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A description of the biomarkers, bioactive substances, and nanotechnology-based therapies linked to Cardiovascular Diseases

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ABSTRACT
The phrase "cardiovascular disease" (CVD) refers to all conditions that affect the heart and vasculature, the organs responsible for the displacement and transportation of the blood, respectively. This complex condition includes a variety of inherited and acquired illnesses. Cardiovascular disease includes rheumatic heart disease (damage to the myocardium and cardiac valves caused by streptococci bacteria), congenital heart disease, peripheral artery disease, cerebral disease, and peripheral artery disease with its subtypes (coronary, cerebral, and deep vein thrombosis), which are more common than hemorrhagic stroke.The leading cause of death is cardiovascular disease in both highly industrialized and undeveloped countries. 30% of all-cause mortality in 2008, or 17.5 million people, were attributable to CVDs. It is anticipated to reach 23.3 million by 2030.The needs of the patient will be met during therapy. Infectious diseases and cardiovascular medicine are currently beginning to adopt these designs as well. Until recently, oncology was the only field using clinical trial designs that assessed a biomarker for prognostic or predictive utility.For treating patients with CVDs, using nanoparticles in medicine provides significant advantages over both traditional and cutting-edge medical techniques.

Keyword: Cardiovascular diseases (CVDs), Risk factors, Etiology, Biomarkers, Bioactive compounds, Nanotechnology

I. INTRODUCTION

The term "cardiovascular diseases" (CVDs) refers to a variety of conditions that affect the heart and blood vessels (1).They cover a wide range of linked disorders, such as deep vein thrombosis, congenital heart disease, rheumatic cardiovascular disease, coronary cardiovascular disease (CHD), cerebrovascular disease (CBVD), and peripheral arterial disease and other related conditions (2). Half of all deaths from heart attacks, strokes, endocarditis, rheumatic heart disease and other avoidable cardiovascular disorders are preventable (3). The most discriminatory screening factor among those without an existing disease is age. Since those aged 55 and over account for 96% of deaths from ischemic heart disease or stroke, treating everyone in this age group would very certainly prevent all such deaths. It would likely not be worth the extra complexity and expense to add slight discrimination by using different age cut-offs for men and women, smokers and non-smokers, or mixing different risk factor values with age and sex to obtain individual estimates of overall risk (4–6).Both in highly industrialized and developing nations, cardiovascular disease is the main cause of death. 17.5 million persons or 30% of all-cause fatalities in 2008, were caused by CVDs. By 2030, it's expected to reach 23.3 million (7). Recent statistics show an alarming increase in the occurrences of CVD-related death and disability in low-income nations. According to a 2008 estimate by Gupta et al., within the next 15 years, more than 50% of all heart disease patients will reside in India, which currently accounts for 25% of all cardiovascular-related deaths worldwide (8). According to a recent estimate from the World Heart Federation (WHF), the number of deaths caused by cardiovascular disease (CVD) increased globally from 12.1 million in 1990 to 20.5 million in 2021. In 2021, cardiovascular disease (CVD) was the largest cause of death globally, with low- and middle-income (LMIC) nations accounting for 4 in 5 of all CVD fatalities. According to the World Health Organization (WHO), low- and middle-income nations account for more than 75 percent of CVD deaths, which has led to an epidemic crisis in recent years (9). In developing countries, these diseases are predicted to rise by 120% for women

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and 137% for men between 1990 and 2020, compared to 30–60% in developed nations (10). The burden brought on by CVD is noticeably greater in India than it is worldwide. For instance, India had a higher age-standardized death rate from CVD than the rest of the world (233 deaths per 100,000 (229-236)), which was 282 deaths/100,000 (264-293) at the time (11). In India in 2016, CVDs were responsible for 28.1% of all fatalities and 14.1% of all disability-adjusted life years (DALYs), respectively, compared to 15.2% and 6.9% in 1990. The prevalence of CVD varies greatly within India, with Kerala, Punjab, and Tamil Nadu having the highest rates. Additionally, the prevalence of high blood pressure and elevated cholesterol is highest in these states.The prevalence of acute coronary syndrome and ST-elevation myocardial infarction (MI) is now the highest in India. Hypertensive heart disease, among other CVDs, is a significant issue in India, with 261,694 fatalities in 2013 (an increase of 138% from 1990)(12). Cardiovascular diseases (CVDs) are based on Omran's epidemiological transition model as follows:

- Phase 1: Infectious infections and malnutrition are the primary causes of cardiovascular disease.
- Phase 2: Growth in society and the economy increase the salt level of food and alter the nutritional composition, causing hypertension and stroke.
- Phase 3: Before the development of coronary heart disease, there is an increase in the consumption of calories and saturated fats, smoking, physical activity declines, and mental stress.
- Phase 4: Delaying the age of clinical development of degenerative cardiovascular disease by reducing risk factors and taking additional treatments. Diabetes and obesity emerge as the key risk factors.
- In several emerging nations, the transition from the second to the third phase happened more quickly than anticipated(13,14).

The reduction of cardiovascular and all-cause mortality is thought to be facilitated by regular physical activity as a primary and secondary preventative strategy for cardiovascular disease (CVD). Guidelines on Sports Cardiology and Exercise in Patients with Cardiovascular Disease, just released by the European Society of Cardiology (15).

TYPES OF CARDIOVASCULAR DISEASES

Significant CVD categories include: CAD: Coronary artery disease Reduced myocardial perfusion, which leads in angina, myocardial infarction (MI), and/or heart failure, is the cause of what is sometimes referred to as coronary heart disease (CHD). It is responsible for between one-third and fifty percent of CVD cases. Stroke and transient ischemic attacks (TIA) are examples of cerebrovascular disease (CVD). Particularly arterial disease affecting the limbs that can cause claudication is known as peripheral artery disease (PAD). Aneurysms in the thorax and abdomen are a result of aortic atherosclerosis (16,17).

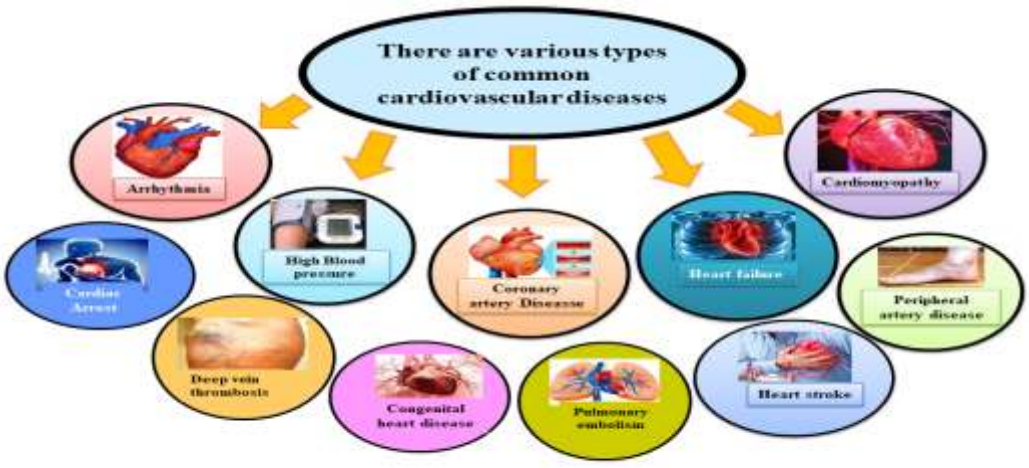

Fig.1: Common cardiovascular illnesses come in a variety of forms.

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Etiology Of Cardiovascular Diseases (CVDs)

Even though various aetiologies, such as rheumatic fever causing valvular heart disease and emboli in a patient with atrial fibrillation resulting in ischemic stroke, may directly cause CVD, addressing risk factors associated with the development of atherosclerosis is crucial because it is a common factor in the pathophysiology of CVD (18). The significant and steady rise in CVD rates over the past few decades may be attributed to the industrialization of the economy, which led to a shift from physically demanding to sedentary jobs, as well as the current consumerism and technology-driven culture, which is linked to longer work hours, longer commutes, and less free time for leisure activities. With regard to the development of atherosclerosis and other metabolic disturbances including metabolic syndrome, diabetes mellitus, and hypertension that are quite common in persons with CVD, inactivity, consuming a high-calorie diet, saturated fats, and sweets are specifically linked (19–22). The American Heart Association has incorporated these findings into health promotion initiatives with a focus on seven recommendations to lower the risk of CVD, including quitting smoking, staying active, eating well, and maintaining normal blood pressure, body weight, glucose, and cholesterol levels (23,24).

RISK FACTORS FOR CARDIOVASCULAR DISEASES (CVDs)

About 80% of coronary heart disease (CHD) and cerebrovascular disease (CD) are caused by behavioural risk factors, such as poor diet, inactivity, tobacco use, and excessive alcohol consumption (25). These risk factors cause people to become overweight and obese, have higher blood pressure, blood sugar, and blood lipid levels. The risk of CVDs has been found to be decreased by quitting smoking, reducing salt intake, eating more fruits and vegetables, engaging in regular physical activity, and abstaining from alcohol abuse. Additionally, treating or avoiding diabetes, hypertension, and elevated blood cholesterol levels will help to lower the cardiovascular risk (26). Additionally, there are a number of underplayed elements that contribute to the development of CVDs, including poverty, stress, and hereditary factors, as well as globalization, urbanization, and population ageing (27).

- **Modifiable risk factors**

Modifiable risk factors such as smoking, dyslipidemia, hypertension, diabetes, abdominal obesity, psychosocial factors, consumption of fruits and vegetables, regular alcohol consumption, and physical inactivity, accounted for 90% of the risk of experiencing a first MI, according to the Inter-heart study, which included participants from 52 countries with high,middleand low income levels. It is significant to note that in this study, smoking was responsible for 36% of the population-attributable risk of MI (24). A considerable connection and predictive value of dyslipidemia, hypertension, smoking, and glucose intolerance have also been discovered in other sizable cohort studies, such as the Framingham Heart Study and the Third National Health and Nutrition Examination Survey (NHANES III). Subjects with at least one risk factor experienced 60% to 90% of CHD occurrences (28).

- **Non-modifiablerisk factors**

However, non-modifiable characteristics like age, gender, and family history have differing effects. Family history is regarded as an independent risk factor, particularly early atherosclerotic disease, which is defined as CVD or death from CVD in a first-degree relative before 55 (for men) or 65 (for females) years of age. Additionally, there is some data that suggests that gender may vary depending on the existence of CVD risk factors. For instance, women were more likely than men to develop CVD if they had diabetes or smoked more than 20 cigarettes per day. With each decade of life, CVD prevalence considerably rises (19,28–31). Microalbuminuria, elevated inflammatory markers, history of mediastinal or chest wall radiation, and the presence of HIV (human immunodeficiency virus) have also been linked to an increased rate and incidence of CVD. Due to severe bias and persistent confounding that are observed in epidemiological studies, it is still debatable to identify specific diet components such meat consumption, fibre, and coffee and their relationship to CVD (32–37).

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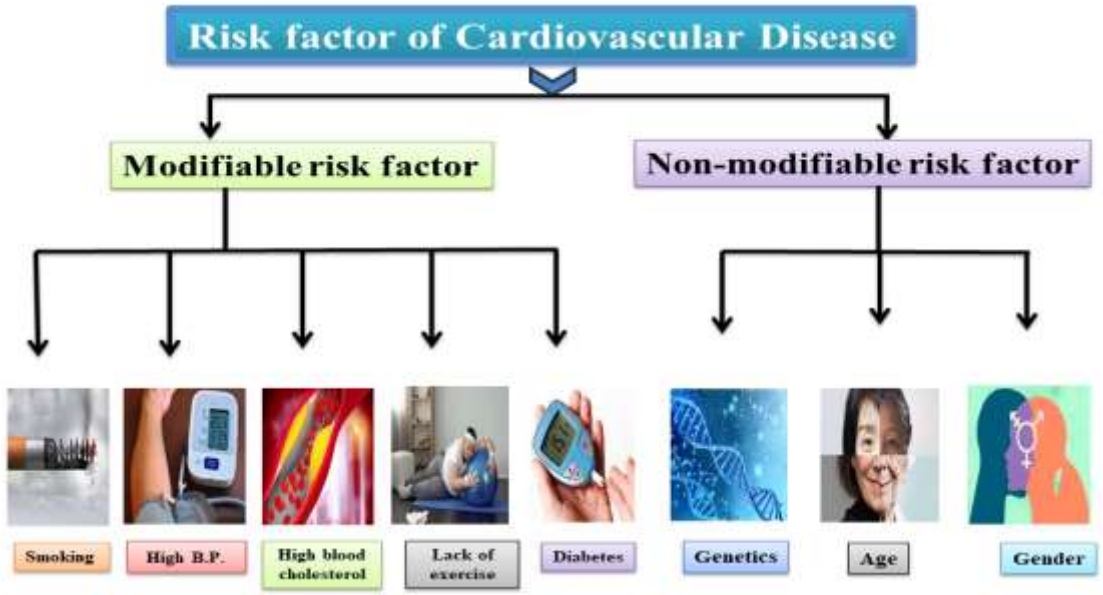

Fig.2: Risk factors of Cardiovascular diseases(CVDs).

PATHOPHYSIOLOGY OF CARDIOVASCULAR DISEASES

Atherosclerosis is a disease-causing process that develops in the arteries and aorta and results in diminished or nonexistent blood flow as a result of blood vessel stenosis (38). It is influenced by a number of variables, including dyslipidemia, immune system events, inflammation, and endothelial dysfunction. These elements are thought to be the starting point for the progressive development of the fatty stripe, which is the characteristic of the atherosclerotic plaque and can start as early as childhood (39). This process includes intimal thickening, followed by a buildup of extracellular matrix and lipid-rich macrophages (foam cells), smooth muscle cell aggregation, and smooth muscle cell proliferation, which results in the creation of the atheroma plaque. Apoptosis of the deep layers may happen as these lesions grow, triggering more macrophage recruitment that may result in atherosclerotic plaques by becoming calcified (40,41). Other factors, such as arterial remodelling and intra-plaque hemorrhage, contribute significantly to the acceleration and delay of atherosclerotic cardiovascular disease (CVD) progression (42).

BIOMARKERS

In addition to helping to develop new medications to treat illness conditions, biomarkers are crucial in the assessment of disease. Biomarkers may even be useful in figuring out the precise doses of a particular drug during the last stages of its development. Biomarkers are now also being thought of as substitute end points for clinical trials in more recent times. Traditionally, biomarkers have been categorized as either prognostic, diagnostic, or screening based on their intended function. A national movement towards the advancement of precision medicine has lately taken place(43). A biomarker is a trait that is reliably tested and analyzed as an indicator of normal biological processes, pathogenic processes, or pharmacologic reactions to a therapeutic intervention, according to the National Institute of Health Consortium in 2001 (44).

- **Biomarkers in the treatment of cardiovascular disease**

The patient's needs will be satisfied in therapy. Until recently, the discipline of oncology was the only one using clinical trial designs that evaluated a biomarker for prognostic or predictive utility; however, currently infectious diseases and cardiovascular medicine are starting to use these designs as well (45). The most commonly investigated indicators in relation to the various processes that contribute to the formation and rupture of atherosclerotic plaque, including endothelial dysfunction, inflammation, oxidative stress, proteolysis, and thrombosis(46).

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- **Endothelial Dysfunction**

Given that it is known that the endothelium is injured in areas of elevated blood turbulence, cardiovascular risk factors and hemodynamic variables are among the causes of endothelial dysfunction. Particularly, lipids play a distinctive function since their elevated plasma concentrations might cause them to accumulate in the subendothelial area, where, after experiencing various alterations, they trigger the production of adhesion molecules and the inflammatory process starts (47,48).

Adhesion Molecules

Cell recruitment to the inside of the vascular wall depends on adhesion molecules. Numerous studies have linked their concentrations with the risk of cardiovascular events since their soluble forms may demonstrate up in plasma (49).

ICAM-1 (intercellular adhesion molecule-1) reaches higher amounts in healthy individuals who would experience acute myocardial infarction (AMI) than VCAM-1 (vascular cell adhesion molecule-1) does, according to evidence from healthy populations (50,51). According to the ARIC (Atherosclerosis in Risk Communities) study, soluble E-selectin levels and ICAM-1 concentrations were both predictive of coronary events and the onset of carotid atherosclerosis (52). The Women's Health Study demonstrated the predictive value of soluble P-selectin for cardiovascular events. According to the Atherogene study, people who experienced cardiovascular events had higher amounts of E-selectin, ICAM-1, and VCAM-1 in populations with coronary heart disease (53,54). While there was no link with ICAM-1, E-selectin, or P-selectin, Mulvihill et al. found that VCAM-1 and C-reactive protein (CRP) were predictors of future cardiovascular events in individuals with ACS. Finally, the predictive usefulness of adhesion molecules is not particularly supported by Malik et al.'s findings in the British Regional Heart Study. Samples from the 643 men who developed coronary heart disease and the 1278 men who remained stable out of the 5661 men who were included in the trial were analyzed. 36% of people who experienced events and 20% of people who remained stable had coronary heart disease symptoms at baseline. ICAM-1, VCAM-1, E-selectin, and P-selectin concentrations did not improve the predictive information offered by the traditional risk variables (55,56). The information currently available on the impact of lipid-lowering medication on the plasma concentrations of several adhesion molecules is dispersed. Fluvastatin (80 mg/d) therapy therefore decreased the plasma levels of ICAM-1 and P-selectin in 26 hypercholesterolemic patients. Other research, however, have not verified similar findings. ICAM-1, VCAM-1, and E-selectin concentrations in the blood of 75 hypercholesterolemic patients were examined by Jilma et al. treated for three months with three different statins and found no changes in the proteins' plasma concentrations. The results of the AIM (Atorvastatin on Inflammatory Markers) trial, which examined ICAM-1 plasma concentrations in 1078 participants at high cardiovascular risk, have just been published. It should be noted that these investigations were conducted in small populations. It was found that 3-month treatment with all of the atorvastatin doses available (10-80 mg/d) reduced ICAM-1 concentrations (57–59).

- **Inflammation**

Chemokines

Chemokines regulate leukocyte entrance into the interior once they have attached to the vascular wall. Alpha and beta chemokines are the 2 most common. The interleukins (IL) and other alpha chemokines are chemotactic for neutrophils or lymphocytes. In addition to drawing in basophils and eosinophils, beta chemokines also draw in lymphocytes and monocytes but not neutrophils. MCP-1, a monocyte chemoattractant protein, is a member of this family(60).

Interleukin 6

The prospective Health ABC cohort research evaluated the utility of IL-6 as a risk predictor. Circulating IL-6 levels were a good indicator of coronary heart disease, heart failure, and stroke in individuals without vascular disease (61). Patients with unstable angina who died, had an AMI, or experienced refractory angina while hospitalized exhibited greater levels of IL-6, according to research by Biasucci et al. concentrations than in people who maintained their stability. In a different trial of 263 patients with unstable angina, IL-6 and CRP concentrations predicted the risk of cardiac death over a 17-month follow-up period and added value to indicators of myocardial damage (62,63). In the FRISC II (Fragmin and Fast Revascularisation During Instability in Coronary Artery Disease II trial) study, 3269 ACS patients were randomized to receive aggressive therapy or a conservative approach. Over the course of a 12-month follow-

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up, the IL-6 concentrations were independent predictors of mortality. Furthermore, individuals with high IL-6 concentrations improved after invasive treatment, suggesting that IL-6 could be used to direct treatment in this population (64).

Monocyte Chemoattractant Protein-1

The primary chemokine controlling monocyte recruitment to tissues with an active inflammatory response, like in atherosclerotic lesions, is this one. Numerous studies have proven the utility of soluble MCP-1 as a diagnostic and prognostic marker. MCP-1 plasma levels have been linked to a variety of cardiovascular risk variables and a higher chance of experiencing a cardiovascular incident in the future. In 2270 patients with non-ST-segment elevation acute coronary syndrome (NSTEACS), the prognostic significance of MCP-1 was examined in the OPUSTIMI 16 research, and it was found that MCP-1 plasma concentrations predicted the probability of mortality or AMI at 10 months. Our team has shown that treating individuals with carotid atherosclerosis with atorvastatin alone or in combination with amlodipine lowers MCP-1 concentrations (65–68).

C-Reactive Protein

The most well-known inflammatory marker is without a doubt CRP. CRP levels have been shown to be predictive of recurrent myocardial instability in patients with unstable angina (69–71). The management of peripheral vascular disease appears to benefit from CRP in a similar way, both in terms of diagnosis and prognosis. CRP has been linked to a higher incidence of reoccurring cardiovascular events in people with coronary heart disease. On the other hand, other investigations on AMI patients found associations between CRP levels and the size and extent of the necrosis as well as with the prognosis (72–75). The ability of baseline CRP concentrations to predict cardiovascular events has been shown in a number of primary prevention studies(76–78).

- **Oxidative Stress**

Lipoprotein-Associated Phospholipase A2

Leukocytes generate a calcium-independent lipase known as lipoprotein-associated phospholipase A2 (LpPLA2), and atheromatous plaques also contain macrophages that are linked to circulating LDL. This indicator of cardiovascular risk has undergone the most extensive research, along with CRP. The use of Lp-PLA2 in primary and secondary prophylaxis has been the subject of more than 25 prospective epidemiological investigations. Even after multivariable adjusting for conventional risk variables, these clinical trials have typically shown that there are significant associations between circulating Lp-PLA2 concentrations and the increased risk of cardiovascular events. Lp-PLA2 is an additional risk factor that is distinct from and helpful from CRP (79–81). The American Heart Association's guidelines, which suggest that Lp-PLA2 could be utilized in clinical practise to fine-tune the prediction of risk in patients at intermediate cardiovascular risk, are supported by these research. also receiving a lot of attention as a potential therapeutic target for coronary heart disease is lipoprotein-associated phospholipase A2. It is created by the inflammatory cells in the lesion or is delivered by LDL particles, and it is found in high amounts in the lipid core of inflammatory plaques. Lysophosphatidylcholine and oxidized fatty acids are produced as a result of its action on oxidized phosphatidylcholine, which is present on the exterior of oxidized LDL. These two bioactive lipid substances promote lipid core expansion and fibrous cap thinning. In an experimental model, the specific inhibition of Lp-PLA2 by darapladib prevented the formation of advanced coronary atherosclerotic lesions (82).

- **Proteolysis**

A significant factor in the weakening and rupture of advanced atherosclerotic plaques is the imbalance between the creation and breakdown of the extracellular matrix. Although the primary mechanism lowering the synthesis of matrix components appears to be the death by apoptosis of vascular smooth muscle cells, enhanced degradation has been linked to increases in the quantities and activity of several proteolytic enzymes. The metalloproteinases (MMP) have received the most research attention of these enzymes(83).

Metalloproteinases

Most of the risk factors for atherosclerosis disease, including, among others, hypertension and diabetes mellitus, have been linked to a rise in the concentrations of different circulating MMP. Likewise, MMP-9 and TIMP-1 inhibitor concentrations are significantly higher in people with coronary heart disease and carotid atherosclerosis(84–88). Both markers' concentrations have been found to rise in those

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who have acquired ACS. Regarding the potential predictive significance of MMP, it has been found that elevations in circulating MMP-9 can predict cardiovascular events in healthy persons in primary prevention. Similar studies in secondary prevention have linked higher MMP-9 concentrations in people with different cardiovascular diseases to higher cardiovascular mortality (89–92).

- **Thrombosis**

The most serious clinical effects of atherosclerosis are caused by the destabilisation, rupture, and subsequent development of thrombus that are caused by the immuno-inflammatoryproteolytic processes present in atherosclerotic plaque. Among patients with ACS, the plaque rupture process happens in 70% of cases. This often features a plaque containing fat that just slightly narrows the vessel, ruptures when it comes into contact with the blood, releasing its tissue factor-rich lipid core, and forms a thrombus that restricts blood flow (93,94).

CD40/CD40L

There have been attempts to determine whether measuring the CD40/CD40L system's plasma levels could offer predictive information given its participation in atherothrombosis.

In healthy women, a rise in soluble CD40L is associated with an increased risk of cardiovascular events (95–97). The majority of the population, however, who experienced cardiovascular events had concentrations similar to those who stayed stable; the difference was caused by a tiny minority that obviously had higher CD40L values. Therefore, it is feasible that soluble CD40L in healthy women can detect a group at special risk of vascular events, but not the majority of them (98). It has been demonstrated that patients with ACS had elevated CD40L expression on platelets. In the CAPTURE research, which compared the effectiveness of abciximab and a placebo, CD40L concentrations were examined in NSTEACS patients preparing for angioplasty (99,100).

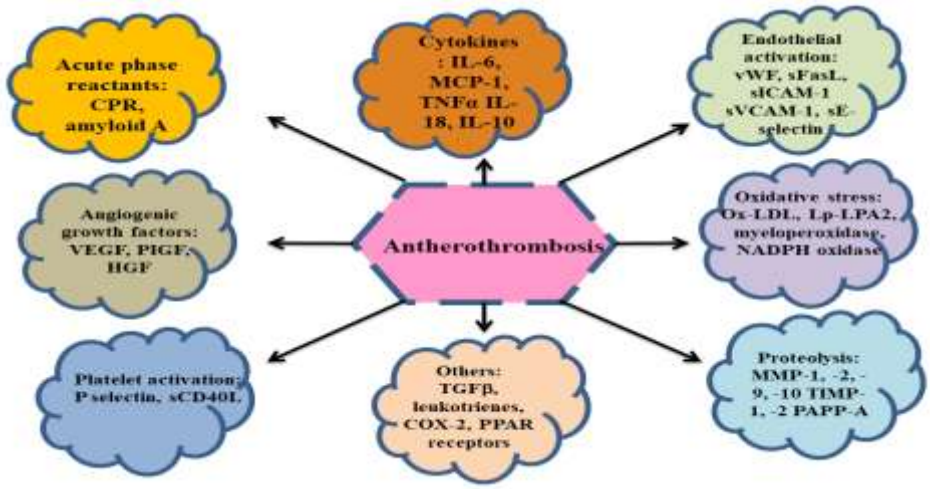

Fig.3: Circulating atherosclerosis-related Biomarkers (46).

BIOACTIVE COMPOUNDS IN CARDIOVASCULAR DISEASES AS ANTIOXIDANTS

It is already known that the development of CVD is linked to oxidative stress, which may be brought on by an imbalance in ROS. Decreases in endogenous antioxidant enzyme have also been associated to cardiovascular disorders (101). In the aetiology of CVD, greater lipid peroxidation and increased ROS generation cause arterial membrane damage. Since oxidative stress is a major factor in both the development of cardiovascular disease and other neurological disorders, addressing oxidative stress would significantly improve the management of cardiovascular disease. Clinical research has demonstrated that boosting endogenous antioxidants and lowering the generation of free radicals can considerably lower the risk of myocardial infarction (102–105). Many diseases have been successfully treated with natural remedies made from plants. In the last ten years or so, numerous studies have shown that foods including vegetables, cereals, spices, fruits, nuts, and mushrooms can prevent CVD and enhance cardio-metabolic health (106–114). A likely explanation for the cardioprotective properties of

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medicinal plants has been suggested by various studies that focus on their antioxidant capabilities. These plant by-products' medicinal qualities are derived from high-value bioactive compounds, or secondary metabolites, commonly referred to as phytochemicals. These compounds include anthocyanins, carotenoids, chalcones, flavonoids, phenolics, quinones, terpenoids, and others, and they can be divided into several categories. The wide range of biological effects that these bioactive chemicals display, including their antioxidant properties (115–117). Antioxidants are more widely used today thanks to their many health benefits. More research is being done on natural antioxidants as a prophylactic tool against cardiovascular problems such ischemia reperfusion. Antioxidants have been shown to lower the risk of heart disease by a radical-scavenging process, which reduces the production of reactive oxygen species (ROS) and increases endogenous antioxidant enzymes. As a cardiac protector, Terminalia arjuna's polyphenol-rich extract controls antioxidant enzyme activities in myocardial infarction caused by isoproterenol (118–120). The antioxidant properties of T. arjuna are attributed to its higher concentrations of polyphenols, flavonols, kaempferol, and phenolic acids. It has been reported that flavonoids can be used to treat cardiovascular disease due to their ability to halt endothelial dysfunction, reduce LDL oxidation, and suppress platelet aggregation, which concludes their cardioprotective activity. The possible cardioprotective effects of Ocimum basilicum have been investigated. Numerous studies have shown that triterpenoids, polyphenols, and steroids are added to plant-based essential oils. One study found that changes in blood pressure caused by isoproterenol-induced cardiotoxicity might be moderated by plant extract. The endothelial nitric oxide synthase (eNOS) activity is increased and oxidative stress is decreased by polyphenols, which also prevent endothelial dysfunction. In angiotensin II-induced hypertension, polyphenols prevent excessive NADPH oxidase-dependent vascular ROS generation from damaging endothelial cells (121–123). The medicinal effects of Allium sativum (garlic) are associated with its antioxidant properties. Nitric oxide generation is increased by garlic, which avoids endothelial dysfunction. The coronary arteries were significantly dilated by garlic juice, enhancing coronary flow both before and after reperfusion. As shown by the decreased concentration of LDH release, the analysis revealed much higher defence against endothelial dysfunction and avoidance of anaerobic metabolism in the heart muscle cells (124–130). According to reports, the bioactive substance Allicin (also known as diallyl thiosulfinate or allyl 2-propenethiosulfinate) is what gives garlic its cardioprotective effects. The primary regulator of the cellular antioxidant defence mechanism is nuclear factor erythroid 2-related factor 2 (Nrf2). Numerous studies have also shown that Nrf2 can stop the development of atherosclerotic lesions, foam cells, and endothelial dysfunction. By regulating the nuclear factor erythroid 2-related factor 2 (Nrf2) signalling pathway, these bioactive substances guard against CVD (131–136).

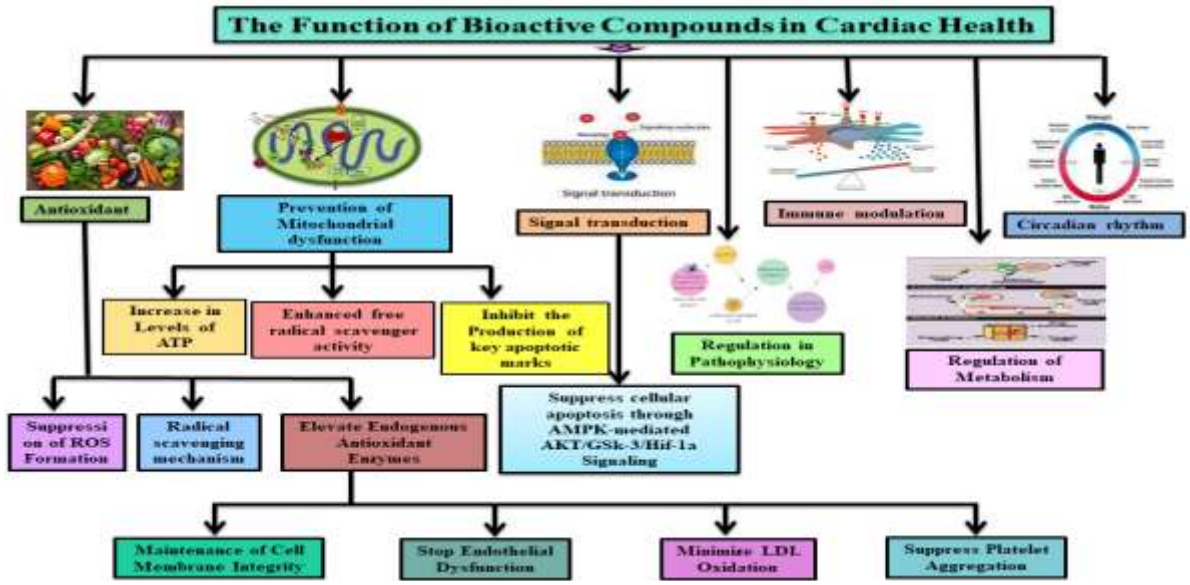

Fig.4: Bioactive Compounds' Impact on Cardiovascular Health (137).

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CARDIOVASCULAR DISEASES TREATMENT WITH NANOTECHNOLOGY

Following recent advancements in the medical area, nanotechnology has being investigated as a potential catalyst for rapid advancement. Improvements made feasible by medical uses of nanotechnology can be made to current drugs, prostheses, diagnostic reagents, prostheses, and patient monitoring (138). It is essential to first emphasise the range of important ailments that can be treated by nanotechnology in order to demonstrate its efficiency. One of the most serious and fatal diseases in the world, "Acute Myocardial Infarction (AMI)", atherosclerosis, hypertension, stroke, and heart failure, among others, have significant health and financial impacts. Nanomaterials supply medications for the treatment of cardiovascular illnesses(139). Recent advances in nanotechnology have greatly increased the possibility for diagnosing and treating CVDs. The application of nanotechnology to the diagnosis and treatment of CVD is yet largely unexplored. However, the issues that CVDs currently confront will likely be faced and addressed by cardiovascular nanomedicine. By developing methodologies, it will also help with therapy, detection, drug administration, and tissue regeneration (140).

- **In Vivo Imaging Technique:**

Provides the ability to see cellular processes utilizing "smart" imaging agents or targeted imaging nanoprobes (particularly magnetic nanoparticles and quantum dots) as opposed to biomarkers in conventional imaging approach (141).

- **Controlled Drug Delivery or Targeted Therapeutics:**

Drugs delivered at the nanoscale increase therapeutic efficacy and create a powerful therapeutic approach (142).

- **Nano-Biosensors and In Vitro Diagnostics:**

For the clinical diagnosis of disease, improved analytical tools/Biomedical or biological Micro-Electro-Mechanical Systems (BioMEMS) are essential for the precise identification of small quantities of disease biomarkers (143).

- **Tissue Engineering:**

Extracellular matrix-like (ECM) materials that are created to be biocompatible may be made available via nanotechnology to facilitate the growth of new and implanted tissue (144,145).

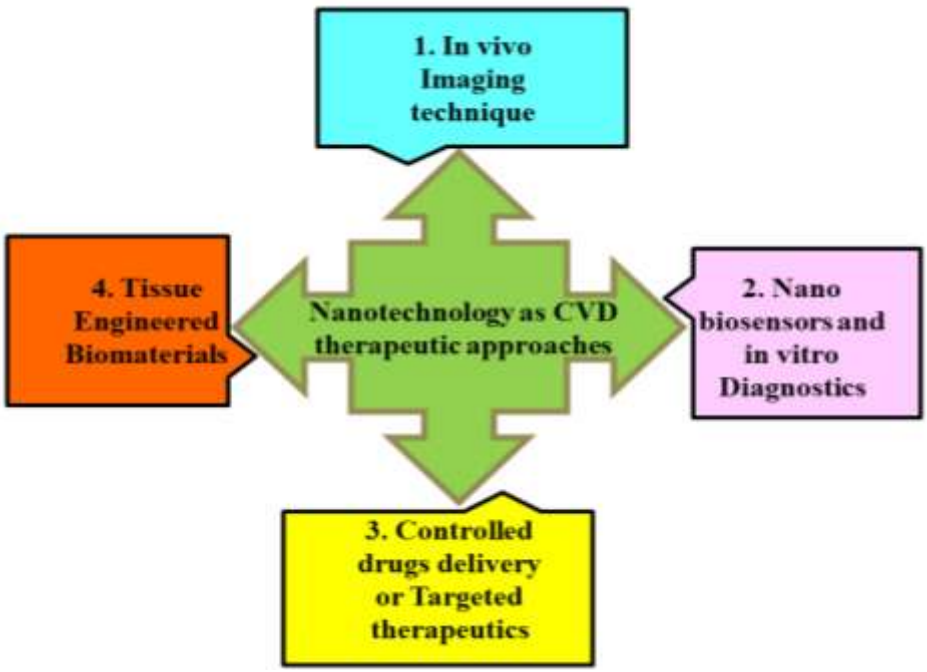

Fig.5: The potential use of nanotechnology in treating CVDs (146).

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(i) In Vivo Imaging Technique

The most significant contributing factor to sudden cardiac events is atherosclerotic lesions, which are best defined as vascular inflammation. Different stages of atherogenesis may be largely influenced by the hydrolytic enzymes released by various cell types (monocyte-derived macrophages and T lymphocytes) during cardiovascular inflammation. Fluorescence-mediated tomography (FMT), an imaging approach that has been created, has made conventional imaging techniques conceivable, including the invention of enzymes that can sense near-infrared imaging probes (using the proteolytic enzyme cathepsin B as a model). Additionally, the FMT approach shares the ability to detect fluorochrome levels ranging from picomole to femtomole in deep tissues at a macroscopic level(147,148).Even though this technique produced positive findings, a few issues still need to be looked at further. The most significant finding is that animals regularly experience accelerated and active atherosclerosis that is rife with inflammation and causes aortic aneurysms. Because inflammation is a crucial mechanism underpinning the development and rupture of atherosclerotic lesions, many molecular imaging investigations of atherosclerosis focus on it.Additionally, methods that evaluate changes in metabolism, blood flow, and biological function are used in the diagnosis, monitoring, and prognostication of CVDs(149,150).The development of multiple strategies for labelling and characterizing the earliest stages of disease before the emergence of pathological symptoms has led to the emergence of nanoscale contrast agents. For cardiovascular imaging, contrast-generating nanomaterials may be radioactive, fluorescent, paramagnetic, super-paramagnetic, electron-dense, or light-scattering particles(151).

Nanoparticles (NPs) -Enhanced Imaging

As in-vivo imaging probes for medical and biological diagnostics, nanoparticles (NPs) are becoming more and more popular. They are capable of satisfying a number of important prerequisites for imaging methods. Ionic strength, pH, solvent polarity, temperature, and other local in-vivo conditions have little effect on the NPs. They also form a stable imaging agent, are easily dispersible, and resist aggregation. These NPs should ideally be safe for safe clearance from the body once imaging is finished and be suitable for long-term quantitative imaging at low dosages(152,153).

Magnetic Nanoparticles (MNPs)

According to their size, magnetic iron oxide nanoparticles (MIONs,(154,155)μm), superparamagnetic iron oxide nanoparticles (SPIONs, hundreds of nm), and ultra-small paramagnetic iron oxide nanoparticles (USPIONs, <50 nm) are all different types of magnetic nanoparticles (MNPs)(156).To obtain high tissue contrast and increase imaging sensitivity, these MNP-based probes have been created for magnetic resonance imaging (MRI). They have also been used for imaging and treatment of atherosclerosis, restenosis, and associated cardiovascular diseases. Dark contrast is usually enhanced and produced by the superparamagnetic contrast agents (SPIONs), which are mainly magnetite (Fe2O3/Fe3O4). At atherosclerotic plaques, the SPIONs' encapsulation of porous silica in a single unit improved contrast(154,155).Biomimetic nanomaterial conjugated MNPs contrast agents with better magnetic and physicochemical properties have been created to meet the high resolution and high sensitivity criteria for in-vivo imaging applications(157).

Quantum Dots (QDs)

The application of quantum dots (QDs) in biology is one of nanotechnology's fastest-moving and most interesting interfaces. In biology and medicine, quantum dots (QDs), which are nanometer-sized light-emitting particles, are becoming a new class of fluorescent markers. They possess distinctive optical and electrical features when compared to organic dyes and fluorescent proteins. They are a well-liked option for fluorescence imaging applications due to their long-term, multiplexed, high fluorescence quantum yields, and high photostability. They have established themselves as potent fluorescent probes(158–160).The fluorescent quantum dots (QDs) have been utilised as contrast agents in CVDs and emit light throughout a wide spectrum, from near ultraviolet to mid-infrared. Reduced blood concentration and easy removal from the bloodstream are crucial factors for in vivo uses of QDs. Additionally, fluorescent QDs will be a superior substitute for magnetic and radioactive imaging contrast agents in preclinical drug screening, validation, and delivery research and will offer crucial information for the rational design of biocompatible drug carriers. Due to its developed synthetic process and readily accessible rescence imaging applications, CdSe/ZnS and CdTe/ZnS QDs are currently among the most

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thoroughly investigated QDs for in vivo imaging(158,161–163).

(ii) Nano-Biosensors and In Vitro Diagnostics

An analytical tool called a biosensor uses a biological sensory system to identify target chemicals. This device can be connected to a physiochemical transducer, which converts recognition into a quantifiable output signal that has been amplified and formatted appropriately. The development of next-generation biosensors with increased sensitivity and lower prices has a tremendous potential to result from the establishment and development of micro- and nanoscale technologies for biology. Additionally, nanomaterials are frequently used to increase the sensitivity of sensors since they work well with the right detecting probes and serve as signal transducers. The material can be constrained into the nanoscale dimension to attain the remarkable sensitivity(164,165).Enzyme-Linked ImmunoSorbent Assay (ELISA) is the foundation of nearly all biochemical tests used to diagnose acute myocardial infarction (AMI). ELISA is an antibody (Ab)-based technique that creates an Ab1/target/Ab2 sandwich with each target for sensitive enzymatic detection by employing an enzyme-linked Ab2 and a surface immobilized Ab1. Although ELISA is one of the most rapidly expanding methods in clinical diagnostics for identifying specific proteins linked to disease, cardiac indicators require additional chemicals for clinical diagnosis of AMI. Additionally, portable test strips can provide qualitative, but not quantitative, information on cardiac biomarkers. Additionally, nanobiosensor (electrochemical immunosensor) is more affordable when compared to commercially available ELISA systems(166–168).An electrochemical nanosensor with immobilized anti-myoglobin (Mb) was created by Suprun et al.(169) The manufactured nanobiosensor was quantified as a biomarker for the detection of acute myocardial infarction (AMI). The detection method uses antibodies, didodecyldimethylammonium bromide (DDAB), and gold nanoparticles to modify the electrode surface where the Fe (III) -heme is located. The suggested approach does not call for labelled secondary antibodies, signal amplification, or enhancement. The working concentration range of the immunosensor is 10–1780 ng/ml (0.56–100 nM), with a detection limit of 10 ng/ml (0.56 nM). Acute myocardial infarction can be expressly diagnosed after the 30-minute procedure(170).

Biomedical or Biological Micro-Electro-Mechanical Systems (BioMEMS)

In recent years, the biological and biomedical applications of micro- and nanotechnology (commonly referred to as Biomedical or Biological Micro-Electro-Mechanical Systems [BioMEMS]) have become more common and have found widespread use in a wide variety of applications, such as diagnostics, therapeutics, and tissue engineering. In general, BioMEMS can be characterized as "devices or systems, constructed using techniques inspired from micro/nano-scale fabrication, that are used for processing, delivery, manipulation, analysis, or construction of biological and chemical entities." All of the interconnections between the biomedical and life sciences and micro- and nanoscale systems are covered by these apparatuses and systems. BioMEMS research and application fields include diagnostics, such as DNA and protein micro-arrays, as well as innovative materials for Bio-MEMS, microfluidics, tissue engineering, surface modification, implantable BioMEMS, and systems for drug delivery, among others(171–176).For the early identification and detection of CVDs, recent advancements in BioMEMS and nanosensors have produced some very potent instruments. As an illustration, the monitoring and detection of acute myocardial infarction are made easier by the use of nanowire integrated potassium and dopamine sensors(177).

(iii) Controlled Drug Delivery or Targeted Therapeutic

As a result of their limitless potential to benefit human health, research in the field of drug delivery has recently endorsed remarkable progress. The shortcomings of current medication delivery technologies include possible cytotoxicity, limited effective targeting, and inadequate bioavailability. In the meantime, advances in nanotechnology offer possibilities for systematic manipulation of matter at the nanoscale scale, including synthesis with regulated composition, shape, size, and morphology(178).In particular, they can improve the therapeutic action by extending drug half-life, enhancing hydrophobic drug solubility, and releasing medicines steadily. Additionally, their surface characteristics can be changed to improve cellular absorption, immunocompatibility, and solubility. Additionally, the enhanced permeability and retention (EPR) effect allows nanoscale particles to passively

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assemble in particular tissues (such as tumours).Nanoparticles, nanospheres, nanocapsules, nanotubes, nanogels, and colloidal carriers like liposomes or dendrimers are some of the promising and adaptable nano-scale drug delivery technologies. They can be used to deliver biomacromolecules such peptides, proteins, plasmid DNA, synthetic oligodeoxynucleotides, growth factors, and/or enzymes that give a persistent therapeutic stimulus at the wounded tissue(179,180).

Nanopaticles (NPs) Based Controlled Drug Delivery

NPs have been used both for medicinal and diagnostic purposes. For a range of ailments, they have been used as a regulated drug delivery system; however, in the realm of cardiology, the majority of NP research has been on myocardial infarction detection. The preferred size range for NPs utilised as medication delivery devices is between 10 and 100 nm(181,182). These NPs-based drugs can target and improve the efficiency or bioavailability of numerous medicinal or diagnostic agents. The NPs made of synthetic or natural polymers, including liposomes, dextrans, poly (lactic-co-glycolic acid) (PLGA), polyaccrylates, as well as metal or metal oxide nanoparticles (such as gold, silver, SPION), and quantum dots, are among the materials most frequently used for cardiovascular drug delivery systems. Here are a few of the frequently tested drug-carrier systems in summary(183).Liposomes are one of the NPss-based drug-delivery vehicles with the lowest toxicity and best therapeutic index. A lipid bilayer made of amphipathic phospholipids, primarily phosphatidylcholine, surrounds an internal aqueous area in liposomes. To increase their stability, phospholipid head groups are frequently functionalized with polymerizable moieties. Several research teams have investigated liposome-mediated site-directed medication delivery of plasminogen activators for the treatment of CVDs. For instance, it has been shown that RGD-peptide conjugated liposomes have an affinity towards active platelets and may be effective for the targeted delivery of thrombolytic medicines. Platelet activation is mediated by the binding of fibrinogen through the RGD (Arg-Gly-Asp) motif(184–187).However, the liposomes can be functionalized with ligands (such as antibodies or polymers) and have low immunogenicity, which is expected to permit safe and recurrent administration. Liposomes were first utilised as transfection reagents for siRNA or gene delivery(188).

(iv) Tissue Engineered Biomaterials for Treatment of CVDs

Although they have been used frequently, the current treatments for the loss or failure of cardiovascular functions, such as organ transplantation, mechanical devices, surgical reconstruction, or the administration of metabolic products, are constrained and complicated(189).A different approach to treating CVDs is tissue engineering. By utilizing cells and biomaterial scaffolds, tissue engineering aims to improve the function of diseased or damaged tissues. The engineering of the various circulatory system parts, including heart valves, blood arteries, and cardiac muscle, has advanced recently. Additionally, numerous pivotal research are carried out for the general use of tissue engineered therapy for CVDs. Engineered scaffolds for skeletal and cardiac tissue constructs should mimic the mechanical properties of the underlying tissue and improve cell alignment(190,191).In order to meet many of the crucial requirements for long-term success, the next generation of functional tissue replacements, such as skeletal and cardiac tissue constructs for the treatment of CVDs, will require new material techniques. It is crucial to take into account the usage of modern materials in light of the rising role of genetics, growth factors, bioreactors, and other technologies given the rapid expansion in the field of tissue engineering(192).Cardiovascular disease (CVD), the leading cause of death in the US, may be better treated with the help of cardiovascular tissue engineering. Recently, a considerable advance in the kind of heart valves utilised to replace diseased and damaged heart valves may be seen. Recent years have seen a significant advancement in tissue engineering. The development and formation of complex tissue constructs to remain viable both in vitro and in vivo upon implantation, however, are the main difficulties of tissue engineering(193).

Copolymer Polylactic-Co-Glycolic Acid (PLGA)

Hu et al. created a type of poly (lactide-co-glycolide70/30) (PLGA-70/30) microtubular orientation-structured blood artery that mimicked natural structure using an enhanced thermal-induced phase separation (TIPS) technology. It was possible to create different microtubular orientation-structured blood vessel scaffolds with varying wall thickness by adjusting TIPS technique

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parameters like temperature, polymer solution concentration, and inner and outer mould diameters of polyethylene (PE)(193–195).A10 cells were used as model cells in an in vitro evaluation of the scaffolds' cell affinity. The findings demonstrated that the ammonia plasma-modified and collagen-anchored vascular scaffolds allowed the A10 cells to grow (seed and migrate). The cells displayed good vitality and quick proliferation and were located in the microtubule direction. In light of this, Ma et al. created novel scaffolds using thermally induced phase separation (TIPS) methods from biodegradable poly (L-lactic acid) (PPLA) to better design blood arteries with small diameters(196).

- **Advantages of medication delivery using nanoparticles in CVDs.**

An growing field in communication technology, information technology, biology, medical technology, biotechnology, and medicine is nanoscience and nanotechnology. Design, manipulation, manufacture, and application of materials smaller than 100 nm are the subjects of nanoscience(197).In the field of medicine, nanotechnology has a wide range of uses, including for imaging, diagnostic, and therapy methods including targeted drug administration, gene delivery systems, and scaffolds for tissue creation(198).Due to their physicochemical characteristics that enhance biological function (reactivity, roughness, high surface energy, and high surface to volume ratio), nanoparticles have attracted a lot of interest in medicine.A promising field called nanomedicine enables the detection, treatment, and management of illnesses or disorders to enhance people's quality of life and physical well-being. The use of nanoparticles in medicine has many benefits over both conventional and cutting-edge medical procedures. These benefits include extended medication half-lives, decreased toxicity, improved biocompatibility of nanoparticles, and decreased pharmacological adverse effects by modifying the characteristics of nanoparticles(199).

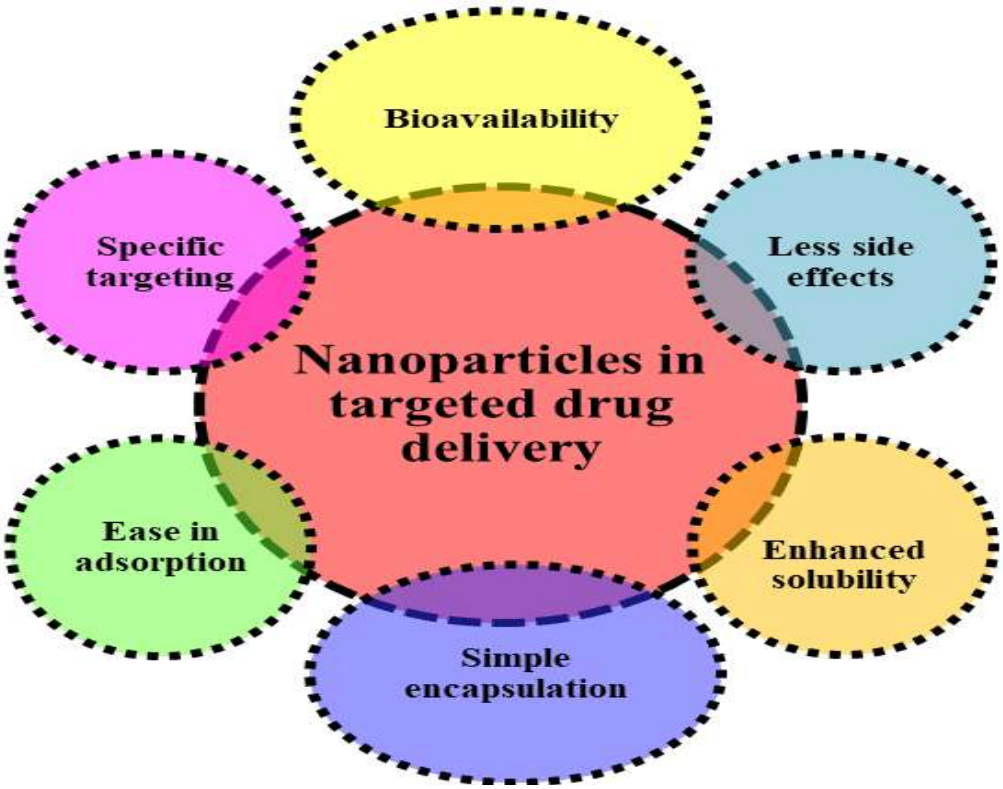

Fig.6Benefits of medication delivery via nanoparticles(139).

CARDIOVASCULAR DISEASE STATISTICS FOR INDIA

As the major cause of death in India, cardiovascular disease (CVD) is anticipated to double between 1985 and 2015, contributing to an increase in mortality(200).By 2015, cardiovascular mortality among Asian Indians is predicted to increase by 103% among men and 90% among women. In fact, it has been estimated that by 2015, CHD will be the leading cause of mortality in the

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Indian population. While the majority of the population still resides in rural areas, urban areas in India have seen a particularly noticeable increase in the prevalence of cardiovascular disorders. While there is a dearth of data regarding the prevention and treatment of cardiovascular disease in rural areas, there is a dearth of information regarding its causes in metropolitan areas(201–204).Studies Rural and urban subjects in India had lower saturated fat consumption (4.9% and 9.2%, respectively) and lower serum cholesterol levels (167 mg/dl, 4.3 mmol/L, and 203 mg/dl, 5.2 mmol/L), which were linked to a significantly higher prevalence of coronary artery disease (CAD) in the urban population (8e13%) compared to the rural population (3%) in the country. According to these findings, there may be an Indian paradox, and Indians may not understand what normal cholesterol levels and normal saturated fat intake signify.When blood cholesterol levels exceed 150 mg/dl (3.89 mmol/L) and saturated fat intake rises above 5% of daily calories, the risk of coronary artery disease (CAD) gradually increases. Regarding the relevance of dietary fat intake and blood cholesterol levels in the aetiology of CAD in Indians, there is some debate, nevertheless(205–209).According to the Indian Lifestyle and Heart research, a cross-sectional research of a cohort of metropolitan North Indians found a substantial relationship between the degree of saturated fat consumption and CAD and coronary risk factors. Consuming more or less saturated fat was linked to a higher prevalence of CAD. In a multivariate study, the relationship between saturated fat consumption and CAD declined after other risk factors were added although age adjustment did not change the significance of the relationship. Subjects consuming high (10% en/day) and low (7e10% en/day) levels of dietary saturated fat were more likely to have hypertension, hypercholesterolemia, obesity, and a sedentary lifestyle than those consuming extremely low (0.7%, en/day) amounts.Although the prevalence of smoking was similar across the three categories of saturated fat intake, more people in the high saturated fat intake group were sedentary than in the low and very low saturated fat groups. The combination between these factors may further raise the CAD risk in urban Indians in addition to the independent risk linked to low saturated fat intake and a sedentary lifestyle. Saturated fat consumption in India's rural, North Indian urban, and South Indian urban populations was 4.9%, 9.2%, and 14.2%, respectively, and the prevalence of coronary artery disease was 3%, 8.6%, and 13.9%.respectively(206,209).In the Indian Lifestyle and Heart Study, men and women who consumed low levels of saturated fat (7e10% en/day) had a prevalence of CAD of 10.6% and 6.2%, respectively, with mean blood cholesterol levels of 5.01 and 5.02 mmol/L. These results imply that even in urban Indians with minimal saturated fat intake, the prevalence of CAD is significant enough to warrant consideration as a public health issue. The Indian Lifestyle and Heart Study also revealed that CAD was less prevalent among populations with low socioeconomic status, no education, and unskilled labour.The vast majority of participants in these subgroups consumed very little saturated fat (7% kcal/day) and engaged in more physical exercise. Data on social class have only been analysed in a small number of Indian research. These investigations revealed that CAD occurred more frequently in higher income groups and less frequently in unskilled employees who performed physically demanding jobs(210–212).

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II. CONCLUSION AND FUTURE DIRECTION

Our review articles start with an overview of cardiovascular diseases (CVDs), types of cardiovascular diseases, risk factors, treatment by biomarkers, bioactive compounds, advance nanotechnology, and CVDS statistics for India. Our review concludes that medicine does cure but not completely and has harmful side effects (like-kidney and liver damage's) on the body, while non-pharmacological treatment gives a good result but takes time and has no harmful effects. On the topic of treating CVDS, further randomized controlled trials are required. We intend to carry out preliminary research on cardiovascular illness in the future. Future counseling-based research will be conducted in our nation or state to evaluate patients' physical and mental health and provide better statistics on cardiovascular disease and its treatment.

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Table.1: Current status of clinical trials oncardiovascular diseases (CVDs).

Drug	Mode of administration	Disease	Enrollment	Allocation/ Intervention model/Masking	Official Title of the study	Status	Clinical trial	Year
Cardiovascular disease risk assessment /Usual care assessment	Interventional	Cardiovascular Diseases	9714	Randomized/ Parallel Assignment / Triple (Participant Investigator Outcomes Assessor)	Improved Cardiovascular Disease health Service Delivery in Australia: Cluster Randomised Controlled Trial (IDEAL Study)	NA	NCT04896021	2022
Capsaicin	Interventional	Cardiovascular Diseases	20	Non-Randomized/ Single Group Assignment / None (Open Label)	Effect of Capsaicin on the Augmentation of Cerebral Perfusion. A Phase II Study.	Phase-2	NCT05543837	2023
Aspirin/Placebo/ ticagrelor	Interventional	Cardiovascular Diseases	9006	Randomized/Parallel Assignment /Quadruple (Participant Care Provider Investigator Outcomes Assessor)	Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention	Phase-4	NCT02270242	2021
Aerobic Exercise Group/ Physical Activity & Health Information Group	Interventional	Cardiovascular Diseases	130	Randomized/Parallel Assignment / Double (InvestigatorOutcomes Assessor)	Behavioural Studies of Cardiovascular Disease	NA	NCT03841669	2023
NA	Observational	Cardiovascular Diseases	80	Cohort	Sleep Patterns as Predictive Markers of Hospitalization or Death Due	NA	NCT05749263	2023

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					to Cardiovascular Disease in Elderly Patients			
Digitally delivered gardening and healthy eating course	Interventional	Cardiovascular Diseases	40	Randomized/Parallel Assignment/None (Open Label)	Growing Health Hearts: An Online Gardening Program for Adults With Risk Factors for Cardiovascular Disease	NA	NCT05720611	2023
RASI and/or a single pill combination based RASI	Interventional	Cardiovascular Diseases	20000	Randomized/ Parallel Assignment/ Single (Outcomes Assessor)	Study of Early Pharmaceutical Intervention for Cardiovascular Disease Prevention in Stage 1 Hypertension	NA	NCT05564780	2022
High self-disclosure/ Low self-disclosure	Interventional	Cardiovascular Diseases	34	Randomized/ Factorial Assignment/ Single (Investigator)	The Role of Vulnerability and Responsiveness in Cardiovascular Disease Biomarkers Associated With Loneliness	NA	NCT04195620	2022
TQJ230/Placebo	Interventional	Cardiovascular Diseases	17	Randomized/ Parallel Assignment/ Triple (Participant Care ProviderInvestigator)	A Randomized Double-blind, Placebo-controlled, Multicentre Trial Assessing the Impact of	Phase-3	NCT05548023	2022

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					Lipoprotein (a) Lowering WithTQJ230 on Major Cardiovascular Events in Patients With Established Cardiovascular Disease			
PolyPill	Interventional	Cardiovascular Diseases	4415	Randomized/Parallel Assignment/Single (Outcomes Assessor)	Effectiveness of Polypill for Primary Prevention of Cardiovascular Disease (PolyPars): Study Design and Rationale for a Pragmatic Cluster Randomized Controlled Trial	Phase-3	NCT03459560	2021
NA	Observational	Cardiovascular Diseases	8000	Cohort	Fujian Province Cardiovascular Diseases Study	NA	NCT02430025	2015
Less than 35 years old/ Greater than or equal to 35 years	Observational	Cardiovascular Diseases	50	Case-Only	Risk of Cardiovascular Disease in Soccer Referees: a Cross Sectional Study	NA	NCT03171285	2017
Exercise	Observational	Cardiovascular Diseases	100	NA	Study on Exercise Safety of Patients With Cardiovascular Diseases	NA	NCT04963478	2021
Placebo/ B	Intervent	Cardiov	60	Randomize	The	NA	NCT0449	2023

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uckwheat husk extract	ional	ascular Diseases		d/ Parallel Assignment /Double (Participant Investigator)	Efficacy Evaluation of Buckwheat Husk Extract on Cardiovascular Disease Risk Factors		0720	
Chinese patent medicine	Observational	Cardiovascular Diseases	20000	NA	Cohort Study on Treatment of Cardiovascular Diseases With Traditional Chinese Medicine	NA	NCT05309343	2022
Physical exercise training/ Cognitive training	Interventional	Cardiovascular Diseases	122	Randomized/ Parallel Assignment /Double (InvestigatorOutcomes Assessor)	The Cognitive and spOrt Virtual EPIC Training Study: Investigating the Effects of Home-based Exercise and Cognitive Training in Cardiovascular Diseases	NA	NCT04661189	2021
Heart Matters	Interventional	Cardiovascular Diseases	143	Randomized/ Parallel Assignment / Single (Participant)	Reducing Cardiovascular Disease Risk Factors in Rural Communities in North Carolina	NA	NCT02707432	2020
Family Meals/ Standard	Interventional	Cardiovascular Diseases	90	Randomized/ Parallel Assignment /Single (Outcomes Assessor)	Family Meals as a Strategy for the Primary Prevention of Cardiov	NA	NCT05180435	2023

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					ascular Disease in Children			
sample blood	Interventional	Cardiovascular Diseases	120	Randomized/ Single Group Assignment / None (Open Label)	Clinical and Imaging Biomarkers Associated With Plasma ad Cellular Determinants of Cardiovascular Disease at the Time of COVID 19 (CardioCovid)	NA	NCT05745753	2023
NA	Observational	Cardiovascular Diseases	104219	NA	Risk of Cardiovascular Disease in Canada and Burden of Health Behaviours: Development of Population-based Risk Algorithms	NA	NCT02267447	2017

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