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Nano-formulation Based Drug Delivery and its Advancement for Cardiovascular Systems

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ABSTRACT

The world's leading causes of mortality and morbidity are cardiovascular diseases (CVDs). The early and long-term effects on patients vary widely despite recent advancements in the management of CVDs, particularly given the difficulties in diagnosing and treating CVDs now. The use of nanoparticles combined formulation to treat illnesses and improve health is made possible by nanotechnology. The dispersion of therapeutic substances in the body is changed by the site-specific, goal-oriented delivery and controlled drug release of precision medicines offered by nanoparticle-based "drug delivery systems (DDS)". Nanoparticles made of metal, lipid, and polymer are the perfect substances to use in cardiovascular treatments. Significantly, in recent years, researchers have found that nanotechnologies may be useful for treating chronic illnesses, particularly cardiovascular disease (CVD). Various approaches to using nanoparticles and their formulation as drug delivery vehicles in CVDs have been put forth; however, disagreements over the choice of nanomaterials and their formulation are delaying their practical application. In order to provide a safer and more effective method for treating CVD, this review concentrates on a nano-based formulation for drug delivery and its therapeutic function.

KEYWORDS: *Nano-Formulation, Cardiovascular Disease, Nanoparticles, Drug Delivery*

1. INTRODUCTION

One out of every four fatalities in the United States is attributable to cardiovascular illnesses (CVD), which include issues with the heart and blood vessels. The main risk factor for CVD is elevated blood pressure, or hypertension, which is frequently disregarded because it is typically clinically asymptomatic. Heart failure, atherosclerosis, arrhythmia, coronary heart disease, peripheral arterial disease, myocardial infarction (MI), deep vein thrombosis, and inflammatory heart disease are all examples of cardiovascular disease (CVD), which is the leading cause of death worldwide. The "World Heart Federation" estimates that CVDs result in "17.3 million" fatalities each year (Prasad et al.,2018). Natural products display exceptional "chemical and biological capabilities with macromolecular specificity," "chemical variety," and "lower toxicity," among other noteworthy traits (Kostarelos et al.,2019). Nanotechnology is an interdisciplinary field of study that includes electronics, biology, and medicine. Paul Ehrlich, a well-known German bacteriologist, proposed the idea of the "magic bullet" at the end of the 19th century. Modern nanotechnologies have facilitated the creation of next-generation drug inventions, such as target-based drug discovery and delivery, as well as the capacity to anticipate the molecular interactions of drugs (Farjadian et al., 2019). To enhance delivery to the heart and vascular system and overcome biological barriers, cardiovascular nanomedicine research has traditionally focused on the fabrication of nanoscale carriers composed of multiple functional elements (nanoparticle

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

core, therapeutic payload, and targeting moiety). Drexler et al. (2019) suggested that cardiovascular nanomedicine, however, has lately gone "beyond designer nanocarriers targeting certain body areas to include biosensors, actuators, and devices that can be integrated at various points of medical care" for better post-operative pain management.

In previous decades, nano-formulation, one of the most active and rapidly developing disciplines of nanotechnology research, has attracted international attention. Drug delivery systems based on nanoformulations have sizes, shapes, structures, and transport functions that are determined by the properties and synthesis methods of various nanomaterials, allowing for the construction and production of ideal nanocarriers (Drexler et al.,2019). Drugs are precisely delivered to atherosclerotic plaques using nanoparticles (NPs), which have improved permeability and retention effects. This is more effective therapeutically and harms tissue less (Preitas,2019). Additionally, nano-formulation can lengthen the duration of drug action, enhance the bioavailability, actively or passively target, lower drug resistance, and minimise negative drug reactions while also improving "local and systematic delivery to arteries and reducing the inflammatory or angiogenic response after intravascular intervention" (Kostarelos et al.,2019). Describe the difficulties of nano-drug delivery systems in clinical applications as well as the advancement of nanoparticles as drug carriers in the treatment of cardiovascular diseases, as shown in Figure 1. More focus is given to "NP-directed therapy" for "atherosclerosis and its concomitant effects," including "arrhythmia," "ventricular remodelling," "MI," and "myocardial ischemia-reperfusion (IRI)" damage, due to their crucial significance as cardiovascular diseases. Nanoformulation-based DDS alter the "biodistribution of therapeutic substances through site-specific, target-oriented administration and controlled drug release of precise treatments." Nanotechnology in terms of nano-based formulations that can be used in therapies for cardiovascular disease by lengthening systemic agent circulation time, decreasing off-target cytotoxicity of drugs, enhancing drug solubility, lowering dosage requirements, fusing diagnostic and therapeutic agents to create theragnostic, and promoting agent accumulation at specific sites. In order to provide a safer and more successful approach to the treatment of CVD, this review concentrates on the nano-based formulation for drug delivery and its therapeutic action.

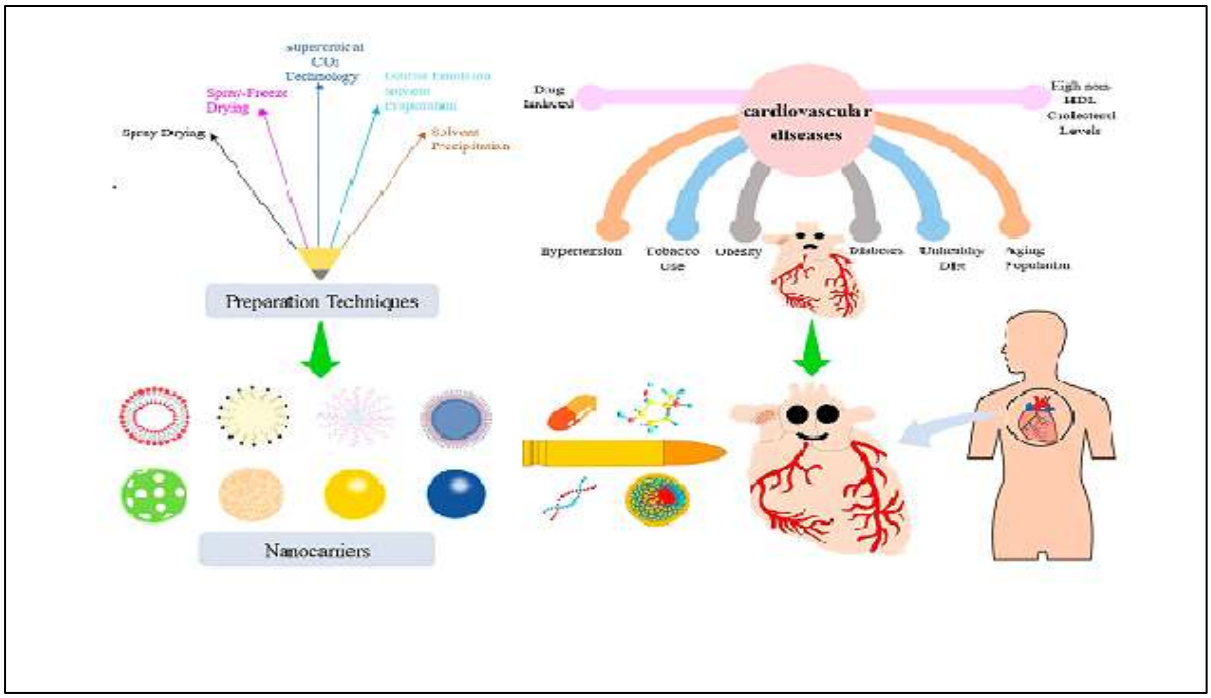

Fig 1: Utilisation of Nanoparticle-mediated DDS for the Treatment of Cardiovascular Disorders **Fangyu et al., (2022)**

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

2. MECHANISMS OF CARDIOVASCULAR DISEASE

Atherosclerosis, which comprises three main stages in its development, is the primary cause of the majority of CVDs. The presence of foam cells indicates the initial stage of atherosclerosis. The endothelial cells that make up the capillary walls become dysregulated when unpleasant internal and external environmental conditions are aroused, which raises permeability to macromolecules, according to a study by (Mali et al.,2018). The vascular wall is more likely to be breached by low-density lipoprotein (LDL), which then accumulates nearby and is altered by enzymes and reactive oxygen species to become oxidised LDL (ox-LDL). In the second stage, "vascular smooth muscle cells (VSMCs)" move from the main membrane to the intima and start to multiply, changing from a contractile to a synthetic character. This is triggered by immune cells and inflammatory stimuli. Certain VSMCs secrete chemicals from the extracellular matrix, such as collagen, to form fibrous caps that lead to the development of neointima and vascular remodelling. Some VSMCs take up "ox-LDL" and change into foam cells that are produced from VSMCs. Over time, foam cells aggregate and undergo programmed cell death or pathological cell death, leading to the formation of neurotic cores. The ultimate progression of atherosclerosis can manifest as either "thrombosis" or "plaque rupture." At this stage, VSMCs secrete matric "metalloproteinases," which degrade extracellular collagen, causing the fibrous cap to shrink. Moreover, persistent "oxidative stress promotes the necrotic core's continued growth" (Jing et al., 2019). Unstable plaque rupture and intravascular thrombosis can be caused by the "development of new blood vessels" and the proliferation of the necrotic core. When persistent arterial spasms persist, "the dreaded lumen occlusions" eventually occur (Jafisco et al., 2019).

3. NANOPARTICLES

Usually, organic or inorganic nanoparticles (NPs) have at least one dimension smaller than 100 nm (Choi & Han.,2018). While organic NPs are made of various biodegradable materials such as lipids, liposomes or micelles, proteins, dendrimers, polymeric vesicles, or hyaluronic acid, inorganic NPs are composed of a variety of minutely scaled structures such as quantum dots, mesoporous silicon, graphene, carbon nanotubes, or metal oxides (Rosler, 2017). Metal-organic frameworks, also known as porous coordination polymers or very porous and crystalline polymers, are composed of organic ligands and metal ions or metal clusters via coordinate bonds (Davoodi et al.,2018). For instance, NPs were used to transport the drug rapamycin by donning a skin constructed of the membranes of their own red or platelet blood cells. It is generally known that biomimetic NPs can inhibit macrophage phagocytosis in vitro and that their therapeutic effectiveness in vivo outperforms that of the more prevalent nano-drug delivery method (Jones et al.,2019). Today, the most effective and complete nanomaterials for the diagnosis and treatment of CVDs include liposomes, micelles, dendrimers, polymer NPs, and metal NPs (Figure 2).

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

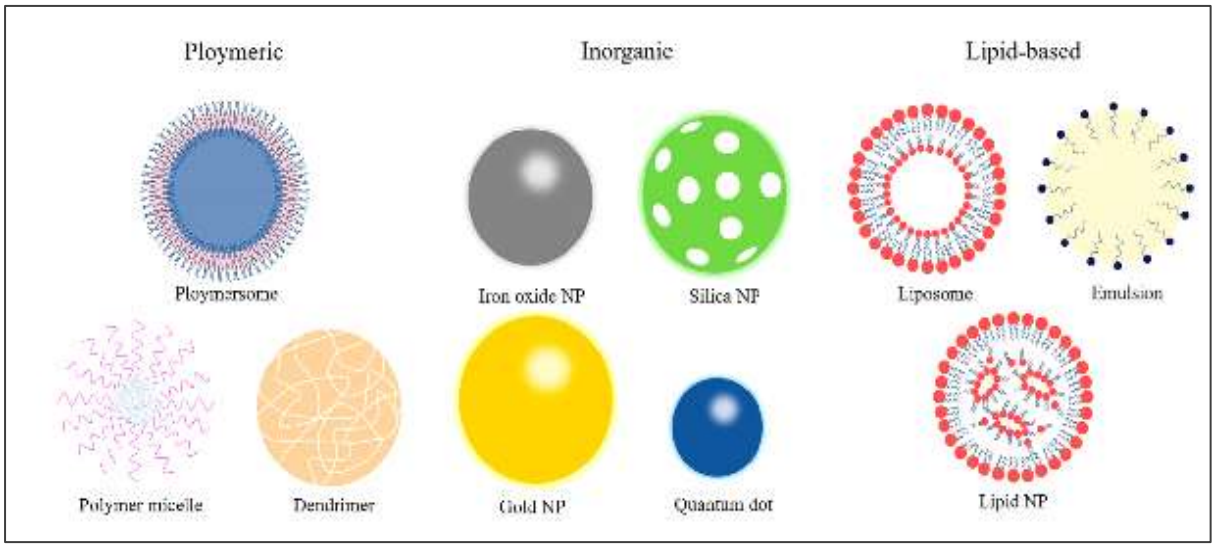

Figure 2: Different types of Nanoparticles (Fangyu et al., 2022)

4. DRUG DELIVERY SYSTEMS(DDS) BASED ON NANO

Recent major improvements in drug delivery systems have made it possible to administer therapeutic agents or naturally derived active substances to their target location for the treatment of a variety of ailments. Although a number of drug delivery techniques have been employed successfully in recent years, some problems still need to be fixed, and state-of-the-art technology needs to be developed in order for pharmaceuticals to be successfully delivered to their target sites. So, the enhanced method of drug distribution will be made possible by the nano-based DDS, which is currently the subject of research.

Davoodi et al. (2018) used "nanoscale materials, such as biocompatible nanoparticles and nanorobots, for diverse applications such as diagnostic, delivery, sensory, or actuation reasons in a living organism." According to research by Anselmo and Mitragotri from 2016, "drugs with very low solubility have a number of biopharmaceutical delivery issues, including limited bioaccessibility after oral intake," less capacity for "diffusion into the outer membrane," a need for "higher dosages for intravenous intake," and unfavourable "side effects prior to conventionally formulated vaccination process." But, by combining nanotechnology techniques into the pharmaceutical delivery system, all of these limitations might be lifted.

Owing to its potential advantages, such as the "ability to modulate essential drug properties," "including solubility," "drug release kinetics," "diffusivity," "bioavailability," and "immunogenicity," nanoscale drug design has garnered significant research attention and emerged as the most advanced strategy in the field of nanoparticle applications. Hence, more convenient administration methods, "less toxicity, fewer side effects, enhanced biodistribution, and a prolonged medication life cycle" may all result from this (Ibrahim et al., 2017). The DDS is either directed towards a specific location or is meant for the controlled release of medicinal chemicals at that location. They are created through self-assembly, in which building blocks assemble themselves into clearly defined structures or patterns (Tran et al., 2017). Jindal (2017) asserts that nanostructures have the capacity to disperse drugs both passively and aggressively. With the former, the hydrophobic effect is mostly utilised to incorporate medications into the interior cavity of the structure. Due to its low concentration and hydrophobic environment, the medication is released in the right amount when the components for the nanostructure are guided to specified locations. In contrast, Hoshyan et al.'s investigation in 2016

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

revealed that a direct conjugation of the drug to the carrier nanostructure material is imperative for efficient drug delivery. In this approach, the timing of drug release plays a critical role, as a deviation from the optimal timing may lead to an inadequate drug concentration at the target site or a premature separation of the drug from the carrier. Conversely, adhering to precise timing enhances the bioactivity and efficacy of the drug. Targeting of pharmaceuticals is a vital aspect of drug delivery, which utilises nanomaterials or nanoformulations as drug delivery vehicles to achieve active or passive targeting strategies (Hotze et al., 2016). Active targeting is achieved by incorporating moieties, such as antibodies and peptides, into DDS, enabling specific binding to receptor structures present at the intended site. In contrast, passive targeting relies on factors such as "pH," "temperature," "molecular site," and "shape," which facilitate the affinity or binding of the drug-carrier complex to the target site during its circulation through the bloodstream. The receptors on cell membranes, lipids in the cell membrane, as well as antigens or proteins on cell surfaces represent the primary targets of drug delivery systems in vivo.

5. NANO-FORMULATIONS IN CARDIOVASCULAR DISEASES (CVDS)

With 17.7 million fatalities reported in 2015 and an estimated increase to 23.6 million in 2030, CVDs are regarded as the leading cause of disability and death globally (Choi et al., 2018). In Europe, cardiovascular diseases (CVDs) account for 3.9 million deaths annually, or 45% of all deaths (Jafisco et al.,2019). With 2 million persons affected, CVDs are the second leading cause of death in the United Kingdom (Rosler et al.,2017). Mali et al. (2019) research demonstrated that congenital cardiac disease, for example, is a major cause of CVDs, while diabetes and hypertension are secondary causes. Despite improvements in the management of CVDs, several conditions, including hypertension, atherosclerosis, thrombosis, cardiovascular, inflammatory disorders such as myocarditis and endocarditis, stroke, "myocardial infarction (MI)," and "pulmonary arterial hypertension (PAH)," are still not well controlled. Cardiovascular diseases (CVDs) face several challenges that impede their effective prevention and treatment, including (i) inadequate identification of gaps between prevention and treatment of CVDs; (ii) insufficient understanding and management of risk factors; (iii) limited recognition and addressing of individual patient needs; (iv) inadequate CVD diagnosis; (v) limited access to first-line treatments; (vi) inadequate recognition and utilisation of advanced CVD treatments; and (vii) inadequate provision of supportive care to patients. By overcoming these obstacles, Tang (2017) predicts that new technologies, diagnostic methods, and the use of contemporary technology will all contribute to the improvement of CVD diagnosis and treatment. To enhance the outcomes of patients with CVD, a number of major issues and obstacles related to drug delivery methods must be addressed. The first issue is innovation, where researchers must comprehend the fundamental molecular processes underlying the emergence of CVD. It is possible to choose appropriate drug delivery methods by comprehending these mechanisms. Second, the tailored therapeutic option was created since different patients would need various delivery methods. More than ever, it is obvious that every patient has unique risk factors, genetic makeup, environmental influences on lifestyle, and disease burden. To enhance the clinical decision-making process, extensive diagnostics, including imaging, DNA sequencing, and proteomics, must be used.

In recent years, various varieties of nanomedicine have been developed and can be used for tasks. The carrier formulation to utilise depends on a number of variables, including "the drug's inherent chemical properties (for example, solubility (logS, logP, and logD7.4)," "molecular weight," and the "therapeutic objective" (Soares et al., 2018). As an illustration, when the primary objective of a drug compound is to treat peripheral organ systems, the formulation strategy aims to protect the compound

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

from metabolism. Alternatively, in other cases, nano-formulation can facilitate the dispersion of the drug to multiple target organs.

For small organic substances, formulations such as “liposomes,” “nanoparticles,” “nanocapsules,” “nanotubes,” “polymeric conjugates,” and “micelles” are employed (Stater et al., 2012). Every one of these nanoformulations has been used to treat different illness states, with cancer and “central nervous system (CNS)” problems possibly being the most common (Anselimo et al., 2015). Other fields like orthopaedics and cardiovascular delivery are also developing as novel delivery-rich areas.

The conventional strategy for developing nanoformulations for small molecule drugs entails encapsulating the therapeutic agent within a polymeric carrier system. This approach leverages the hydrophobic interactions between the lipophilic drug molecules and the polymeric material to facilitate self-assembly and create a protective barrier between the drug compound and the aqueous surroundings. Alternative techniques involve conjugating the drug compound to the polymeric material or forming a complex with the carrier system using ligands such as “glutathione” or “folate” (Tran, 2017). In their study, Stater et al. (2021) demonstrated the addition of a targeting system, which may be a complex of medicines or antibodies “[CGS 21680, N-(methylsulfonyl)-2-(2propynyloxy)-benzenehexanamide,” “trans-4-[3-adamantan-1ylureido]cyclohexyloxy]”. The nanoparticle was coated with benzoic acid, “N-methylsulfonyl-12,12-dibromododec-11-enamide, rosiglitazone, and T0070907].” An examination of the development of clinical trials involving nanoformulations since 2000 indicates a gradual increase starting in 2007, with the highest number of nanoformulations entering clinical trials observed between 2013 and 2015 (Stater et al., 2021). To date, the US “Food and Drug Administration (FDA)” has approved 52 nanomedicine formulations, while the “European Medicines Agency (EMA)” has approved 34 (with a single nano-formulation approved solely in the Netherlands) (Stater et al., 2021). The majority of the nanomedicine formulations used to treat CVD are shown in Figure 3.

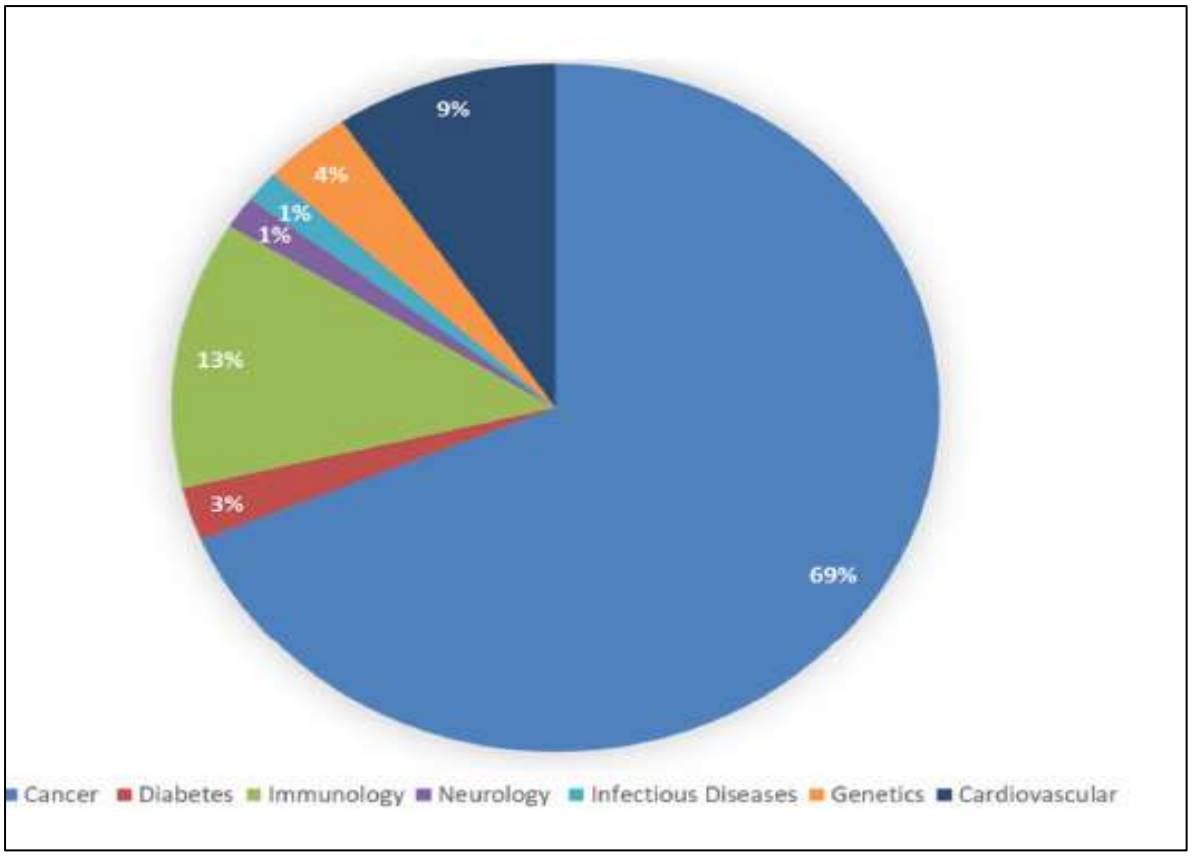

Figure 3: Percentage of nanomaterials used in each medical speciality (Nura et al., 2022)

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

6. NANOTECHNOLOGY BASED ON NATURAL PRODUCTS AND DRUG DELIVERY

According to a WHO report, traditional medicine in poor nations provides for the fundamental medical needs of 80% of the population or more (Suk et al.,2016). The focus of the contemporary scientific study is on identifying bioactive substances, delving into their chemistry, and assessing the pharmacological potential of various plant species. The objective is to create novel active ingredients with fewer negative side effects than those now in use (Ahsan et al., 2018).

Plants still have a tonne of resources that can be used tremendously to create new, powerful medicines. They have long been acknowledged as important sources of natural chemicals with the potential as medicines. Yet, as they come from living things whose metabolite composition might change in response to stress, the finding of active chemicals derived from natural sources is rife with difficulties.

To produce synthetic substances, the pharmaceutical industries have decided to pool their resources (IIinskaya et al.,2015)

Many natural chemicals' makeup and activities have already been investigated and established. The bioactive molecules present in plants include, among others, "alkaloids," "flavonoids," "tannins," "terpenes," "saponins," "steroids," and "phenolic compounds" (Mohammad, 2022). Unfortunately, these compounds often have low absorption rates because their large molecular sizes prevent them from passing through lipid membranes, which reduces their bioavailability and effectiveness (Tang et al.,2018). These compounds also have high systemic clearance, which necessitates frequent administration and/or high doses and reduces the therapeutic efficacy of the medicine. The scientific development of nanotechnology has the potential to change the design of formulations based on natural products by bringing instruments capable of resolving the issues previously mentioned that prevent the widespread use of these substances in nanomedicine (Agarwal et al.,2019). According to Manda (2021), the materials made from natural products may be divided into two groups: those that are mostly employed in the synthesis process and those that are released in specific regions to cure a range of illnesses. The majority of research is focused on creating cures for the disease because cancer is currently the leading cause of death worldwide (Hoshyar et al.,2016). The global market for plant-derived pharmaceuticals will expand from "$29.4 billion in 2017 to around $39.6 billion in 2022," with a "compound annual growth rate (CAGR)" of "6.15%" throughout this time period, according to Herman, (2021) report (BCC-RESEARCH). Some of the nanostructure-based products discussed in this section have previously received FDA approval. Information on FDA-approved nanotechnology-based products has been supplied by (Saeidienik et al.,2018).

7. FUTURE OF NANOTECHNOLOGY-BASED NANO FORMULATION AND DDS

The field of nanoformulations represents one of the most captivating domains of research in contemporary times. Numerous clinical trials and extensive research carried out in this area over the last two decades have resulted in the submission of around 1500 patents. Undoubtedly, nanomedicine and nano-drug delivery systems are at the forefront of current and future trends in research and development that will likely continue to dominate this field for decades to come.

This is due to the fact that these methods employ various nanoparticle kinds to precisely deliver medication to the places that need it, such as those impacted by cardiovascular disease, without interfering with the physiology of healthy cells.

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

The true impact of nano-formulation and drug delivery systems on the healthcare system, especially in cardiac therapy/diagnosis, is still quite limited, despite the widespread recognition of their future potential. This is because the industry has only recently undergone two decades of serious study and is still mostly undiscovered. Despite the significant advances made, there remain several fundamental characteristics that remain unknown. One such critical aspect is identifying the fundamental markers of unhealthy tissues, such as essential biological markers that enable precise targeting while preserving normal cellular function. This represents a vital area for future research. As our understanding of diseases continues to expand, particularly at the molecular level or those that exhibit nanomaterial-subcellular scale equivalent marker identification, the use of drugs based on nanotechnology will continue to progress, paving the way for innovative therapeutic and diagnostic options. The use of treatment systems based on nanoparticles is anticipated to bring about a new revolution in the management of CVDs as many disciplines are developing.

8. CONCLUSION

In conclusion, the review explores that nanotechnology in the form of nano-formulation has distinct benefits and possibilities and offers novel theories, strategies, and techniques for the detection and treatment of cardiovascular diseases (CVDs), as well as a promising future for doctors. Contrary to conventional drug delivery methods, nano-drug delivery involves the introduction of different ligands into corresponding nanocarriers in accordance with distinct pathogenic mechanisms and treatment approaches to selectively target the lesion site. By increasing medicine concentration and focusing on the cardiovascular region, this strategy more efficiently enhances myocardial blood flow. For the targeted and extended delivery of innovative therapies, including biological and chemical molecules, a number of unique technologies have been created. The practice of administering medications to the cardiovascular system with precise targeting has a lot of promise and advantages. The nano-formulation is a new technology in biology and medicine. They have a number of physicochemical and biological characteristics because of their size, shape, and surface, which make them a good starting point for alternative, non-traditional therapies. In order to go from the lab to the medicine market, a nano-formulation must take into account a number of other elements. They require a thorough examination of the chemical and biological properties of nanoformulations, the establishment of the requisite moral standards and other legal requirements, and estimations of the market’s size, costs, and stage of commercialisation. Collaboration with pharmaceutical companies could facilitate the rapid and successful translation of preclinical research findings into novel precision medicine treatments.

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