM FTIR	Alloxan-injected rats, Sprague–Dawley (SD) rats	CKMB, TROP T, cardiac index (CI), stroke volume index (SVI) and heart rate (HR)	Improved levels of creatine kinase-MB (CK-MB) and cardiac troponin I (cTnI).	[34]

8	Silver Nanoparticles (AgNPs)	Achillea biebersteinii	12 ± 2 nm	TEM UV-visible EDS	Isoproterenol (40 mg/kg) in in C57BL/6 mice	Type I Collagen Extraction and Preparation of Collagen Matrix and Aortic Ring Culture	Potential anti-angiogenic property	[35]
9	Copper Nanoparticles (CuNps)	Berberis vulgaris leaf extract	15.11 to 48.94 nm	(FT-IR), (UV–Vis, FE-SEM, TEM	isoproterenol (40 mg/kg) in C57BL/6 mice	Gene expression of interleukin-1β (IL-1β), tumor necrosis factor alpha (TNFα) and interleukin 6 (IL-6)).	Decreased the proinflammatory cytokines upregulation (interleukin-1β (IL-1β), tumor necrosis factor alpha (TNFα) and interleukin 6 (IL-6)).	[36]
10	Silver Nanoparticles (AgNPs)	Spilanthes acmella Leaf Extract	6.702 nm	FTIR SEM EDS XRD	20 mg/kg of doxorubicin (DOX)	AST, ALT, LDH, GSH, SOD ABTS, DPPH, and O2•– assays	Decrease Serum enzyme markers, confirming its antioxidant potential.	[37]

Table 1: Plant-Derived Nanoparticles for Cardiovascular Disease Treatment.

Conclusion

Increasing developments in the biomarker industry, helping in understanding the potential spectrum of CVDs, promise rapid expansion in the future with the application of nanomedicine [38]. The combination of nanomedicine with the detection of biomarkers promises a significant therapeutic approach in biomedicine by playing a major role in the diagnosis and treatment of damaged biological tissues. Nevertheless, it is indispensable to elevate the nanotechnological applications leading to the effective enhancement of the CVD treatment.

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