PROJECT REPORT

A review on

"Nano-particle approaches for the treatment in atherosclerosis"

A dissertation submitted to the Department of Pharmacy, Daffodil International University, slightly fulfills the needs for the Bachelor of Pharmacy degree (B. Pharm).

Submitted To

The Department of Pharmacy,

Faculty of Allied Health Sciences,

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In the partial fulfillment of the requirements for the degree of Bachelor of Pharmacy

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APPROVAL

This project **"A review on Nano-particle approaches for the treatment in atherosclerosis"**, submitted to the Department of Pharmacy, Faculty of Allied Health Sciences, Daffodil International University, has been accepted as satisfactory for the partial fulfillment of the requirements for the degree of Bachelor of Pharmacy and approved as to its style and contents.

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DISSERTATION ACCEPTANCE FORM DAFFODIL INTERNATIONAL UNIVERSITY, DEPARTMENT OF PHARMACY.

This is to certify that the results of the investigation that are embodied in this project are original and have not been submitted before in substance for any degree of this University. The entire present work submitted as a project work for the partial fulfillment of the degree of Bachelor of pharmacy, is based on the result of author's (ID: 183-29-149) own investigation.

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DECLARATION

I hereby declare that, this project report is done by me under the supervision of Dr. Sharifa Sultana, Associate Professor, Department of Pharmacy, Faculty of Allied Health Science, Daffodil International University, impartial fulfillment of the requirement for the degree of Bachelor of Pharmacy. I am declaring that this project is my original work. I am also declaring that neither this project nor any part thereof has been submitted elsewhere for the award of Bachelor or any degree.

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ABSTRACT

One of the key factors of atherogenesis is chronic inflammation. Traditional atherosclerosis treatments are not particularly effective at reducing inflammation caused by atherosclerosis. The majority of these medications are non-selective, anti-inflammatory, and immunosuppressive, which restricts their systemic administration. They also have negative side effects and very little anti-atherosclerotic activity. To selectively administer therapeutic medicines to atherosclerotic plaques, new methods utilizing nanoparticles have been researched. Although appealing, the utilization of drug delivery technologies such polymeric nanoparticles, liposomes, and carbon nanotubes has several drawbacks. For instance, depending on the pathophysiological processes of the illnesses, nanoparticles may change the drug's kinetics. Pathophysiological updates supporting the use of nanoparticles in many experimental models to lower inflammation and maybe stop atherogenesis. High-quality atherosclerotic plaque viewing is made possible by non-invasive molecular imaging technology. Selective nanotechnology imaging techniques can identify the distinct epitopes produced on the macrophage surfaces. Selected nanoparticles were developed to enhance the transport of image processing agents to proinflammatory macrophages in atherosclerotic plaques, enhancing imaging contrast. In MRI iron-oxide and Gd-containing nanoparticles provide high resulation imaging. Macrophages(53%) are mostly targeted in atherosclerosis therapy on the other hands lipid-based(28%) nanoparticles are mostly used.

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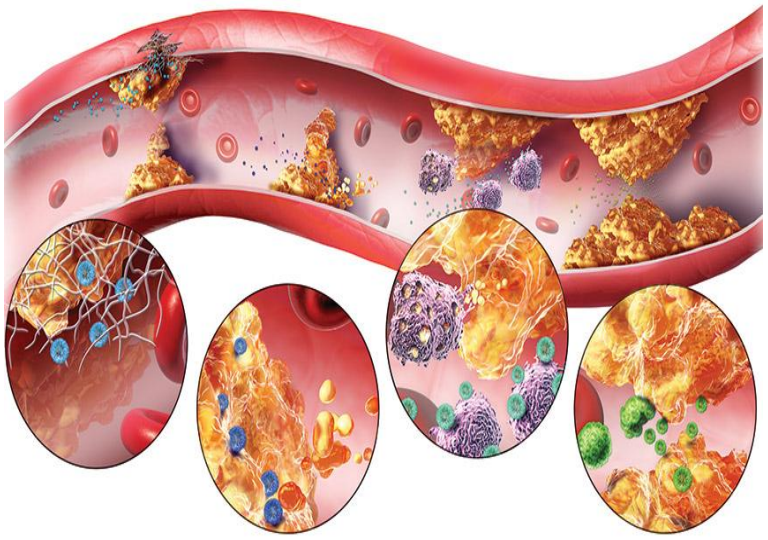
Chapter One

Introduction



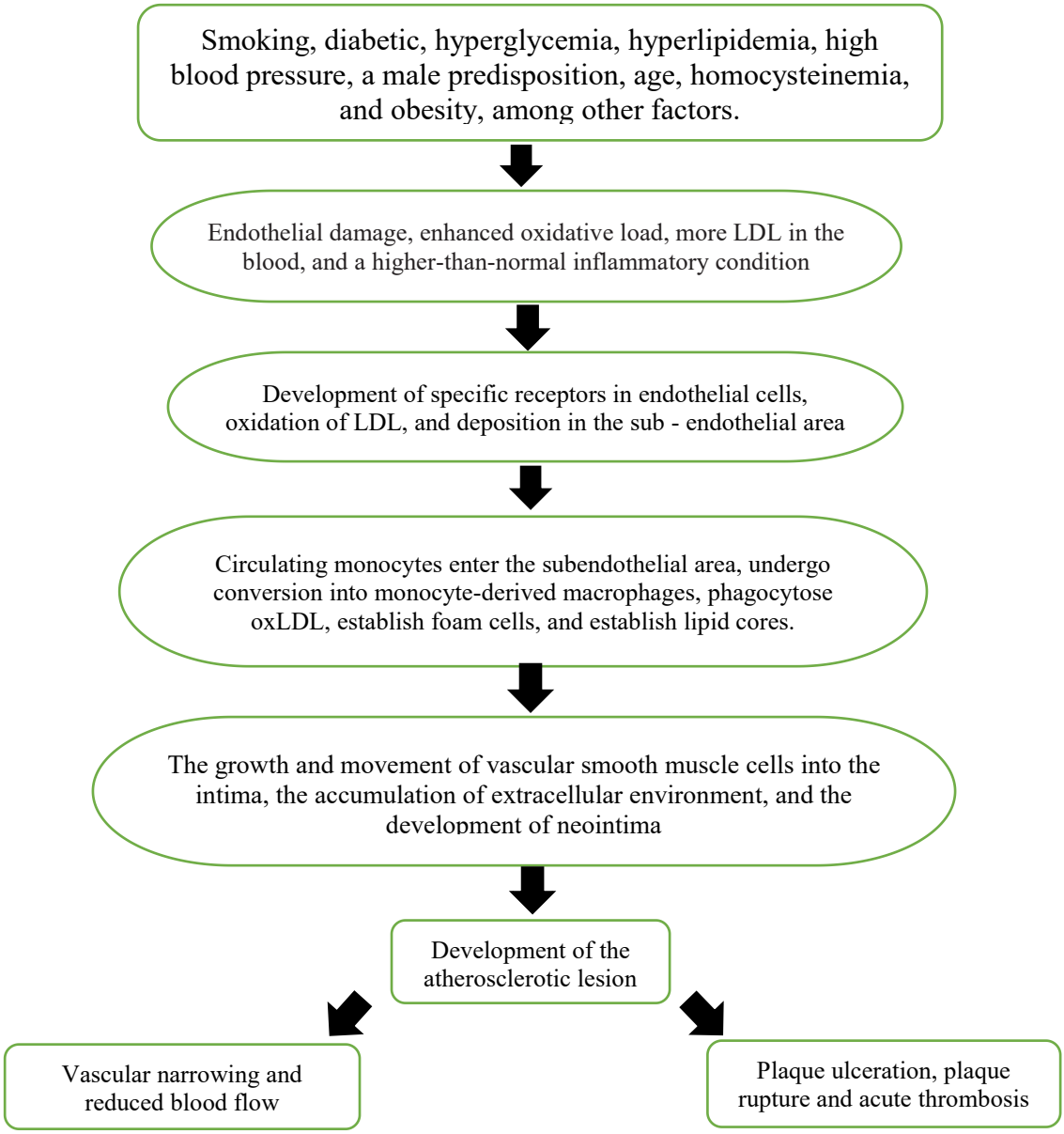
1. Introduction

1.1. General Information

Cardiovascular diseases (CVD) are thought to be the twenty-first century's pandemic. Cardiovascular disease, cerebrovascular disease, and peripheral vascular disorders are all included in the cardiovascular spectral region [1]. These place a heavy load on healthcare systems across the world, primarily in emerging nations. According to the World Health Organization (WHO), eighteen million people worldwide pass away from CVD per year. Despite improvements in coronary and pharmacological development, by 2030, CVD will be the leading cause of 24 million deaths worldwide [1]. A moderate inflammatory response inside the arterial wall triggers arteriosclerosis, which progresses across a number of stages to eventually create atherosclerotic plaques [2,3]. It has a direct impact on the vessel's intima, or inner lining, and is linked to lipid and cholesterol buildup as well as inflamed tissue invasion. With greater understanding of its pathogenesis, The explanation for atherogenesis has changed throughout time. Inflammatory cell infiltration results from a compensating reaction brought on by endothelial damage. In addition, the initial step that triggers atherogenesis is indeed the persistence of low-density lipoprotein (LDL) as well as the involvement of the matrix in the subendothelial region. The key component of atherosclerosis is oxidative LDL (oxLDL). It functions like an effective chemoattractant for circulatory mononuclear cells. By entering the subendothelial region, some inflammatory cells take on the phenotype of phagocytosis and form cholesterol-ester-rich mast cells by absorbing oxLDL through surfactant protein ion channels [3]. Atherogenic plaques are formed gradually when established lesions build up and might develop medically as a result of issues associated with the plaques. Atherosclerotic plaque growth can result in a vessel's lumen gradually becoming smaller until it is completely blocked. Pathological changes of such prolonged development are brought on by an imbalance between the amount of oxygen delivered to and the amount of oxygen required by the organs that are subjected to impeded blood flow. Angina brought on by physical activity, for instance, is frequently reported by people who have stable CAD. Localized responses to pro-inflammatory growth factors and proteinases can also make atherosclerotic plaques more and more unsustainable, eventually rupturing or ulcerating. Due to its significant pro-coagulant properties, the visible lipid core puts the vascular lumina at risk for acute thrombosis.

It is primarily dependent on the arterial region affected by the illness; this may manifest initially as severe circulatory abnormalities such as acute myocardial infarction (AMI) or stroke [4]. Due to the multifaceted nature of atherosclerosis, several methods of both diagnosis and therapy have been tried. The creation of innovative drug delivery systems (DDSs) with the capacity to locate certain organs or cellular components is in high demand. Recent developments in nanotechnology have opened up new perspectives on preventing disease and made it feasible to manage atherosclerosis in alternative ways.

Both established and emerging risk factors



A mechanism for the origins of atherosclerosis.

Nanoparticles are very small particles with diameters measured in nanometers (1 nm = 10^{-9} meter). In addition to being produced by human activity, nanoparticles also occur in the natural world. Manufactured nanoparticles may have practical uses in a number of fields, including medical, chemistry, biochemistry, and environmental remediation. This is because they are submicroscopic in size and have unique material properties.

1.2. Basic concept of nanoparticle drug delivery systems

Although the dynamic range might span the entire nm scale, nanoparticles are defined as particles having a diameter between 1 and 100 nm. A drug delivery system (DDS) should be between 10 and 100 nm in size. They may be divided into a number of groups based on their form, physical and chemical characteristics (such as pH sensitivity, saturation magnetization, and stealthy nanoparticles), and the substances employed in their manufacture (natural, synthetic, hybrid, or gold nanoparticles). Their tiny size bestows a number of useful physical, ocular, structural, and biochemical capabilities that are entirely distinct from those of materials found in the universe —. One such instance is their capacity to travel freely throughout the bloodstream and focus on a specific area without being identified as "intruders" by the immune system.Through subsequent surface property changes, they can, for instance, interfere with and have an impact on the physiology of cells and tissues. By adding nanoparticles to bioactive substances or medications that may have poor pharmacokinetics or be harmful to living organisms, DDS enables the smooth delivery of therapeutic agents. These methods can be utilized to accurately manage the pharmacokinetics, absorption, targeted therapies, non-specific toxicities, and immunogenicity of a drug's effects. DDS is used more frequently in a multimodal manner and offers a number of advantages over traditional disease therapies [5]. The optimal design for a functional DDS should resemble its in vivo physiological counterpart and allow for either regional or systemic delivery. Additional modifications may be performed to the hydrophilicity, lipophilicity, DDS to drug binding, bioavailability, biocompatibility, and form [6] according to the particular application.

1.3. Diversity of nanoparticles

Nanoparticles (NPs) are defined by the International Union of Pure and Applied Chemistry (IUPAC) as particles of any shape that range in size from one to one hundred nanometers (nm); however, the word is frequently used to describe substances that are up to several hundred nm in size. The ability of NPs to enhance the effectiveness of therapy and diagnostics as well as to offer a greater understanding of plaque biology and pathophysiology seems to be the core of their capabilities for managing atherosclerosis. The summary that follows demonstrates the variety of nanomaterials covered in this review and gives readers some context.

1.3.1. Polymeric nanoparticles

Polymers make up polymeric NPs, which are generally in the 10–100 nanometer size range. Poly(d,l-lactic-coglycolic acid) NPs are among them and have received the most attention from researchers studying polymeric NPs for the treatment of atherosclerosis [7-13] due to their excellent biocompatibility and biodegradability. In the review, several varieties of polymeric NPs were discussed, such as polyglucose [14], which has significant potential for imaging and treating plaque macrophages. For the purpose of approaching and/or selective formation in plaque phagocytosis, the outer layer of polymeric nanoparticles can be derivatized with a variety of specific ligands (such as S2P peptide and RGD peptide) or biomimetic materials (such as erythrocyte membrane, microvesicles, and extracellular matrix components) [15–17]. Another type of polymer, like polyethylene glycol, may be added to prolong their blood circulation.

1.3.2. HDL-like nanoparticles

Phospholipids and apolipoprotein A-I make up HDL, an endogenous lipidic NP with a size range of 7 nm to 13 nm (apoA-I). Through the mechanism of cholesterol absorption, HDL may transfer cholesterol from lipid-rich plaque macrophages to the liver. Because it takes time to extract apoA-I from human plasma, several genetic apoA-I 192, 196 variations or recombinant apoA-I 194, 195 were utilized to substitute human plasma apoA-I in order to get reconstituted HDL or HDL-like NPs with comparable neuroprotective properties to those of HDL. As a result, a lot of research

has been done on HDL-like NPs as nanocarriers for the delivery of medicines or cell imaging for the treatment of atherosclerosis [18].

1.3.3. LDL-like nanoparticles

NPs that resemble the makeup of protein-free LDL are called LDL-like NPs, and their sizes range from 18 to 25 nm. For the therapy of atherosclerosis, LDL-like NPs have been widely employed to distribute anti-inflammatory and anti-proliferative medicines because they may be actively overtaken by plaque macrophages via cellular membrane receptors [18].

1.3.4. Inorganic nanoparticles

Inorganic NPs that are made of metal or metallic derivatives and typically vary in size from 6–100 nm, including superparamagnetic iron oxide NPs, Gd complex-containing NPs, Gd inorganic nanoparticles, gold NPs, upconversion NPs, and quantum dots. It is possible to derivatize the outer layer of these nanoparticles with macrophage-targeting ligands (like dextran, osteopontin immune response, macrophage receptor with collagen fibers framework immune response, and annexin V) or the biomimetic substances mentioned above in order to focus on and/or preferentially accumulate in plaque macrophages. According to what is said in the subsection on macrophage-targeted nanosystems for diagnostic testing of atherosclerosis [18], these inorganic nanoparticles can be good imaging reagents for the detection of macrophage-rich plaques at threat of fracture.

1.3.5. Liposomes

Liposomes are circular organelles made up of phospholipid and cholesterol bilayers. The liposomes are around 100 nm. Liposomes feature both hydrophilic and hydrophobic divisions that can be employed to transport a variety of diagnostic reagents or therapy tankers to atherosclerosis macrophages [19-21]. Liposomes, like other nanoparticle systems, may have their surfaces modified with PEG and targeting ligands to extend their sustained release in the bloodstream and aggregation in plaque phagocytic cells.

1.4. Basic understanding of Atherosclerosis

Atherosclerosis is a lipid-fueled, multicenter, immunoinflammatory disorder of the medium- and large-sized vessels. The primary participants in the pathogenesis of this illness are blood vessels, leukocytes, and intimal smooth muscles. Overlaid thrombosis causes the most catastrophic effects of atherosclerosis, such as coronary heart disease.Therefore, the crucial topic is not why atherosclerosis occurs but rather how atherosclerosis, following decades of sluggish progress, eventually turns difficult with luminal thrombosis. Atherosclerosis seems to be a more benign condition if thrombosis-prone plaques could be identified and prevented. Periodontitis is responsible for approximately 76% of all serious cardiac thrombus formation. Men (80%) are more likely than women (60%), on average, to develop cardiac thrombus as a result of plaque formation. Massive lipid-rich cores, a fibrillar cap, numerous macrophages, angiogenesis, adventitial infection, and outward remodeling are the characteristics of ruptured plaques. The most frequent cause of coronary thrombosis is plaque rupture. There are certain pathoanatomical characteristics of ruptured plaques and, consequently, of plaques that are prone to rupture that may be helpful for their identification in vivo by imaging [22]. Atherosclerosis can occur despite the lack of other identifiable risk variables, making higher plasma cholesterol one of the several heart disease risks that is most likely unique in this regard [23]. Symptomatic illness would be uncommon if all people had blood cholesterol levels of 150 mg/dl. Another set of risk factors, including diabetes, high blood pressure, alcohol intake, being a man, and perhaps inflammatory indicators like C-reactive protein and cytokines, appear to hasten a condition that is fueled by atherogenic lipoproteins, the first of which is low-density lipoprotein (LDL). The significant variation in symptomatic manifestation of illness among people with similar overall cholesterol levels supports the importance of risk factors other than cholesterol. When the endothelium in large and medium-sized arteries becomes disorganized, atherosclerotic plaque formation begins [22, 24]. This is caused by cardiac risk variables like prolonged smoking, high blood pressure, and chronic hypercholesterolemia. A key physiopathological component of atherosclerosis is a dysfunctional endothelium, which increases the permeability of cellular components like lipoproteins and the enrollment and buildup of macrophages [22]. By eating low-density lipoproteins (LDLs) that contain apolipoprotein B (APOB), these monocytes ultimately develop into macrophages that

can eventually be converted into foam cells. The initial phase of atherosclerosis is characterized by the persistence of lymphocytes and low-density lipoprotein in the artery wall below the endothelium. Depending on how the inflammation is resolved, the persistence of lymphocytes and lipoproteins either decreases or leads to plaque advancement, cell death, and angiogenesis over a period of several years or decades [25, 26]. The lipid or necrosis core, which contains a significant amount of necrotic cells and lipids, may eventually be present in established atherosclerotic plaques. When an atherosclerotic plaque develops, the artery's lining is altered. It either remodels outside to let blood be pumped to continue reaching distal regions or remodels inside to cause stenosis and so restrict blood circulation, which can result in tissue ischaemia. Atherosclerotic lesions may rupture due to the disintegration of the fibrous cap that surrounds the lipid center due to inflammatory conditions, which may then result in thrombus deformation and diagnostic outcomes [27, 28]. Active inflammation, thin fibrous caps with substantial lipid centers, endothelium denudation with superficial platelet aggregation, fissured plaques, or luminal stenosis greater than 90% are characteristics of lesions that are most likely to rupture [29]. Most acute coronary syndrome-causing occlusions originate from non-stenotic lesions, also known as susceptible plaque, rather than lesions with significant constriction [30]. There would be significant health advantages if people with such rupture-prone plaques were identified and treated before symptoms occurred.

1.5. Nanoparticle targeting in atherosclerosis

The aforementioned approaches and the associated biochemical and biological occurrences offer a variety of options for nanoparticle-based atherosclerotic plaque targeting. Surprisingly, a number of these processes—including hypoxia-induced vascular structures, endothelial dysfunction, transparency of the microcirculation, and the overexpression of binding proteins to aid in cell recruitment—occur in cancers, as the majority of those are inflammation-related. In principle, proactive arterial or tumor targeting is intended to highlight (via synthesized nanoparticles), and random targeting (via improved permeable and passive targeting) can be used to treat cancer.

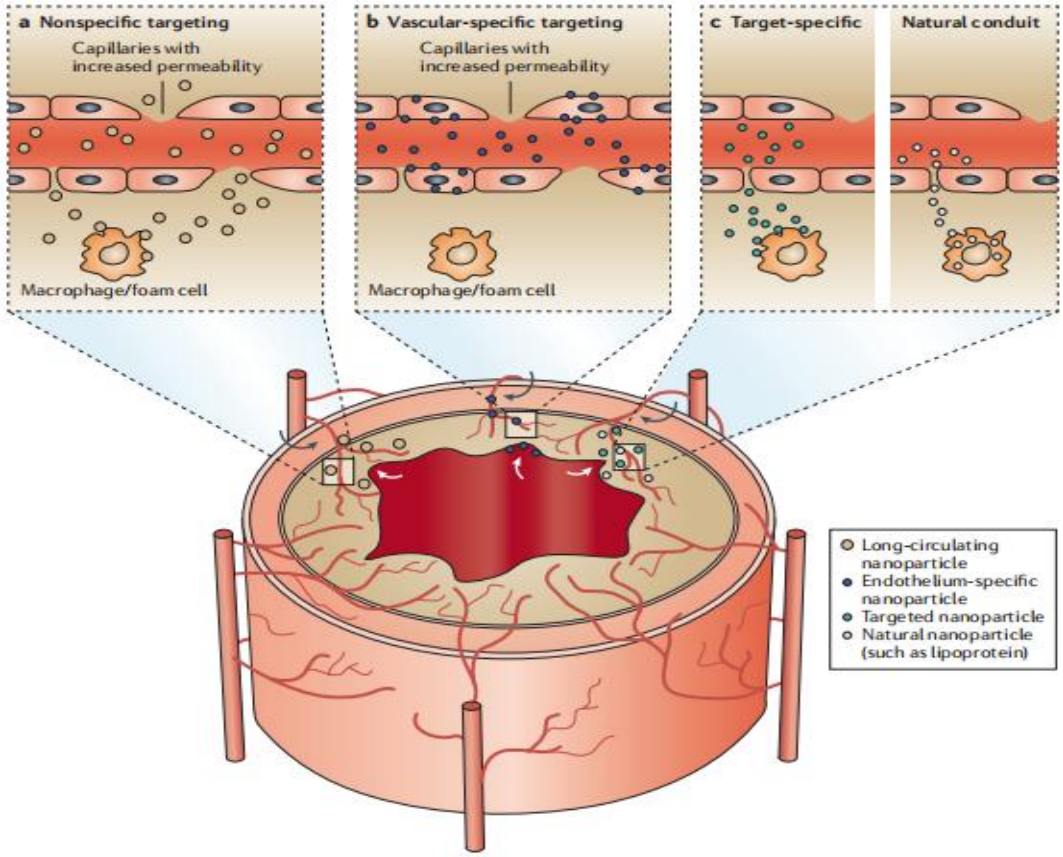


Figure 1 | Approaches for atherosclerotic plaque profiling. The luminal and the vasa vasorum, a connection of tiny microvasculature, provide the bigger capillaries' tiny blood vessels with nourishment. The endothelium becomes more permeable, and the cell-surface transmitters are upregulated in the lesioned vessel wall's vasa vasorum, which experiences angiogenesis growth with neovessels penetrating into the plaque's base. The endothelium on the luminal surface of the plaque is similarly impacted by the increasing permeability and overexpression of receptors. The primary tracking principles can be divided into three categories: poorly defined targeting of the plaque (part a), selective targeting of the vascular system (part b), and selective targeting of plaque elements (part c), such as the extracellular environment or macrophages, through the use of artificial nanomaterials or bonding with a biological connector. Following the relevant lines on the diagram, the targeting of the plaque proceeds via the vasa vasorum and the major lumen at lesioned areas. The circulation of nanoparticles within cells within the plaque may depend to some extent on the targeting approach used [34].

Since this was initially mentioned in 1986, the improved absorption and absorption characteristics have undergone extensive research. Tight (2 nm) endothelial crossings produced by normal cell biology will limit nanoparticle allocation, whereas a corrupt and inefficient endothelium causes large disparities that allow natural polymers and nanoparticles to extravasate from the bloodstream at specific locations and remain

preserved locally due to impaired lymphatic vessel drains. The veracity of this phenomenon has recently come under scrutiny from certain researchers, who have suggested that a separate method might be to blame for the buildup of nanoparticles. Although it hasn't been completely studied in atherosclerosis, poorly defined targeting can be used because of the luminal endothelium's permeability, which was already discussed, in addition to the capillary permeability and porousness of the neovessels of the vasa vasorum. Additionally, after intravenous administration, nanoparticles may link up with circulatory or splenic cells that later go to inflammatory sites. This finding has been observed in the context of inflammation linked to heart attacks and strokes, and it could potentially happen in atherosclerosis [34].

1.6. Nanoparticles for diagnostic imaging.

Molecular imaging technology allows for such viewing of atherosclerotic plaques at a significantly higher risk of breakage or deterioration with high spatial and temporal resolution, meeting the critical necessity for robust and trustworthy image analysis agents to aid in the formation of atherosclerotic medication candidates. Towards that end, the functionalization of nanomaterial-based image processing contrast agents that can primarily affect macrophages in plaques can provide critical insights into plaque physiology, in addition to aiding in quantifying atherosclerosis workload and evaluating therapy effectivity at the atomic, cellular, and functional levels. The most recent non-invasive visualization techniques, such as magnetic resonance imaging, computed tomography, PET, fluorescence imaging, photoacoustic imaging (PAI), and combined imaging modalities, are discussed in this section, along with the correlating nanomaterial-based contrast media, to identify atherosclerotic plaques rich in phagocytosis that are at risk of bursting or deterioration and to evaluate the effectiveness of treatments designed specifically to target these cells (Fig. 2).

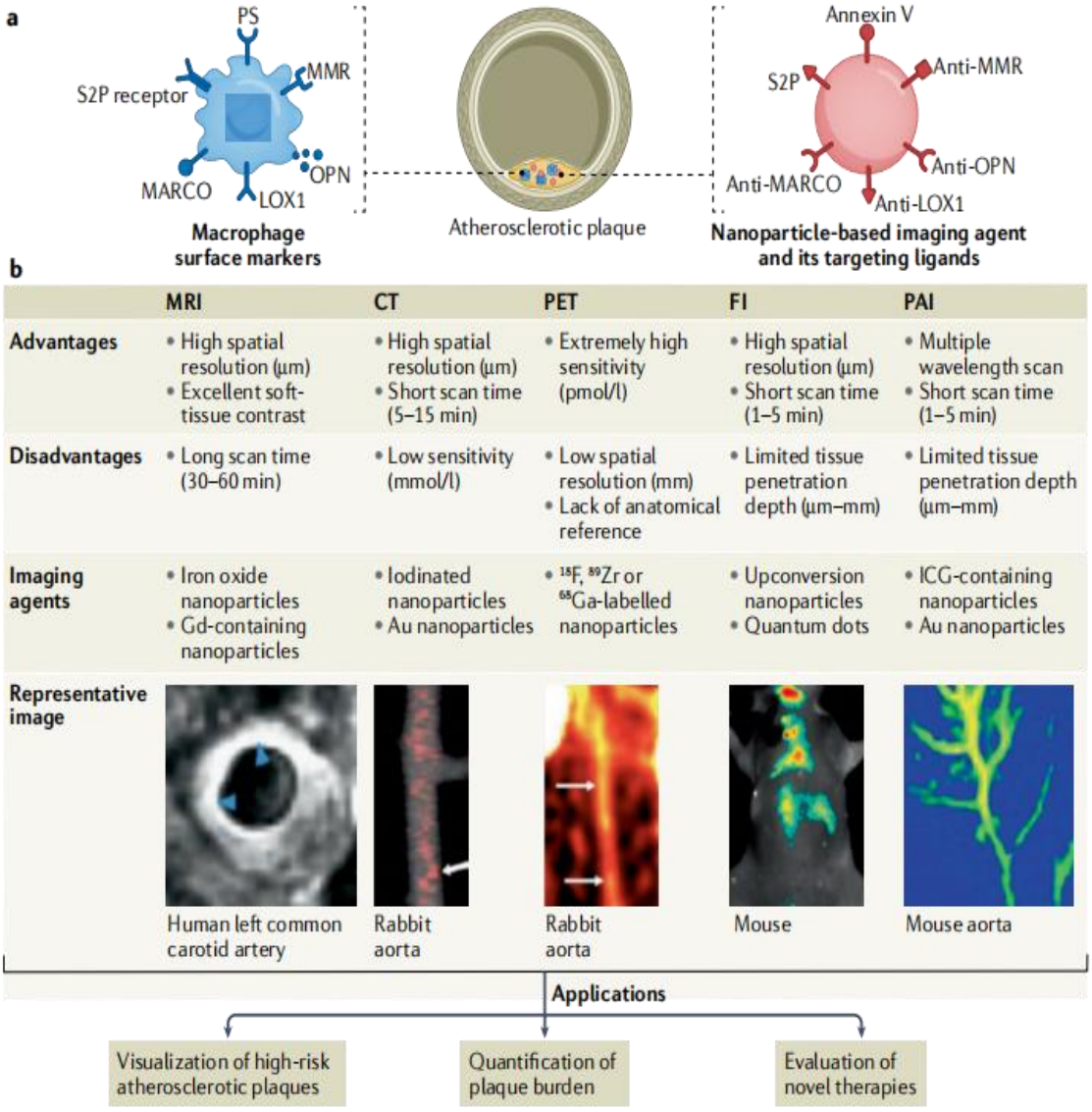


Figure.2| **Nanoplatforms that target macrophages and non-invasive atherosclerosis imaging diagnostics [35].** High-quality atherosclerotic plaque viewing is made possible by non-invasive molecular imaging technology. Selective nanotechnology imaging techniques can identify the distinct epitopes produced on the macrophage surfaces. Selected nanoparticles were developed to enhance the transport of image processing agents to proinflammatory macrophages in atherosclerotic plaques, enhancing imaging contrast. b | Different non-bioimaging techniques, benefits, drawbacks, and the related nanotechnology imaging contrast agents for plaque visualization. The arrows and arrowheads indicate regions with strong substance absorption. Non-intrusive bioimaging enabled by nanoparticles can assist in measuring the incidence of atherosclerosis, assessing the effectiveness of therapeutics at the atomic, cellular, and functional levels, and giving insights into the physiology of atherosclerotic plaques. LOX1 stands for lectin-like oxidized LDL receptor 1. MMR stands for macrophage mannose receptor. OPN stands for osteopontin. PAI stands for photoacoustic imaging. PS stands for phosphatidylserine.

MRI. Superparamagnetic iron oxide nanoparticles (SPIONs), and that have excellent protection profile information and are easily phagocytosed by plaque macrophages, are examples of nanoparticle-based image analysis contrast agents that, when administered systemically, can enhance the difference of plaques in vascular wall by inducing signal attenuation in T2-weighted images [36]. More significantly, coating the surface of the SPIONs with targeting molecules, including dextran [37–39], human ferritin protein cage [40], osteopontin (OPN) [41], or annexin V, can direct the SPIONs to the correlating epitopes on the macrophage surface and promote the accumulation of the SPIONs in susceptible plaques in the arterial or common carotid artery. The effectiveness of lipid-lowering treatment and macrophage-associated inflammatory loads have already been evaluated in clinical settings using SPION-enhanced MRI [38, 42]. It should be noted that the recently created ultra-high-field MRI scanner (10.5 T), which can produce pictures with an unusually high signal-to-noise ratio, could give more thorough information at the cellular and molecular levels for clinical cardiometabolic studies [43]. Due to the low endogenous 19F signal in living cells, 19F MRI has been deemed an appealing technique for the characterization of the plaque inflammatory response in addition to traditional MRI, which captures the phase transition of 1H [44]. More fascinatingly, 19F MRI-generated combinatorial visuals might be utilized to explore numerous clinical indicators of lesional macrophages and to analyze the pathophysiological mechanisms of atherogenesis following delivery of perfluoro-nanoemulsions with discrete chemical changes [45].

CT imaging. CT is an effective technique for monitoring atherosclerotic macrophages in blood vessels in diagnostic conditions because of its improved spatial resolution and quick collection time [46]. Moreover, due to the low specificity of CT, a lethal dose of nanoparticles must be administered to attain detectable image contrast improvements (100 mg of iodine per kg for mice [48] and 250 mg of iodine per kg for rabbits [47]). Iodine-containing nanoparticles with a strong X-ray absorption coefficient are especially beneficial in characterizing pro-inflammatory macrophages in susceptible atherosclerotic plaque in the coronary vessels and the abdomen. Before any further clinical application, a thorough investigation of the possible toxicity of such a large dosage of nanoparticles is required. Considering that problem, the utilization of CT for atherosclerosis identification is growing since results from PET-

CT dual-modality tomography have been widely used as surrogate indicators in many clinical studies [49, 50]. Interestingly, in the last ten years, spectroscopic multicolor CT has clearly demonstrated tremendous potential in that it can differentiate between CT imaging agents and different X-ray absorption spectra and can be used to describe the proportion of improved atherosclerotic plaques susceptible to rupture [51, 52].

Photo-acoustic imaging. According to research from a clinical trial published early in 2020, non-invasive PAI, which integrates the sensitivities of optical coherence tomography with the acoustic resolution and viewing depths of ultrasonography, is a great imaging technique for examining the structure of plaque in the internal carotid artery [53]. When compared to other imaging techniques, using macrophage-targeting PAI nanoprobes for susceptible plaque monitoring may significantly increase the area PAI concentration. For example, IV delivery of Ti_3C_2 nanosheet-indocyanine green nanomaterials that preferentially attack macrophage-derived mast cells increased the PAI comparison of susceptible lesions in the mouse aortic arch [54]. Additionally, the investigation of inflammatory mediator activities of macrophages in rupture-prone plaques in mice was made possible by self-assembled bovine serum albumin-based nanoprobes that had unique PAI sensitivities to glutathione and H_2O_2 [55]. These visualization nanoprobes may help distinguish developed susceptible plaques from clinical symptoms depending on the picture layout and level of data augmentation.

1.7. Nanotherapeutics in atherosclerosis

The development of atherosclerosis is significantly influenced by the pro-inflammatory or anti-inflammatory signal transduction that is activated and suppressed in macrophages. As a result, the excitation or inhibition of macrophage signal transduction, including modifications that support the activities of macrophages in inflammatory resolutions, has clinical promise in the treatment of atherosclerosis [56]. This section reviews and discusses the most recent advancements and breakthroughs in the use of macrophage-targeted drug delivery applications for the therapy of atherosclerosis. Go over the construction and strategic elements of how nanoparticles could effectively convey and create a stable enclosed medicine. Additionally, concentrate on using logically developed nanoparticles to significantly increase the transport effectiveness and therapeutic efficacy of

biomolecules in macrophages. Individual molecules are also presented that may significantly improve macrophages' ability to absorb nanoparticles. Monocyte recruitment, macrophage development and reproduction, faulty efferocytosis, arterial irritation, and cholesterol and oxidized LDL buildup are the main pathogenic mechanisms that contribute to atherosclerosis. These mechanisms have been regarded as intriguing appropriate treatment options for the regression and stability of the arterial wall [57].

1.7.1. Treatments Targeting Inflammation in Atherogenesis

The "standard" physiological and pathological theory holds that lipid buildup inside the vascular wall is the etiology of atherosclerosis. According to current thinking, atherosclerosis is a moderately long-term inflamed disorder in which the innate immunity response is critical to the formation, development, and maintenance of plaques [58]. The pathological changes are brought about by the damage of atherosclerotic lesions, which is then followed by embolism and ultimately artery lumen blockage [59]. Immune cells can produce chemicals that promote inflammation, such as matrix metalloproteinases (MMPs), that can promote plaque degradation and fragility [60, 61]. These messengers can be targeted with specialized anti-inflammatory therapies in both primary and secondary treatment of CV disorders. The current pharmacological approaches for atherosclerosis prevention focus on lowering traditional health issues including smoking, high blood pressure, and lipids. Statins have been demonstrated to block the endogenous production of cholesterol, especially in hepatic cells, although they also have multiple effects [62–64]. For example, such medications can increase endothelial dysfunction, lymphocyte adherence to the arteries, and LDL particle penetration into the vascular endothelium region [65–67]. Statins can thereby reduce cholesterol while also reducing non-specific atherosclerotic irritation. Recent research suggests that more targeted anti-inflammatory medications may be able to target the IL-1 signaling system. Canakinumab, a monoclonal IL-1 inhibitor, was used in a clinical study to suppress this mechanism, and the findings were encouraging [68, 69]. Another anti-inflammatory medication, methotrexate (MTX), that is used to treat autoimmune pathological conditions, may lower the risk of heart problems in those who have chronic inflammation [70, 71]. Additionally, MTX has been demonstrated to have positive impacts on atherosclerosis development

in treated mice [72] and to reduce macrophage migration to the vascular wall. Although it is unclear how MTX could affect the progression of atherosclerosis and its negative consequences, it has been shown that it can inhibit the production of pro-inflammatory mediators and adhesion molecules and affect the endothelium and immune cells [65].

Despite the positive outcomes that anti-inflammatory medications have been linked to, systemic usage of these medications is restricted due to their harmful side effects, including neutropenia, stem cell inhibition, and immunosuppression. According to the stage of the progression of arteriosclerosis, either the excitation or the suppression of the inflammatory reaction may be advantageous or detrimental [73]. It appears that work is required to develop strategies that are advantageous while also controlling the immunological strategy to reduce adverse effects. Of course, the perfect medication should be able to work in a large percentage of the various stages of atherogenesis. Resolvin E1 was said to aid in the reduction of irritation and have positive impacts on atherosclerotic plaques in both the early and late stages of the illness [74]. Another tactic is to reduce the release or activation of substances that may contribute to the formation of atherosclerotic plaques and/or cardiovascular consequences. These techniques may include the use of glutamyl-modified biomolecules to reduce the high amounts of the gamma-glutamyl transferase (gGT) enzyme in atherosclerotic plaques [75]. Reduce the increased serum material of the lesions or modify the routes that cause monocytes and macrophages to differentiate into plasma cells in the vascular endothelium [76].

1.7.2. The Potential of Nanoparticles as to Prevent and Treat Atherosclerosis and Related Complications

Study implemented structured and targeted delivery systems for anti-inflammatory drugs, including drugs that could be encapsulated into nanomaterials, in order to prevent side effects and increase application satisfaction [77]. For medication delivery, several different kinds of nanoparticles have been created (Table 1). Several of these products' characteristics and manufacturing processes have recently been studied [78–81]. Inconveniences and restrictions for therapeutic application do exist. Although nanoparticles are often deposited in the reticuloendothelial system, they have limited options for properly controlling their metabolic activity (RES). Additionally, when

multipurpose capabilities are sought, they are notorious for their high manufacturing costs and low repeatability [78, 82]. Nevertheless, it is possible to alter the nanoparticle properties during their manufacturing, allowing for the improvement of linked drugs and the precision of nanoparticle targets [81, 83]. While arteriosclerosis is physiologically active, targeting pro-inflammatory molecules throughout atherosclerotic lesions with nanomaterials linked with anti-inflammatory chemicals may be an effective strategy, perhaps reducing therapeutic adverse reactions. Anti-inflammatory drug-conjugated or drug-loaded nanocomposites can influence inflammation and cerebrovascular cell activities. The simultaneous detection of vulnerable atherosclerotic lesions is made easier by the conjugation of nanomaterials with chemicals utilized for lesion detection. These versatile substances, known as theranostics, can transport diagnostic and curative compounds to particular plaque locations by targeting macrophages, integrin V_3, and VCAM-1 [86]. Fe_3O_4 nanoparticles coated with dextran, gold nanotubes, carbon nanofibers, hyaluronic acid-polypyrrole nanomaterials, hybridization nanostructured lipid carriers, and liposomes are a few examples of nanoparticles used for therapeutics and macrophage targeting. Similarly, magnetic microcapsules that target VCAM-1 and paramagnetic nanotubes that influence integrin V_3 have been described in the publications. There have also been reports of theranostic medicines, including compounds like dextran and mannose as well as autoantibodies like CD11b and anti-VCAM1, that target macrophages inside the lesion [87]. Similar methods that feature atherogenesis elements and utilize scanning technology like computed tomography (CT), optical imaging, ultrasonic, and photoacoustic (US-PA), as well as nuclear image analysis utilizing single photon and positron emission tomography (SPECT, PET), are currently researched [70, 87]. A few ideas have been established, despite the fact that the accuracy of nanoparticle aiming has not yet been thoroughly characterized. Nanoparticle formation may be facilitated by altered hemodynamic stresses at plaque formation locations [88]. The endothelial cells include gaps that allow tiny molecules to pass through. Additionally, the delivery of nanoparticles to the areas of irritation may include the immune system [89]. A protein crown surrounds the nanoparticles once they are administered to living organisms, changing their bioactivity. Typically, the creation of a covering by a native protein is regarded as the initial step in the RES's sequestration of nanoparticles. To prevent this catastrophe, many measures have been created. Although flexible molecules are less likely to be ingested by

macrophages in RES at off-target regions, emerging techniques are centered on regulating the hardness of nanoparticles [90,91]. Another method relies on encapsulating and functionalizing the protein crown with materials like polyethylene glycol (PEG). PEG appears to be an excellent antimicrobial agent that can modify the protein corona's composition [92]. Additionally, PEG has the ability to elicit immunological responses, but this ability requires the inclusion of additional functionalizing substances, like ganglioside, that can reduce the sensitivity of PEGylated liposomes while maintaining their therapeutic potential [93]. To reduce the serum-protein adhesion reaction, peptides can alternatively be thought of as possible coating molecules (zwitterionic peptides) [94]. Aptamer-like peptides are also an illustration; they are utilized to enhance the protein crown with certain substances in the bloodstream. When properly structured, these nanoparticles may be effective [95]. The half-life of nanomaterials in blood and other body fluids may be extended using such techniques. By using microwave or photothermal radiation, nanomaterials can also be triggered. For example, optical pulse stimulation of nanoparticles containing iron oxide coated with dextran and gold inside organisms was demonstrated as a promising method for suppressing macrophages. Along with MRI, photothermolysis of nanoparticles was also studied [96]. A diagnostic experiment using the same technology and nanoparticles made of silicon capsules that had been encapsulated with gold examined it. Atherosclerotic plaques were treated with magnetostrictive nanoparticles utilizing a mechanical visualization approach or an on-artery patch. A near-infrared (NIR) laser used to degrade nanoparticles caused a notable reduction in the surface area of atherosclerotic lesions, and treatment follow-up data on occasion revealed a considerably decreased rate of cardiac mortality in the nanotechnology unit versus controls [97]. When utilizing nanoparticles, the gene regulatory strategy has additionally been proposed to be helpful in the treatment and prevention of atherosclerosis. CCR-2, which has been linked to the entry of inflammation-producing monocytes into areas of arterial wall and ischaemic cardiac damage, has been shown in studies to be down-regulated by siRNA-loaded nanoparticles [98, 99]. Comparatively to animals given other siRNAs, 89Zr-labeled dextran nanoparticles reduced photonic and positron emission (PET) signaling [100]. Additionally, the cellular activity of the metalloproteinase 3 (TIMP3) genotype was down-regulated when ApoE/mice were given positively charged lipid nanoparticles containing microRNA-712 (targeting VCAM-1). The injection of the nanoparticles

slowed the development of the lesion [101]. The silence of Src similarity zone 2 domain-containing tyrosine phosphatase-1 (SHP-1) in cardiac myocytes prevents their death in hypoxic conditions [102]. A different strategy could include preventing monocytes from adhering to the location of atherosclerotic lesions and from transforming into macrophages. The peroxisome proliferator-activated receptor (PPAR), which is responsible for the control of triglycerides, is a receptor, and pioglitazone is a PPAR agonist. These two compounds may be combined to form nanoparticles that can modify macrophage development. These nanoparticles were tested in ApoE-infected animals fed a high-fat diet (HFD) and treated with a renin-angiotensin-aldosterone reuptake inhibitor (ANKI), which caused monocyte-mediated irritation. The balance of pro- and anti-inflammatory monocytes improved two days after nanoparticle delivery, with an emphasis on anti-inflammatory macrophages. The rupture risk was lower, and atherosclerosis lesions were relatively permanent [80, 103]. It has also been shown that nanoparticles containing MTX can stop the onset of inflammation [104]. In the lipid-rich regions, macrophages specifically captured nanoparticles. In contrast, there have been significantly fewer atherosclerotic plaques in the aortic arch in ApoE animals given the HFD diet and treated with MTX-conjugated nanomaterials [71, 105]. The therapy was more successful when MTX was given in combination with etoposide. It's also been investigated how MTX interacts with a variety of other biologically active compounds. Investigations into the interaction of paclitaxel- and MTX-conjugated LDL-imimicking nanoparticles were conducted [71]. In New Zealand white rabbits fed an atherogenic diet, MTX-conjugated nanomaterials and paclitaxel-conjugated low-density lipoprotein nanoparticles reduced the size of atherosclerotic plaque and improved the inner layer thickness.Other drugs used in cancer chemotherapy, including doxorubicin and glucocorticoids, have also been shown to have comparable anticancer activity [106, 107]. The reduction in macrophage activity appears to have contributed to the positive benefits of this mixture, and the application of mixed chemotherapeutics in nanoparticles can have more potent activity on severely inflamed atherosclerotic plaques.

However, these medications come with a non-specific systemic reduction in macrophages, which increases the risk of infectious diseases. In order to lessen adverse effects, non-ablation strategies focusing on macrophage functioning have emerged. When fatty sequences are being produced by shear force during the initial

stages of atherosclerosis, magnetic microspheres coupled with P-selectin are beneficial [108]. Similar to this, stopping angiogenesis could stop systemic problems. Through inhibiting vasa vasorum extension, fumagillin-loaded paramagnetic nanomaterials with an adhesion receptor are beneficial in trying to stabilize or even reverse atherosclerotic plaque [109, 110]. Production of reactive oxygen species-scavenging nanoparticles is a further strategy to stop the evolution of ischemia, organ ischemia, and atherosclerosis consequences [111]. It has been demonstrated that using liposomes that provide phosphatidylserine (PS) can reduce post-myocardial infarction damage by reducing macrophage activation. Since PS is primarily produced on apoptotic cells, it causes a "non-inflammatory" elimination by macrophages, with the predominant production of tumor growth factor and interleukin-10 in place of cytokines such as tumor necrosis [112]. (Table 1) (Figure 3)

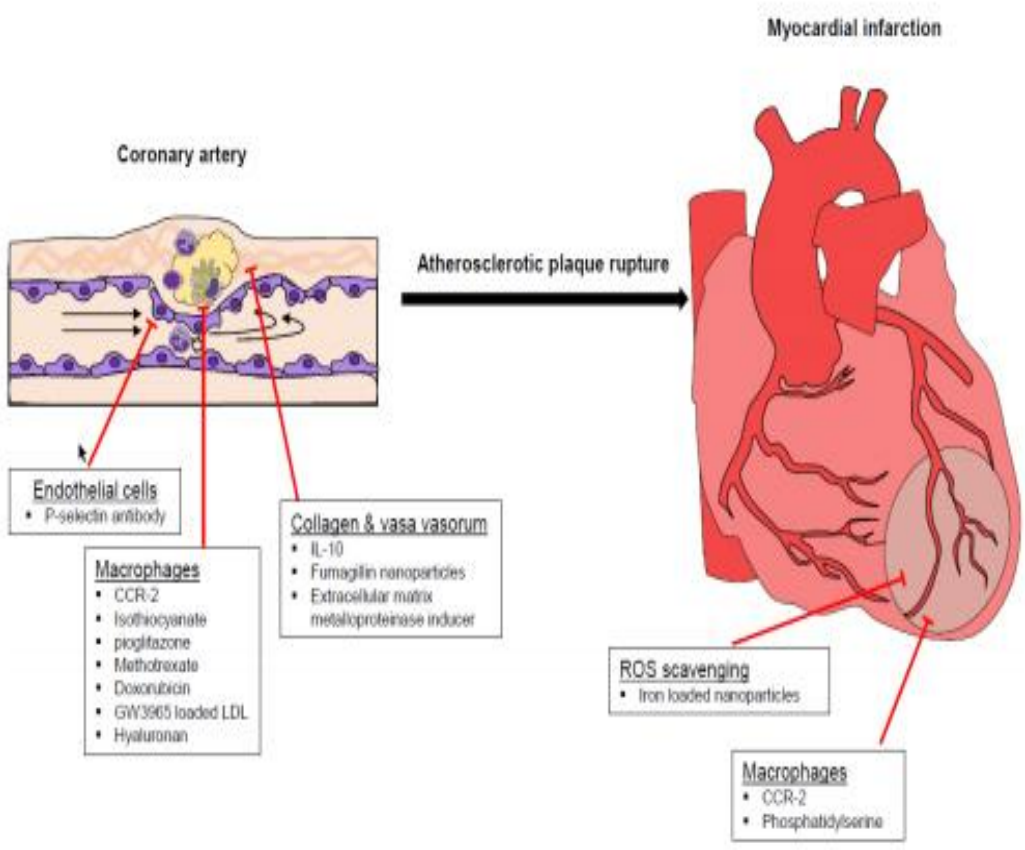


Figure-3: Studies on nanoparticles in atherosclerosis range from the early symptoms of fatty lines through the atherothrombotic effects. The major components of current strategies include vascular endothelium, extracellular matrix, and particularly macrophage recruitment and activity. IL stands for interleukin; CCR for C-C chemokine receptor; and ROS for reactive oxygen species [113].

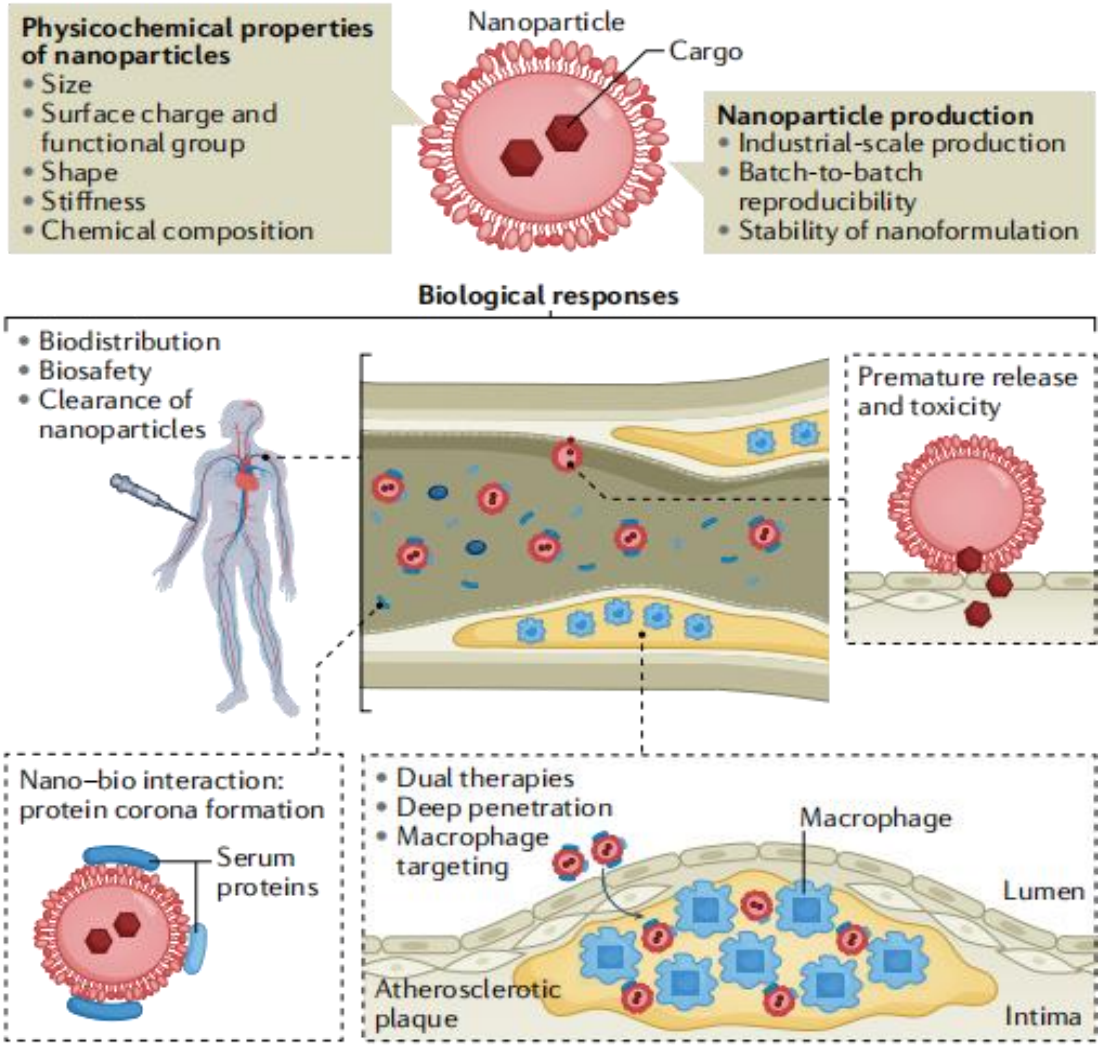
Table 1. Recent findings on the application of nanoparticles in the therapy of atherosclerosis and related complications.

Nanoparticle	Target	Outcome
siRNA		
siRNA targeting CCR2	Monocytes, macrophages.	Reduction of atherosclerosis Attenuated infarct inflammation, post-infarction left ventricular remodeling
Sulphate-based nanoparticles		
Nanoparticles loaded with fluorescein isothiocyanate and/or pioglitazone.	Monocytes, macrophages.	Modified polarity of monocytes in the periphery. Decreased development of inflammatory macrophages. Destabilized atherosclerotic plaque and rupture.
Lipid-based nanoparticles		
Lipid coated nanoparticles loaded with MTX	Macrophages, foam cells	Decreased plaque coverage in the aortic arch
Library of LDL mimicking nanoparticles loaded with GW3965	Monocytes and Macrophages for reversing cholesterol efflux.	Decreased total lipids in aortic macrophages. Decreased monocyte number.
Lipid core nanoparticles carrying MTX and/or PTX	Macrophages	Decreased size of the plaque and of intima area. Reduced number of macrophages in aortic lesions. Downregulation of MMP-9 and TNF-α.
Liposomal nanoparticles loaded with prednisolone	Macrophage lipid loading, ER stress and apoptosis	Lipotoxicity
Lipid core nanoparticles carrying doxorubicin	Macrophages	Anti-inflammatory and anti-proliferating effects
Liposomes presenting PS	Macrophages	Shift toward anti-inflammatory phenotype with consequent improvement of myocardial healing
Glycosaminoglycan		
Hyaluronan nanoparticles	Atherosclerotic plaque, macrophages	Decreased size of the atherosclerotic lesions. Decreased macrophage number. Increased collagen content.
Other approaches		
Nanoparticles loaded with the EMMPRIN (extracellular matrix metalloproteinase inducer) Ldlr, low density lipoprotein receptor) binding peptide AP-9.	EMMPRIN	Ameliorated heart contractility. Decreased cardiac necrosis. Decreased levels of MMP-2 and MMP-9
Nanoparticles containing IL-10 and targeting peptide collagen IV	Collagen IV	Reduced oxidative stress in lesions. Stabilized atherosclerotic plaques.
Magnetic microbubbles modified with P-selectin antibody	Endothelial cells	Leukocyte rolling
Fumagillin nanoparticles	Vasa vasorum	Reduced neovascularization
Iron oxide–cerium oxide core–shell nanoparticles	Macrophages	ROS scavenging with reduced atherosclerotic burden and improved myocardial healing

MTX, methotrexate; LDL, low-density lipoprotein; PTX, Paclitaxel; MMP, matrix metalloproteinase; TNF, tumor necrosis factor; IL-10, interleukin-10; ER, endothelial reticulum; ROS: Reactive oxygen species; PS: Phosphatidylserine [113].

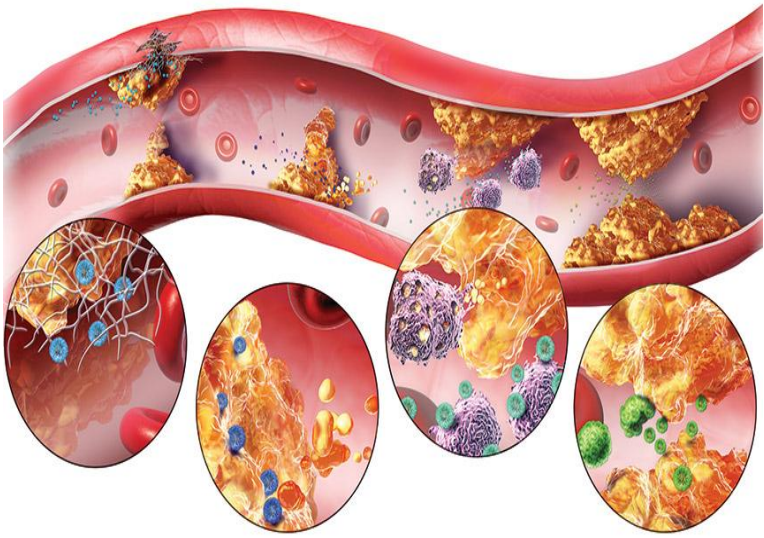
1.8. Nanoparticle-associated challenges and considerations

- Evaluating the physiological and biochemical activities at the nano-bio interface, which include protein corona generation, and their impacts on blood vessels, pharmacokinetics, pharmacodynamics, intra-plaque transmission, drug-release pattern, drug absorption, and internal transportation of nanoparticles [124].
- Nanotherapeutics and nanoparticle-based imaging agents are being evaluated for their biosafety, tolerability, immuno genicity, and elimination.
- Developing the longevity of the nanoformulation and comparing the pharmacological features of the nanoformulation to those of the free medication alone (such as bioavailability and adverse reactions).
- Focusing on the impact of nanoparticles' physiochemical characteristics on atherosclerotic plaque extravasation, lesional macrophage targeting, plaque penetration, macrophage-specific uptake, and subcellular distribution.
- Production of nanoparticles and the precise nanoformulation at industrial scale using GMP and CMC for batch-to-batch repeatability
- Effectiveness of targeted administration of two or more medicines on various anti-atherogenic routes for synergistic anti-atherosclerosis treatments.


Physicochemical properties of nanoparticles
• Size
• Surface charge and functional group
• Shape
• Stiffness
• Chemical composition
Nanoparticle
Cargo
Nanoparticle production
• Industrial-scale production
• Batch-to-batch reproducibility
• Stability of nanoformulation
Biological responses
• Biodistribution
• Biosafety
• Clearance of nanoparticles
Premature release and toxicity
Nano–bio interaction: protein corona formation
Serum proteins
• Dual therapies
• Deep penetration
• Macrophage targeting
Macrophage
Lumen
Atherosclerotic plaque
Intima

Chapter Two

Article Review



2. Article Review

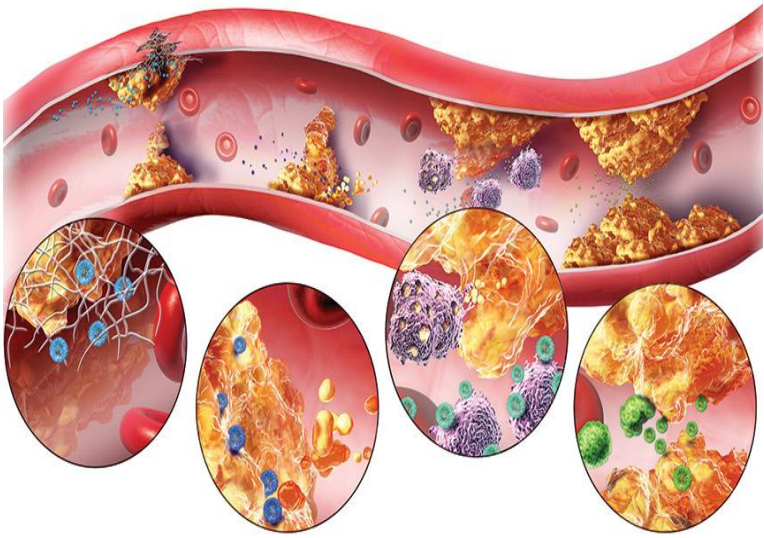
Nanoparticles for diagnosis and therapy of atherosclerosis and myocardial infarction: evolution toward prospective theranostic approaches.

The primary killer globally is heart disease. Despite preventative measures, it is still difficult to identify the common pathophysiological process underlying cardiovascular disorders, and overt coronary artery disease or myocardial infarction is frequently the early diagnostic presentation. Atherosclerosis may be prevented, diagnosed, and treated using nanoparticles, and emerging multipurpose nanoparticles with integrated therapeutic and diagnostic capabilities show promise for therapeutic approaches to this condition. This review is concerned with the advancement of nanoplatforms as theranostic instruments and their use in the treatment and detection of vascular complications, cardiovascular disease, and ischemic stroke. Along with the difficulties faced by nanomaterials in clinical application, there is also the use of nanomaterials in noninvasive imaging, targeted medication administration, and photothermal therapy.

Reference: Bejarano, J., Navarro-Marquez, M., Morales-Zavala, F., Morales, J. O., Garcia-Carvajal, I., Araya-Fuentes, E., Flores, Y., Verdejo, H. E., Castro, P. F., Lavandero, S., & Kogan, M. J. (2018). Nanoparticles for diagnosis and therapy of atherosclerosis and myocardial infarction: evolution toward prospective theranostic approaches. *Theranostics*, *8*(17), 4710–4732. https://doi.org/10.7150/thno.26284

Chapter Three

Goal of my studies



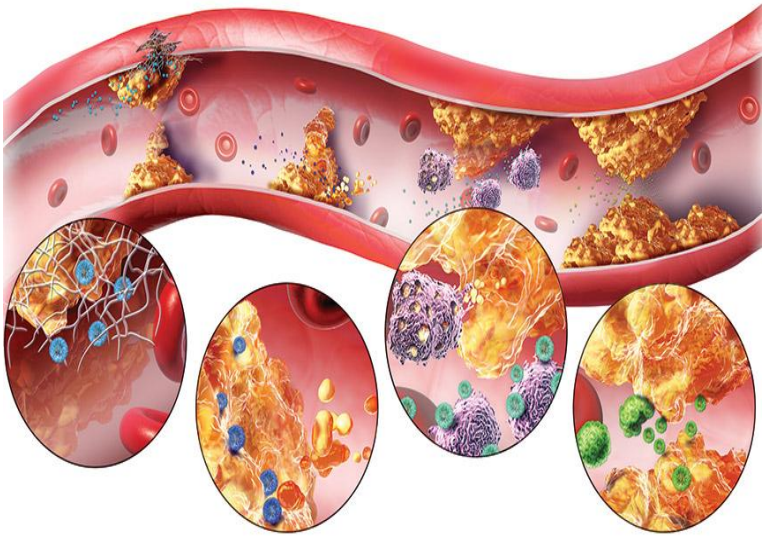
3. Goal of my studies

The aim of this paper is to evaluation the developing the approaches of nanoparticles in the treatment in atherosclerosis.

- To identify atherosclerosis by using nanoparticle.
- To determine nanoparticle targeting in atherosclerosis.
- To determine the nanotherapeutics in atherosclerosis.
- Nanotherapeutics in atherosclerosis
- Finally, assess the neuroprotective potential nanoparticles that may be employed in atherosclerosis.
- Compile the data for further uses.

Chapter Four

Methodology



4. Methodology

4.1. Introduction:

A literature review leads the examination. Around 111 papers are reviewed for this study.

4.2. Research Design:

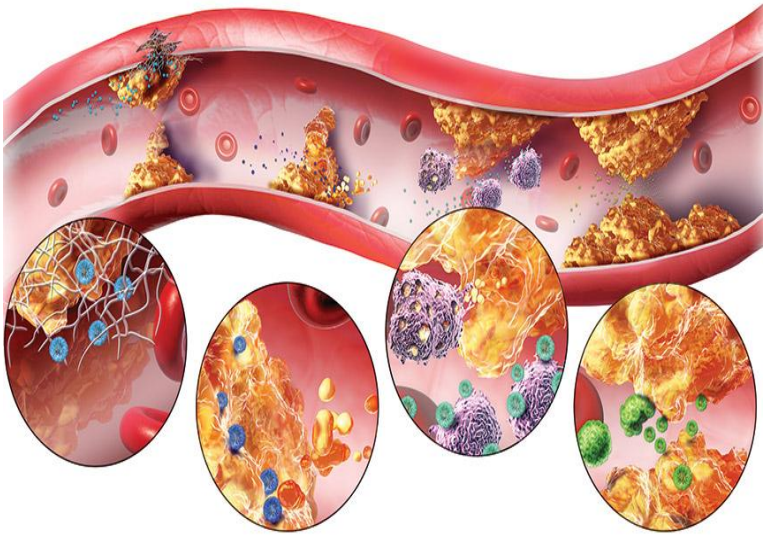
This exploration was planned through google scholar, scopus, ResearchGate and many other websites to find literature on “Nanoparticles on atherosclerosis”, “Diagnosis, therapy and treatment of atherosclerosis”, search term also included “atherosclerosis”.

4.3. Method of Data Analysis:

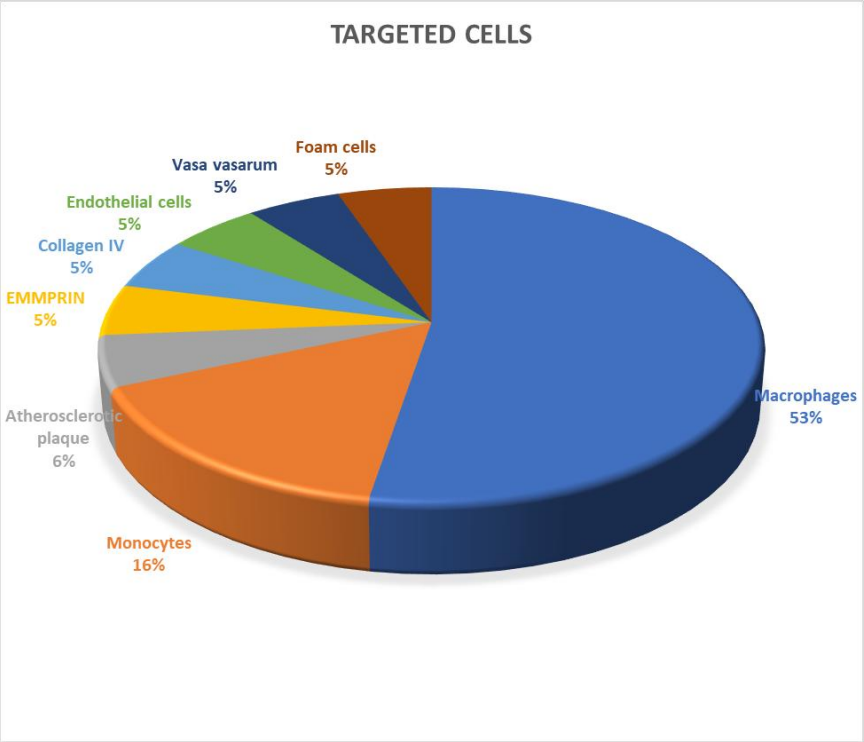
After an assortment of information, all information was checked for precision and internal consistency to deny missing or clashing data, and those were discarded. Informationinvestigation was done through Microsoft dominate refreshed rendition. All collected information is from 1998 to 2021.

Chapter Five

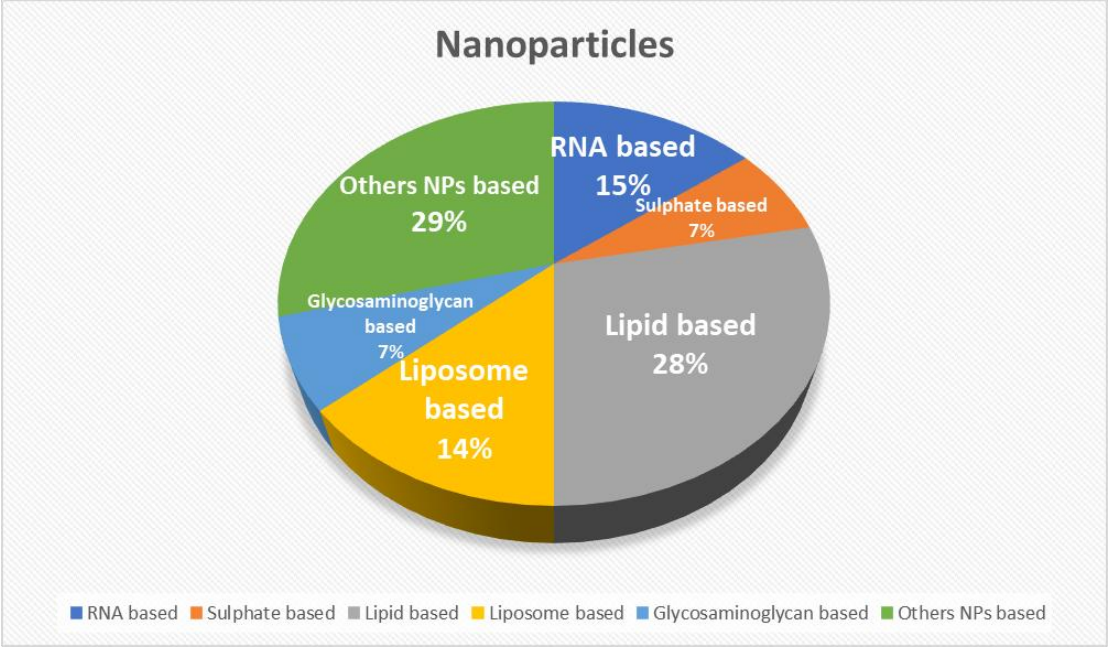
Result and Discussion



Macrophages have received considerable attention as a therapeutic target due to their importance in atherosclerotic progression and regression and plaque stabilization. Thus, modulating macrophages with therapeutic agents has brought new possibilities in atherosclerosis treatment. In addition many cells are targeted like monocytes, atherosclerotic plaque, EMMPRIN, endothelial cells, vasa vasarum, foam cells etc.

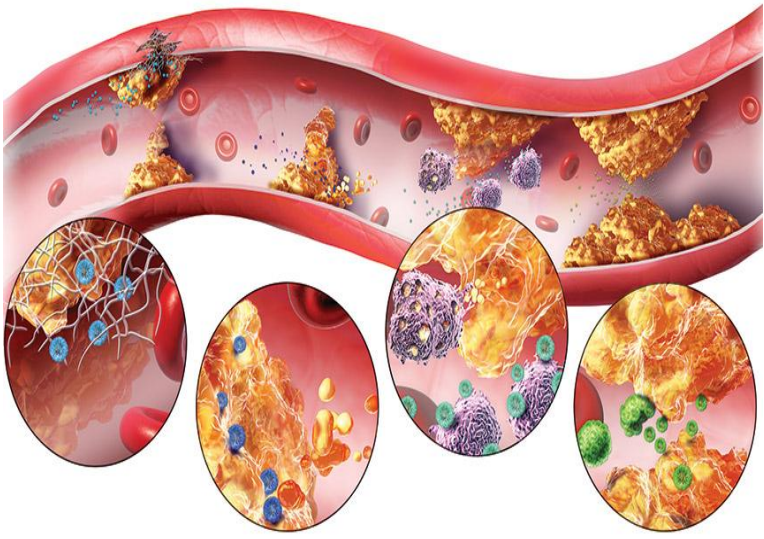


Nanoparticles (NPs) are defined by the International Union of Pure and Applied Chemistry (IUPAC) as particles of any shape that range in size from one to one hundred nanometers (nm); however, the word is frequently used to describe substances that are up to several hundred nm in size. The ability of NPs to enhance the effectiveness of therapy and diagnostics as well as to offer a greater understanding of plaque biology and pathophysiology seems to be the core of their capabilities for managing atherosclerosis. The summary that follows demonstrates the variety of nanomaterials covered in this review and gives readers some context.


Nanoparticles
RNA based
15%
Sulphate based
7%
Lipid based
28%
Liposome
based
14%
Glycosaminoglycan
based
7%
Others NPs based
29%
RNA based
Sulphate based
Lipid based
Liposome based
Glycosaminoglycan based
Others NPs based

Chapter Six

Conclusion



Atherosclerosis is a disease which cannot be easily detected with the available imaging techniques in the initial steps of development. Currently available therapeutic strategies are aimed at the systemic, but not local and targeted, prevention and treatment of atherosclerosis. All of them have limited efficacy and some adverse effects. Targeted delivery of diagnostic contrast substances or therapeutic drugs by nanoparticles to sites of incipient atherosclerotic lesions is considered to be a sophisticated strategy for the diagnosis as well as prevention and therapy of atherosclerosis. Targeted delivering approach using nanoparticles can promote the stability and bioavailability of the drugs, improve the detection sensitivity, enhance the therapeutic efficacy, improve the pharmacokinetics of the drugs, and reduce the adverse systemic side effects. Nevertheless, there are still a number of drawbacks in such nanoparticles with respect to stability, structure design, toxicity, targeting efficacy, and production, requiring optimization to devise nanoparticle-based therapeutic/diagnostic approaches for atherosclerosis that are clinically favorable. Application of porous compounds combined with imaging agents is an interesting option and studies in the future need to concentrate on enhancing its stability and efficacy in vitro and in-vivo. It has to be emphasized that possible beneficial effects of nanoparticles have largely been obtained from the in vitro experiments and experiments using animal models. Therefore, it will be a challenging effort to translate the results of these studies into possible clinical use. Current nanoparticle-based strategies have mainly focused on the anti-inflammatory effects by targeting the development of macrophages/foam cells as well as the recruitment of monocytes to the atherosclerotic plaques. However, gene-therapy, monoclonal antibodies, and combination therapies can be promising if merged with the potential beneficial use of nanoparticles. Moreover, multifunctional nanoparticles can be developed that could facilitate the imaging and targeted delivery of drugs in humans, i.e., in a clinical setting. Although the application of nanoparticle technology in the prevention and treatment of atherosclerosis is an emerging field, the progresses and the results obtained so far have been promising. This might open new horizons in the therapy of atherosclerotic cardiovascular diseases

Chapter Seven

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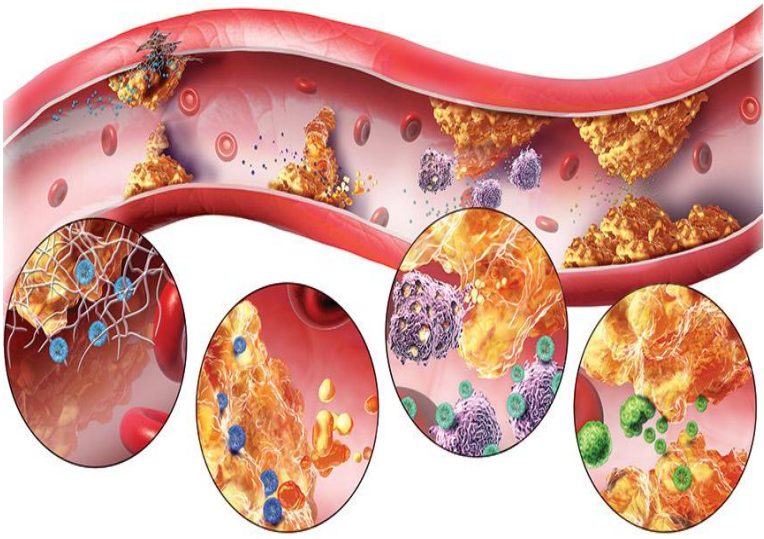

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