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Advances in nanocarriers as drug delivery systems in Atherosclerosis therapy

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ABSTRACT

Cardiovascular diseases (CVDs) are known as killer diseases and to overcome these diseases, novel approaches are needed. Although many approaches were able to control this disease, they still had high risks for the patients. One of the best ways to control CVDs is to use targeted Nanosystems, with the help of Nanotechnology and Biology Sciences. Despite current therapeutic strategies to reduce risk, patients still experience the consequences of CVD. Improve visualization of early atherosclerotic lesions to decrease residual CVD risk is one of its goals. Nanomaterials used as Nanocarriers are mainly Polymeric based, Magnetic, Metalic, Silica based and Liposomes. In addition, some drugs can be loaded to these Nanocarries. In this review, we focused on nanocarriers to manage Atherosclerosis, which is the most prevalent type of CVD. We divided these nanocarriers into five main groups: Polymeric nanocarriers, Magnetic nanocarriers, Metalic nanocarriers, Liposomes and Silica-based nanocarriers.

Keywords: *Atherosclerosis, Targeted therapy, Nanocarriers, Polymeric nanocarriers, Magnetic nanocarriers, Metalic nanocarriers, Silica nanocarriers*

1. Introduction

Atherosclerosis is the most prevalent type of cardiovascular disease (CVD) often leading to a brain or heart attack[1]. Atherosclerosis is caused by the constant development of plaques in the arterial wall and then their separation, developing inflammation in the endothelial and its malfunction [2]. The atherosclerotic plaque is made of lipids, macrophages, inflamed endothelial, foam, and vascular smooth muscle cells with many other elements that amass over time, results in calcification and thrombus development. Figure 1 Shows the Process of Atherosclerosis plaque formation. Leukocytes express proinflammatory cytokines when they are engaged to the endothelium followed by the infiltration of monocytes and their maturation into macrophages located in the vascular wall, which incorporate lipids and become foam cells. The injury of endothelium are sometimes are caused by these plaques. When injury is happened, the endothelial cells release inflammatory phenotype and attract macrophages to the injured site, thereby secreting linkage molecules. Attachment of monocytes and leukocytes to the injured endothelium causes extravasation into the tissue area just after the chemokines are produced. Then, monocytes evolve into macrophages, which are expert phagocytes employed to absorb extra lipids at the injury site [3].

Many atherosclerotic biomarkers and features assist in vascular-targeted drug distribution during the disease development. Several studies have assessed drug transporters' capability to carry

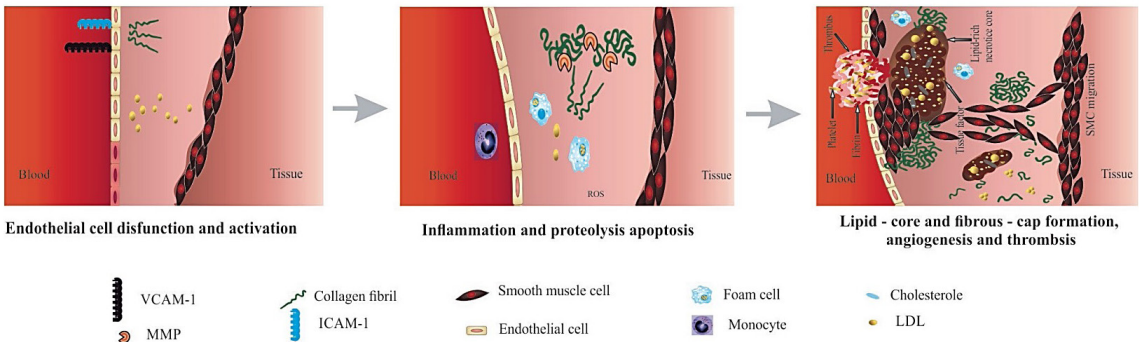

Fig. 1- Atherosclerosis initiation and development process (ICAM-1: Intercellular Adhesion Molecule-1, VCAM-1: Vascular cell adhesion protein Molecule-1, LDL: Low-Density Lipoprotein) [4].

imaging agents and medicines to the vascular area in atherosclerosis. Endothelial cells and macrophages are the two cell targets owing to their unique secretion of inflammatory reagents (E-selectin (endothelial-leukocyte adhesion molecule 1), ICAM, P-selectin (Granule Membrane Protein), and VCAM-1) and qualities ('leaky' vasculature displayed by endothelial lining). The accumulated lipids damage the tissue, thereby releasing proinflammatory chemokines. Several enzymes oxidize these lipids.

Commonly, stenting and nanocarriers are two ways to treat atherosclerosis[5]. Although, both the drug-loaded stent and the pristine metal stent lead to restenosis and stent thrombosis to a certain range[6]. In order to use nanocarriers for the treatment of atherosclerosis, nanocarriers should be biocompatible and not toxic. Therefore, some treatments are needed to produce a non-toxic, biocompatible nanocarrier such as coating nanoparticles with natural cells [7].

Nanocarriers are divided into three main groups: Targeting, Imaging and Therapeutic nanocarriers. This review focuses on Targeting and Imaging. Targeting nanocarriers are also divided into passive and active groups. Passive one uses the body's certain biophysical features of the illness to pinanoparticlesoint nanocarriers. However, active one changes the external structure of nanocarriers to include ligands to biochemical signs overexpressed in or exclusive to the plaque area.

Application of bio-nanoparticles to advance the specific delivery of therapeutic or imaging or targeting molecules to atherosclerotic plaques get more complicated and more effective every day[8]. Recent studies determine that biomimetic nanoparticles can attain lasting blood circulation [9], have more active immune avoidance and better aiming than traditional nanoparticles [10]. Besides, biomimetic nanoparticles are more likely regarded as "self" and establishing better biocompatibility against traditional nanoparticles [11]. The nanoparticles cores' surface can show ligands for steering different basic tissues, cells, and receptors of atherosclerotic plaques. Besides, these drug delivery systems can effectively carry phospholipid bilayers from natural cells to nanocarriers without harming active surface proteins [12]. In this review, we discuss the materials used for drug delivery in atherosclerosis approaches. At first, we discussed nanocarriers into two main groups: Targeting and Imaging. After that, we divided the materials used for each group and in a combination, we divided materials into five groups (Liposomes, Polymeric materials, magnetic materials, metalic materials, Mesoporous silica-based materials). We described every of these materials below.

2. Advanced nanocarriers for atherosclerosis therapy

Biomimetic Nanocarriers technology has been gradually and increasingly applied in treating CVDs. They can be categorized into three types of the whole cell, cell membrane, and vesicles-based Nanocarriers (Figure 2) [13]. Encapsulation and carrying celastrol within a nano-carrier increase its solubility in water and change its biological distribution and half-life in the serum [14]. Nano-vessels can enhance the discrimination power of encapsulated goods by aiming at definite cells or tissues [15]. Lastly, nanocarriers can encapsulate more than one loading at the same time, allowing the combined transfer of different reagents to precise cells [16]. These advantages can remarkably lower the dosage of medicines, lessen toxicity, and increase protection [17].

2.1. Targeted nanocarriers

So far, efficacious policies for restricting nanocarriers to atherosclerotic plaque have employed passive or active aiming [1,18]. In atherosclerosis, passive targeting uses the enhanced vascular permeability and retention (EPR) of vessel endothelium due to chronic and local inflammation. This feature is found in plaque microvasculature, too [19,20]. Quick angiogenesis after the vasa vasorum through plaque development result in these microvessels, inhibiting pericyte employment and the resulting vessel solidity [21,22]. In the late stage of atherosclerosis, passive targeting uses the faster blood velocity at contracted points of exceedingly blocked vessels, leading to greater local shear stress [23].

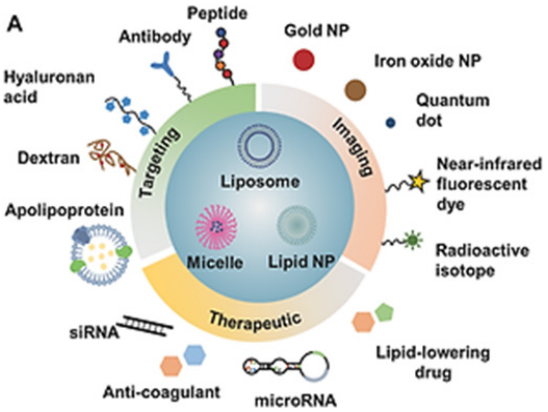

Fig. 2- Contemporary design of atherosclerotic nanomedicines, They can be categorized into three types of the whole: Liposomes, Micelles and Lipid nanoparticles [8].

On the other hand, active targeting changes nanocarriers' superficial features to include ligands to biochemical signs overly expressed or certain to the plaque area (Figure 3). These cues are proteins seen on injured endothelium, foam cells, and oxidized lipids aimed by antibodies, oligonucleotides, and peptides [1,18,24]

2.1.1. Polymeric nanocarriers

Polymeric nanocarriers are one of the promising nanocarriers for drug delivery systems (Table 1). Polymeric nanocarriers are so famous, because of their capacity to be surface-modified and be copolymerized or even can be conjugated with targeting agents and delivery of the encapsulated agents[26]. Natural or synthetic polymers can be used to produce polymeric nano particles. A polymerization reaction of monomer units can result in polymeric nanosystems. Under certain conditions, they can be structured and assembled with a nanometric size (10–100 nm) [27,28]. The most applicable natural polymer for atherosclerosis carrier is Chitosan. Synthesis polymers are more common to be used in the fabrication of polymeric nanoparticless. Some synthetic polymers are poly(lactic-co-glycolic) acid, poly(ethylene glycol), and poloxamer. The hydrophilic poly(ethylene glycol) (PEG) is an FDA-approved that has lots of properties such as reduction protein absorption, increasing half-life of the serum, and also it has little immunogenicity[29]. In the following section, some experimental progresses in producing Polymer

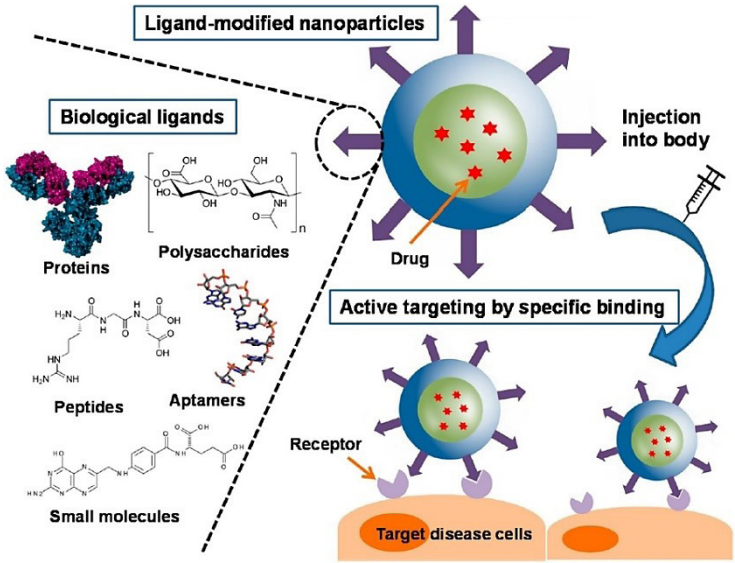

Fig. 3- Surface functionalizing of nanocarriers by biological ligands for active targeting purposes[25].

Table 1- Polymeric nanocarriers characteristics and their target for atherosclerosis therapy

Polymeric Nanocarriers	Target	Model	Therapeutic mechanism	Reference
poly-lactic/poly-glycolic acid (PEG–PLGA)	Platelets	In-vitro & Vivo	Catalase enzyme	[38]
polystyrene or PLGA	ICAM	Mouse	bound to tumor necrosis factor-activated ECs	[39]
Polystyrene	ICAM	Mouse	Catalase enzyme	[40]
PLGA Nanoparticle–Peptide	ICAM	In-vitro	Endocytosed to Lysosomes	[41]
Methoxy-poly(ethylene glycol)-poly(D,L-lactide) (MPEG-PLA)	(sVCAM-1), THP1	In-vitro	Exposed to HUVECs	[42]
poly(ethylene glycol)-block-poly (propylene sulfide) (PEG-b-PPS) micelles loaded into hydrogel	NF-κB	Mouse	induce the proliferation, expansion and homing of Foxp3+ Tregs	[43]
hyaluronic acid (HA)-coated poly (ethylene glycol)- poly(tyrosine-ethyl oxalyl) (PEG-Ptyr-EO)	CD44-positive inflammatory macrophages	Mouse	Targeting of CD44s via simavastin loaded nanocarriers	[44]
Pluronic-F127/Chitosan methacrylate	RGD peptide and collagen VI	Mouse	Delivery of nanocarries via iron-oxide nanoparticles	[45]
Polycaprolactone (PCL)/α,β-poly(N-2-hydroxyethyl)-DL-aspartamide (PHEA) graft copolymer	CD36	In-vitro	Internalization of nano carriers by macrophage via an organic specie on surface of Nanocarrier	[46]
PLGA-Maleimide-PEG	PDGFR	In-vitro	Targetting via S2P peptide	[47]
EGFP-EGF1-conjugated poly(lactic-co-glycolic acid) (PLGA) nanoparticle	CD142	Mouse	Delivery of Nanoparticles to vascular smooth muscle cells	[48]
Rapamycin-loaded poly (lactic-co-glycolic acid) copolymer (PLGA) nanoparticles coated with Macrophages	CD47	Mouse	Inhibition of plaque formation via macrophage layer	[49]

based nanocarries are mentioned in Table 1.

2.1.1.1. PEG-based nanocarriers

Poly(ethylene glycol) is a synthetic most used polymer [30] in biological applications because of its great properties. Here are some experiments using PEG-based nanocarriers for Atherosclerosis.

The small hydrophobic molecule of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) inhibitor celastrol was put into poly(ethylene glycol)-b-poly(propylene sulfide) (PEG-b-PPS) micelles by Allen et al. [17]. PEG-b-PPS micelles displayed excellent packing efficacy, little polydispersity, and no shape variations upon packing. Celastrol within these nanovessels considerably decreased cell toxicity versus free celastrol. Further, celastrol-loaded micelles effectively decreased Tumor Necrosis Factor Alpha (TNF-α) excretion after Lipopolysaccharides (LPS) stimulus of RAW 264.7 cells and lowered neutrophils and inflammatory monocytes in the atherosclerotic plaques of Low Density Lipoprotein Receptor Knockout Mouse (ldlr-/-). This decrease in inflammatory cells corresponded to the decrease in plaque area, signifying that these nanovessels can work as an anti-inflammatory treatment for atherosclerosis. Also, Mishra et al. [31] encapsulated Glycosylceramide synthase inhibitor (D-PDMP) within poly ethylene glycol and sebacic acid. The dwelling time of D-PDMP in vivo was increased by polymer-encapsulation from < 1 hour to > 4 hours (up to 48 h or longer). Polymer encapsulation increased in vivo endurance that it resulted in increasing hinder with atherosclerosis and cardiac

hypertrophy in apoE/ Apolipoprotein E Knockout mice (apoE-/-) who were nourished by a diet with high fat and cholesterol.

Ma et al. [32] evaluated the transfer of microRNA (miR)-146a and miR-181b with an E-selectin-targeting multistage vector (ESTA-MSV) so that to suppress atherosclerotic plaques in the injured endothelium. They used polyethylene glycol-polyethyleneimine nanoparticles to cover Cyanine 5 (Cy5)-conjugated miR-146a and miR-181b and loaded Cy5-conjugated miR-146a and miR-181b into ESTAMSV microparticles. Both miRs were undergone downregulation in TNF-α-treated endothelial cells.

Wu et al. [17] used the block copolymer micelles of poly(ethylene glycol) and poly(propylene sulfide) loaded with Andrographolide to decrease inflammation and the amount of Reactive oxygen species (ROS) to cure atherosclerosis. Because of the ROS-responsive property of PEG-PPS, the micelle works like a stimuli-responsive drug carrier to promptly discharge the encapsulated drug, and also the micelle ingests ROS at the pathologic sites; also, the release of pro-inflammatory cytokines are lowered, and oxidative stress is controlled.

2.1.1.2. PLGA-based nanocarriers

Poly(lactic-co-glycolic acid) (PLGA) is one of the best developed polymers for biological applications[33]. Due to its biodegradability, good interaction with biological materials, possibility to target nanoparticles to exact organs or cells, PLGA is so successful to be used nanocarriers. Some examples of using PLGA as nanocarriers for Atherosclerosis is mentioned below.

Gaytan group [34] prepared a combined polymer/ High Density Lipoprotein (HDL) nanoparticle comprising a lipid/apolipoprotein cover that put in a nutshell a poly(lactic-co-glycolic acid) (PLGA) core. This new HDL-like nanoparticle (PLGA–HDL) exhibited natural HDL features, such as favored taken by macrophages and a decent cholesterol efflux ability, with a characteristic PLGA nanoparticle sluggish discharge profile. In vivo studies (with an ApoE knockout mouse model) of atherosclerosis displayed an obvious buildup of PLGA–HDL nanoparticles in the plaques, colocalized with macrophages. This biomimetic stage mixes the aiming ability of HDL biomimetic nanoparticles with the typical flexibility of PLGA-based nanocarriers.

Zhang et al. [35] established this method using platelet membrane-coated PLGA nanoparticles to attack atherosclerotic lesions in ApoE-/- mice. The multivalent attachment relations of platelet membranes were long-established by colocalizing the nanoparticles to stimulated endothelium, macrophages, and collagen type IV. Furthermore, the platelet-PLGA nanoparticles were displayed to attach to stimulated endothelium in atherosclerosis-prone sites, showing their potential to target atherosclerosis at early and final disease stages.

Song et al. [36] stretched the platelet-PLGA nanocarrier approach to transfer rapamycin, an immunosuppressant, to sluggish plaque development. However, platelet-membrane coatings have many restrictions that may impede clinical application, such as uneven coating, set to set inconsistency, scalability, and the risk of denaturing endogenous membrane proteins, which could cause an autoimmune response [37].

2.1.1.3. Chitosan-based nanocarriers

Chitosan is a natural widely available polymer that is able to enhance bioavailability [50]. It can also be used into nanocarriers for Atherosclerosis applications. Some usage of Chitosan as nanocarriers are in the following paragraphs.

Hong et al. [51] did the encapsulation of (-)-Epigallocatechin gallate (EGCG) (chief bioactive ingredient in green tea) into self-assembled nanoparticles of chitosan and aspartic acid and the efficiency of EGCG against rabbit atherosclerosis was considerably increased by integrating EGCG into the nano-formulation.

Gao et al. [52] developed a macrophage membrane which was coated with ROS-responsive nanoparticles used for the biomimetic drug delivery system. This membrane shuns the removal of nanoparticles from the reticuloendothelial system and directs nanoparticles to the inflammatory areas. There, the ROS-receptiveness of nanoparticless allows precise payload release. Besides, the combined effects of pharmacotherapy and cytokines confiscation from this biomimetic medicine transfer system results in better cure of atherosclerosis. ROS responsive nanoparticles were organized through self-assemblage of amphiphilic oxidation-sensitive chitosan oligosaccharide.

Yin et al. [53] made hydrophobically-modified glycol chitosan (HGC) nanoparticles to target activated endothelial cells. HGC nanoparticles amplified aiming specificity toward activated endothelial cells. Therefore, HGC nanoparticles

are attuned toward Red Blood cells, platelets, and endothelial cells. In addition, HGC is employed to detect stimulated endothelial cells at atherosclerotic lesions and bring medicines.

Yu et al [54] investigated the effect of Chitosan-oligosaccharides (COS) on atherosclerosis in apolipoprotein E. This experiment resulted in decreasing of cholesterol and TG in non-high density lipoprotein.

2.1.2. Liposome nanocarriers

Liposome nanoparticles as drug carriers are used to gain discerning localization of active drug in injured areas [55], and one of their use is in Atherosclerosis and they are used as noninvasive in vivo imaging of atherosclerotic plaques or early atherosclerotic lesions, which allows the active transfer of drugs, genes, cells, and contrast agents. Liposomes can be altered for different purposes, for instance, Liposomes can be PEGylation, in this process, PEG molecules will be attached to the surface of Liposomes. This process, expand Liposomes' chance to target the plaques[3]. Many pioneering strategies for the aiming of plaques by liposomes have been explored. These strategies grasp the different stages in the progression of atherosclerosis and some of them are mentioned below.

Benne et al. [56] encapsulated GW3965 (a promising therapeutic compound that increases plasma and liver lipid amounts) in liposomes and activated by the cyclic peptide Lyp-1. These liposomes demonstrate favored in vitro uptake by foam cells and higher amassing in atherosclerotic plaques in mice versus non-aimed liposomes, as shown by in vivo imaging. Furthermore, Kelley et al. [57] prepared biomimetic liposomes made of synthetic liposomes hybrid by platelet membranes (P-Lipo) for aiming atherosclerosis. P-Lipo has the multivalent aiming features derived from membranes of platelets and the benefits of synthetic liposomesas drug carriers. Using an atheroprotective medicine, rapamycin, as the model drug, P-Lipo strongly subdued atherosclerosis development compared with all treatments without causing systemic toxicity.

On the other hand, Li et al. [58] developed an anti-inflammatory cytokine interleukin-10 (IL10) transfer system to ease atherosclerosis plaque inflammation effectively. The targeted transfer of IL10 to the atherosclerotic plaques was realized by cyclic arginine-glycine-aspartate motif peptides (cRGD) conjugated liposomes (IL10-cRGD-Lip). The in-vitro analysis obviously advocates that IL10-cRGD-Lip endures the release of IL10 and could considerably decrease ROS .

Huang et al. [59] fabricated anti- Intercellular Adhesion Molecule-1 (ICAM-1) antibody with liposomes for guided transfer of a water-insoluble liver X receptor (LXR) agonist (T0901317) to prevent Vascular smooth muscle cells (VSMC) production. With the help of a confocal laser scanning microscope and flow cytometry, the aiming precision of the anti-ICAM-T0901317 liposomes was assessed, and it showed the stronger inhibition effect of VSMC creation than free T0901317.

Li et al. [60] altered liposomes using an aiming ligand (E-selectin-binding peptide) to deliver both Arsenic-tioxide and Curcumin to impaired Endothelial Cells (EC) and overexpressing E-selectin. Employing reverse transcription quantitative polymerase chain reaction, flow cytometry, and immunofluorescence staining, the molecules contributed to the hang-up of connection (E-selectin and (ICAM-1)) and inflammation (IL-6 and monocyte chemotactic protein 1 (MCP-1)) in aortic ECs were assessed. The antiatherosclerosis properties of liposomes which is co-loaded with Ato and Cur were estimated in vivo using (ApoE-/-) mice. This treatment decreased foam cell formation and the excretion of inflammatory factors (IL-6 and MCP-1) by hindering monocyte transfer into the intima.

Benne group [61] developed anionic phospho-lipid 1,2-distearoyl-sn-glycero-3-phosphoglycerol (DSPG)-liposomes encapsulating an LDL-derived peptide antigen. This material was experiment-ed on atherosclerotic mice and it showed that the plaques became stabilized and the plaque forma-tion was decreased to 50%.

2.2. Imaging

Molecular imaging empowers the study of lesions at the cellular and molecular levels and precise diagnosis of the atherosclerotic plaque. In the previous few decades, magnetite (Fe3O4), a magnetic iron-oxide nanoparticle for magnetic resonance imaging (MRI), has drawn considerable attention because of its excellent biocompatibility [62–66]

2.2.1.Magnetic nanoparticles

Magnetic nanoparticles are a group of materials that have made great strides in the field of MRI

imaging in recent years, both for diagnosis and treatment. Magnetic nanoparticles are being considered as a new generation to help improve MRI imaging by enhancing contrast[67–69].This is caused by their exclusive physical features and performance at the cellular and molecular altitudes and biological interfaces. They are also used for targeted and topical drug delivery. As a result, this fact has attracted the attention of researchers for the first time in the past decades. An important challenge in the development of these magnetic nanoparticles is their function in the body environment. These materials are usually detected and cleared by the reticuloendothelial system (RES) before reaching the target tissue or site. In addition, there are many biological barriers in the way of their final delivery[70]. The morphology, charge and surface chemistry indicate that these particles can be used intravenously or other methods must be used. These physical and chemical properties of particles determine their biological distribution as well as their function in the body.

There are several methods that can be used to reduce the delay in the operation of magnetic nanoparticles and also increase their presence time in the bloodstream, thus increasing the likelihood that they will reach the target tissue, including these methods Particle size reduction or grafting nonfouling polymers can be mentioned .Recently, a new generation of magnetic nanoparticles has been introduced which can facilitate MRI imaging contrast. For instance, performing better in drug delivery and targeted drug delivery have been detected. The nucleus and functional ligands are used in the composition of carriers to improve the diagnosis and delivery of the drug. The use of certain materials and compounds such as doped iron oxide nanocrystals or metal alloys that are nanoparticles or nanocomposites can improve imaging by amplifying the signal in the background and magnetic moments[71][72].

The use of suitable coatings such as silica nanoparticles or gold nanoparticles allows us to use even a toxic nucleus in a drug carrier. Due to the fact that these coatings can be self-assembled monolayers)SAMS(, they provide more complete and better coverage for the core[73].

2.2.1.1. Properties of magnetic nanoparticles

The influences of magnetic fields on the tissues of the human body, as well as the possibility of controlling, detecting and accessing magnetic materials while they are inside the body, have long been studied for use in medicine The reason that magnetic nanoparticles have been considered for imaging is that they can provide descriptive images with high contrast and resolution. This high imaging power can help diagnose malignant and healthy tissues. In addition, if a lesion such as vascular plaque is detected, a change in the external magnetic field can cause the drug-carrying nanoparticles to accumulate in the area[68]. One of the most widely used methods for coronary artery imaging to diagnose or treat coronary artery disease is MRI. The MRI technique has evolved as a powerful non-invasive method for diagnosis. It is based on the use of a magnetic field that generates magnetic alignments of protons in the direction of the field. When radio frequency is transmitted, the direction of magnetization changes, followed by the change in the direction of the field.

2.2.1.2. Magnetic Fe2O3 Nanoparticles

Magnetic Fe2O3 nanoparticles are composed of a core of magnetite (Fe3O4) or gamma-Fe2O3 and an appropriate cover of polymeric, metallic and ceramic materials, such as liposome, mesoporous silica and chitosan (figure 4). Superparamagnetic Iron Oxide Nanoparticles (SPIO) and Ultrasmall superparamagnetic iron oxide nanoparticles (USPIO) are among colloidal Fe2O3 magnetic nanoparticless that have been broadly researched for their biomedical applications caused by their outstanding biocompatibility and easy production [74,75].

A variety of synthesis, processes produce iron oxide nanoparticles. These processes range from wet chemistry solution-based [77] to unusual

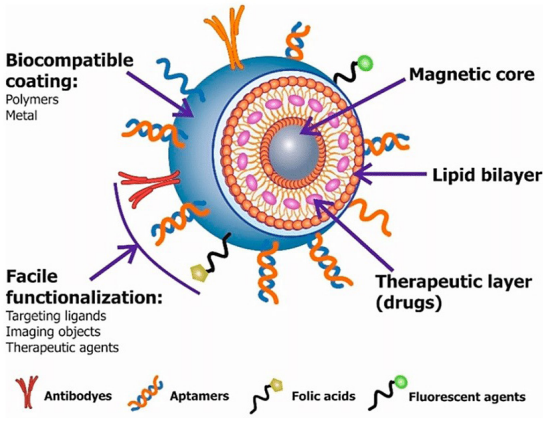

Fig. 4- Schematic of a magnetic nanoparticle with different coatings for drug delivery and imaging [76].

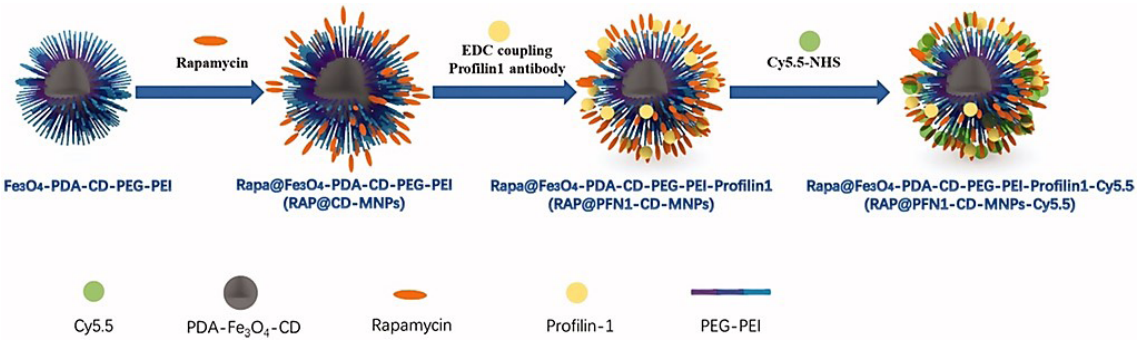

Fig. 5- Schematic diagram of Fe3O4 nanoparticles functionalized with rapamycin and profilin1 antibody [66].

techniques like laser pyrolysis or chemical vapor deposition. Presently, SPIO and USPIO have clinical applications as contrast agents in MRI. They are predominantly made by an liquid co-precipitation technique along with the coating material [78]. In hydraulic systems, controlling the amount of pH of the solution and the coating material affects the formation of particles and their properties. They need to further improve the surface engineering of SPIONs to minimize toxicity and improve biocompatibility[79]. SPIONS are able to be conjugated with antibodies in order to binding with Vascular cells and integrating with anti-inflammatory drugs (Figure 5) [66]. When magnetic particles of iron oxide are placed in an external magnetic field, the particles align their magnetic orientation with the direction of the magnetic field, which increases the flux. After removing the magnetic field, Brownian motion is sufficient to generate random magnetic moments. Hence their magnetic properties are lost. This property is referred to superparamagnetism, which only some nanometer-sized magnetic materials have. In fact, it depends on the size of the particles[80].

Due to their excellent magnetic properties as well as their corresponding surface properties, nanometer iron oxide is broadly employed for biomedical usage like targeted drug transfer, hyperthermia and also MRI imaging.

Another reason why we use nanometer iron oxide is to increase their biosensitive properties such as biocompatibility. Some properties such as hydrodynamic diameter, surface charge and density of the coating are important in determining the viability of nanoparticles in medical applications. These parameters strongly affect the possibility of interaction as well as their ability to maintain superparamagnetic behavior[81].

2.2.2. Metallic nanoparticles

Chemical instability for materials such as cobalt, nickel, and iron causes them not to receive much attention in biological applications. These magnetic nanoparticles, which oxidize rapidly in the presence of water, oxygen, or moisture, must be coated with materials such as gold or silica to improve properties such as reducing toxicity[82]. Although these nanoparticles generally have complex synthesis methods, researching them continues due to their unique benefits. Among these materials, iron oxide nanoparticles have very high magnetic properties, which are called superparamagnetism. These iron oxide nanoparticles are able to maintain their magnetic properties in larger particle sizes compared to their oxide part[83].

In a study by Peng et al. They showed that Fe3O4 can have better resistance to deep oxidation having crystalline structure than having an amorphous structure and a better protective layer was established. after the nanoparticles were obtained by heat degradation, the formation of an oxide layer and its amount and thickness were controlled by the oxygen transfer method.Fe/Fe3O4 nanoparticles have a 4-nm central radius and 2.5-nm oxide thickness. The magnetic account of nanoparticles verified that the particles have superparamagnetic property and a Ms of 102.6 emu/g Fe [84].

Metalic nanoparticles generally using ceramic coatings, polymers, liposomes and dendrimers, etc. can have better biocompatibility and also help in targeted drug delivery (Table 2).

2.2.2.1. Gold nanoparticles

CT)Computed Tomography) scan is one of the best and most common methods for coronary artery imaging, which is also a non-invasive method[93]. Modern CT scanners allow you to take high-speed and comfortable images with good resolution of

Table 2- Summary of approaches to metallic nanoparticles atherosclerosis theranostics

Nanoparticles	Target	Model	Imaging technique	Therapeutic mechanism	Reference
Iron-oxide loaded-solid lipid	Platelets	In-vitro	MRI	-	[85]
Ironhydroxyapatite	Inflammation	Rat	-	Magnetically-induced release	[86]
SPION	Phosphatidylserine	Hyperlipidemic Rabbit	-	-	[87]
Gadolinium-loaded liposomes	MRP8/14 (calprotetin)	ApoE−/− mice	-	-	[88]
USPIO	VCAM-1	ApoE−/− mice	-	-	[89]
Gold nanoparticles	mesenchymal stem cells and Bone-marrow	In-Vitro	-	Potentiates the cardiogenic differentiation of stem Cells for infarcted myocardium regeneration	[90]
Gold nanoparticles	myocardial cells	Heart failure Wistar rat model	-	Effective inotropic agent that increases myocardial contractility in patients with heart failure	[91]
Gold nanoparticles	miR-155	Ovariectomized diabetic mouse model	-	management of cardiovascular diseases in postmenopausal diabetic patients	[92]

the heart and coronary arteries, and can also reduce errors related to the movement of the heart muscle and breathing[94].The use of X-rays and CT scans has received a lot of attention due to the fact that cell imaging has recently become a favorite of researchers. It has been observed that the ability to image cells labeled by gold nanoparticles with high resolution and scale of a cell is very important[95] [96]. Imaging techniques such as Single-photon emission computerized tomography (SPECT) and MRI have problems with the movement of the heart muscle and chest to the respiratory tract, which has been eliminated in CT imaging. Therefore, gold nanoparticles can give us hope for non-intrusive imaging and monitoring of monocyte buildup in atherosclerotic plaques. Gold nanoparticles have been studied for medical uses because of their ability to regulate particle shape, size, biocompatibility and unique physical properties. The mentioned properties of gold nanoparticles make us more inclined to use them in biomedical applications, and adding a factor to them can give much more desirable properties. For example, by adding polyethylene glycol (PEG) coatings to gold nanoparticles, they can be prevented from being absorbed by the reticuloendothelial system, which increases their shelf life in the bloodstream, resulting in greater efficiencies for targeted drug delivery. Gold nanoparticles are useful both as a blood pool and as a contrast enhancer in CT[97,98].

3. Mesoporous silica-based nanocarriers

Mesoporous silica is a mineral polymer nanomaterial with a pore size of 2 to 50 nm and many outstanding features like extraordinary specific surface area, evenly adaptable pore size, and excellent drug-carrying ability, outstanding biocompatibility, and easy modification of the surface. Based on how the mesoporous is ordered, it is categorized into disordered mesoporous silica and ordered one. This research centers on the ordered one because of its too ordered channel construction, even pore size spreading, and many mesoporous forms appropriate for drug transfer. In 1992, Kresge et al., the Mobil Company scientists, introduced an ordered mesoporous substance called MCM-41. The pore structure of this nanomaterial has a two-dimensional hexagonal arrangement with even particle and pore size that can be endlessly accustomed in the range of 2–10 nm. By adjusting the production conditions, different forms of mesoporous silica are continuously produced. [99].

The drug bearing ability of mesoporous silica nanoparticles make it as a great candidate for overwhelming the drug resistant tumors. This fascinating ability introduced mesoporous silica

as an useful agent for diagnosis and therapy of atherosclerosis.They are able to track macrophages for plaque's imaging,whose are principal part of atherosclerosis plaque.They also could be utilized as nanocarriers for targeting[100].For instance,The aza-dibenzocyclooctyne polymerized PEGylated mesoporous silica nanoparticles (DBCO-MSNs) were developed by Jeong et al. using biological orthogonal F-18 tagging to chase macrophage cells by Positron Emission Computed Tomography (PET) [101]. The results indicated that [102] F-DBCO-MSNs tagged macrophage cells (RAW264.7) could stay and amass at the atherosclerotic plaque and be checked by PET images. Such DBCO-functionalized MSNs can offer a novel way for the diagnosis of Atheroscelorosis with PET imaging. Ji et al. invented anti-CD68 receptor-targeted Fe-doped hollow silica nanoparticles (CD68-Fe-HSNs). It is a double-modal US/MRI contrast to detect macrophages of aorta ventralis atherosclerotic plaques in ApoE-/- mice [103]. Besides, the CD68-Fe-HSNs were eco-friendly, though they were mineral mesoporous nanosystems. This shows their capacity for drug transfer and AS theranostic. Because AS is an inflammatory disease, the extraordinary appearance of inflammatory agents can also be utilized as targets for AS tracking. Xu et al. developed mesoporous silica nanoparticles that were able to aim vascular cell adhesion molecule 1 (VCAM-1) released by endothelial cells [104]. VHPKQHR peptide-modified magnetic mesoporous nanoparticles (FITC-VHP-Fe3O4@SiO2) were built by joining fluorescein isothiocyanate (FITC) into Fe3O4@SiO2 and adjusting VHPKQHR (Val-His-Pro-Lys-Gln-His-Arg) peptide on their surface. In vitro fluorescence imaging and in vivo magnetic resonance imaging displayed that FITC-VHP-Fe3O4@SiO2 were able to pinanoparticlesoint atherosclerotic plaque areas. In this article, the authors did not intend for drug transfer, but they showed the likelihood of future precise transfer of drugs by MRI guided with FITC-VHP-Fe3O4@SiO2 for AS [100]

For the example of targeting silica mesoporous nanocarriers ,Pham et al[105] developed a nanocarrier system based on mesoporous silica ,loaded with Rosuvastatin and coated hyaluronic acid (HA), poly (l-lysine hydrochloride) (PLL), and methoxy-poly (ethylene glycol)-block-poly (l-glutamic acid sodium salt) (PGA).This carrier was also surface modified with CD9, an overexpressed protein by plaques macrophages for separating imflammatory cells. The results showed that the drug is fully sheltered in mesoporous silica while hyalororonic acid coating allowed release of CD9 antibody via its degradation.The prescence of PLL and PGA coating helped the stability of mesoporous silica. This nanocarrier system helped the plaque destruction via hindering the senescence process of cells by using loaded drug and surface-conjugated antibody.

4. Conclusion and future prospectives

Nowadays, atherosclerosis is one of the major issues for cardiac infarction and causes a lot of death annually. Several invasive (such as endovascular surgery) and noninvasive methods have been used for atherosclerosis therapy. Noninvasive methods including medicine therapy and targeted therapy have been utilized for alleviating the symptoms. Seeking into literature, targeted therapy with nanocarriers attracted lots of attention in recent years. In this review, we concentrated on novel metallic, polymeric, magnetic, silica based and liposome based nanocarriers for atherosclerosis therapy and their theranostic approaches. In near future, these fresh methods will be replaced the common therapy methods and will decrease the morality rate of people suffering from atherosclerosis disease.

The futuristical insights include using various coating and surface modifications on nano-carriers for effective targeting and imaging of atherosclerosis.Developing of novel compsite or core-shell system for multiple aims of utilizing nanocarries would be another perspective. .Using less cytoxic materials also could be considered in designation of nanocarries.

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