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Application of nanodrugs in the treatment of cardiovascular diseases

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ABSTRACT

Cardiovascular disease is still a disease with high incidence rate and mortality. Although advanced technology continues to increase our understanding of cardiovascular disease, its diagnosis and treatment still have limitations. As an emerging interdisciplinary method, nanotechnology has shown enormous clinical application potential. Nanomaterials have unique physical and chemical properties, which help to improve the sensitivity and specificity of biosensor technology and molecular imaging technology in the diagnosis of cardiovascular diseases. This paper first summarizes the versatility of nanomaterials, the physicochemical adjustability of biomolecular engineering, the design strategy of nanoparticles in cardio cerebral Vascular disease, the application of nanomaterials in the diagnosis and treatment of common cardiovascular diseases, and the use of nanomaterials can significantly improve the diagnostic sensitivity, specificity and therapeutic effect. Subsequently, the article summarized various nanomaterials. Finally, the article demonstrated the potential of the antioxidant/anti-inflammatory and photoelectric/photothermal properties of nanomaterials to be directly applied to the treatment of cardiovascular diseases.

KEYWORDS

Cardiovascular diseases; Nanomaterials; Diagnosis; Treatment

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1. Introduction

Cardiovascular disease (CVD) is one of the most important diseases endangering human health and life. China's cardiovascular disease report in 2015 showed that the death rate of cardiovascular disease ranked first in the composition of disease deaths, and its incidence rate showed an upward trend [1]. Although there are many clinical techniques and methods for the diagnosis and treatment of cardiovascular diseases, they still cannot fully meet the clinical needs. For example, in diagnosis, although traditional imaging technology has been able to diagnose diseases such as Atherosclerosis plaque and Stenosis. However, due to the poor specificity and short half-life of traditional small molecule contrast agents, they cannot achieve sufficient resolution and sensitivity, which leads to certain defects in the early diagnosis of Atherosclerosis and the discovery of vulnerable plaque in the later stage; In terms of drug therapy, traditional dosage forms of drugs have problems such as short plasma half-life, high clearance rate, and significant toxic side effects.

Nanomedicine is an interdisciplinary subject formed after the combination of nanotechnology and modern medicine. It has developed rapidly, providing new methods and new ideas for the diagnosis and treatment of many diseases [2-3], and also providing new ideas and ways to solve the shortcomings and shortcomings of traditional diagnosis and treatment technologies and methods of cardiovascular diseases. Nanocarrier technology is an important part of nanomedicine, which is widely used in the diagnosis and treatment of many diseases. There have been many drugs transformed by nanotechnology in clinic. Nanocarrier technology uses natural materials, synthetic materials, etc. as packaging materials to disperse, adsorb, crosslink, or package drugs, diagnostic reagents, or active molecules in nanoscale particles. Due to the unique properties of nanodrug carriers and their ability to further functionalize or assemble, they have significant advantages in drug delivery: (1) significantly improving the saturation solubility of insoluble drugs; (2) It can improve the stability of the drug carried in the body and prolong the circulation time of the drug in the body; (3) It can effectively help drugs reach the target of action and improve the therapeutic effect of drugs; (4) It can significantly increase the absorption rate of drugs and improve their bioavailability; (5) It can improve the distribution of drugs in the body, reduce the accumulation of drugs in normal tissues, and reduce the toxic side effects of drugs [4-7]. Nanodrug carriers have made great progress in tumor treatment, with an increasing number of nanodrug carriers entering clinical trials and applications [8-9].

Nanocarriers also have obvious advantages and potential in the diagnosis and treatment of cardiovascular diseases. They can improve the stability of contrast agents or drug molecules in circulation, especially water-insoluble molecules; Through the directional delivery of cardiovascular disease focus tissues and cells, the concentration of contrast agents or drugs at the focus can be increased, and the accumulation of other tissues can be reduced, so as to improve the imaging resolution, improve drug efficacy and reduce toxic and side effects; Assisted by controlled release or stimulus response release technology, contrast agents, diagnostic reagents, or drugs can be accurately delivered to achieve the goal of precise diagnosis and treatment. This article will review the research progress of nanomaterials in the diagnosis and treatment of CVD, and provide new methods and ideas for the diagnosis and treatment of CVD.

2. Nanomaterials for CVD

Nanomaterials are defined as engineering materials that are 1-100 nanometers in at least one dimension. Nanomedicine refers to the application of nanomaterials and nanodevices to the prevention, diagnosis and treatment of diseases [10-20]. The versatility of nanomaterials and the physical and chemical adjustability of biomolecular engineering, including (1) highly modular and controllable physical and chemical properties; (2) Size (large enough to transport a therapeutic or imaging contrast agent payload larger than small molecules, but

small enough to maintain the ability to travel throughout the body (through the blood); (3) Large surface to volume ratio, high affinity, and payload capacity; (4) Multifunctional potential (e.g., combined therapy diagnostic payloads ("therapeutics") and multiple diagnostic molecular types to achieve multimodal imaging. The characteristic of therapeutic nanomaterials is the ability to carry a large number of therapeutic molecules and release them through sustained and/or triggered acute or chronic release. The typical feature of diagnostic nanomaterials is their ability to generate signals to visualize the accumulation of specific sites representing biomedical, cellular, or molecular states (such as inflammation), typically using imaging or in vitro detection strategies [21-30].

After myocardial infarction, cardiomyocyte apoptosis, myofibroblasts and macrophages form scars, which affect the contractile function of the heart and eventually lead to heart failure [26]. In order to overcome these bottlenecks, research based on cell therapy and tissue engineering has gradually become a popular direction. Nanomaterials refer to materials that have at least one dimension of material in the range of 1-100 nm in three-dimensional space. They are typically made of metals, ceramics, polymers, organic materials, or composite materials because they are synthesized at the nanoscale, with significantly increased surface area volume ratio and roughness, thereby enhancing mechanical, conductive, optical, and magnetic properties. The excellent material properties of nanomaterials have shown promising results in heart tissue engineering.

3. Design strategy of nanoparticles in cardio cerebral Vascular disease

Nanotechnology has been widely used in the field of biomedicine in the past few decades. Nanoparticles, ranging from a few nanometers to several hundred nanometers, have special Kubo effects, small size effects, surface effects, and quantum properties, which have attracted widespread attention from researchers [31-35].

3.1. Passive targeting strategy

The normal vascular endothelial junction is only about 2 nm tight, while the dysfunctional endothelium and the neovascular gap in the plaque increase, so there is an EPRE similar to solid tumors, which is the basis of the passive targeting strategy of nanoparticles for Atherosclerosis [35-37]. Langer et al. [38] first confirmed that nanoparticles can target Atherosclerosis plaque with EPRE in 2014. When designing nanoparticles based on passive targeting strategies, multiple factors such as size, shape, and potential need to be considered [39].

3.2. Active targeting strategy

The active targeting strategy of ligand modification on nanoparticles can further improve their targeting ability. In Atherosclerosis, the active targets are mainly divided into cells (endothelial cells, macrophages, vascular smooth muscle cells) and non cellular components [40-45]. VCAM-1 and Integrin on endothelial cells, scavenger receptors on macrophages and VSMCs are the most common biological targets. The non cellular components are mainly extracellular matrix components such as collagen.

3.3. Biomimetic strategy

The synthetic functionalization strategy has been successfully applied in the field of Atherosclerosis, greatly improving the performance of nanoparticles. However, synthetic strategies are difficult to replicate all the functions of biological system. Therefore, researchers have used biomimetic strategies as a guiding principle for the design of next-generation nanoplatforms. Compared to traditional nanoparticles, nanoparticles designed based on biomimetic strategies can directly interact with the immune system to make the body believe they are

part of themselves [46]. Biomimetics generate similar functions by simulating natural ingredients in various forms, the most important of which is the simulation around cells. Among them, biomimetic strategies based on cell membranes and extracellular vesicles are the most common.

3.4. Cell delivery strategy

In the early 1970s, scientists noticed that the semi permeable Red Cell Membrane (RCM) could protect the enzymes encapsulated within it [47]. Subsequently, research on the use of cells as nanoparticle carriers gradually increased. Generally speaking, cell delivery has the advantages of long cycle time, strong targeting ability, high biocompatibility, and being able to overcome physiological barriers. In Atherosclerosis, the most commonly used cell systems are red blood cells, platelets, Monocyte and neutrophils.

4. Application of nanoparticles in CVD treatment

Cardiovascular diseases are a group of circulatory system diseases, including Atherosclerosis, thrombosis, myocardial/cerebral infarction and subsequent ischemia reperfusion injury, which are the main causes of disability and death worldwide. In the past few decades, people have made tremendous efforts in the medical care of these diseases. However, existing imaging diagnosis and drug therapy still face issues such as poor bioavailability of contrast agents and drugs, resulting in low signal-to-noise ratio and unsatisfactory therapeutic effects. The rapid development of nanotechnology has reshaped modern medicine.

Nano imaging: pre-clinical CVD nano imaging, especially Atherosclerosis, uses magnetic, nuclear, acoustic and optical nano materials and their combinations. The signals generated by these nanomaterials are matched with their related imaging methods, such as magnetic iron oxide nanomaterials used for MRI and magnetic particle imaging (MPI), and gold nanomaterials used for computed tomography (CT). Careful selection of appropriate in vivo CVD imaging mode requires consideration of (1) Penetration depth and spatial resolution requirements, (2) potential toxicity of nanomaterials (such as the amount of injection materials) and modes (such as ionizing radiation or invasive optical methods, intravascular catheters) for clinical imaging; (3) The matching between the information needed by cardiologists to make clinical decisions and the data provided by nanoimaging strategies.

In vitro diagnosis: Imaging based diagnosis can serve as a benchmark, not only for detecting diseases, but also for spatial localization at millimeter level and below. The detection of endogenous biomarkers in clinical samples (including blood, saliva, and urine) is often hindered by background signals, requiring more sensitive and specific strategies. Nanomaterials have advantages in detecting molecular and cellular biomarkers related to CVD, including C-reactive protein (CRP) and Troponin, and improve sensitivity by amplifying signals and using magnetic and other physical and chemical properties.

4.1. Application of nanoparticles in the diagnosis and treatment of coronary heart disease

With the improvement of science and technology, molecular imaging of coronary artery disease based on nanotechnology is developing to detect some targets of atheromatous plaque. Targeting macrophages in plaques using cross-linked ferric oxide fluorescent nanoparticles, detecting certain targets associated with apoptosis and oxidized low-density lipoproteins using radioisotopically labeled reagents and superparamagnetic nanoparticles (ferric oxide and gadolinium), targeting integrin αvβ3 using gadolinium coated perfluorocarbon nanoparticles, etc., to classify plaques at risk of rupture.

Nanoparticles have gradually attracted attention in the field of Atherosclerosis treatment due to their advantages such as increasing the retention time of drugs in the whole body, reducing the non-targeted cytotoxicity of drugs, improving the solubility of drugs, reducing the required dose, increasing the cumulant of

drugs at specific sites, and combining the diagnosis and treatment of drugs. For example, functional pravastatin loaded nanovesicles targeting macrophages can be used for high-dose treatment, In order to reduce the toxicity of other tissues and improve the efficacy, absorbable nanoparticles are used to deliver Pioglitazone to circulating Monocyte to regulate inflammatory reaction and prevent Atherosclerosis plaque rupture [3]. In addition, hirudin combined with nanoparticles can inhibit the formation of further fibrin clots after Coronary occlusion and reduce the risk of systemic bleeding [4]. Restenosis after coronary angioplasty is influenced by mechanical injury, inflammatory response, and stent endothelialization rate. Inhibition of stent thrombosis and restenosis are the main factors determining the long-term effectiveness of stent implantation [5]. Research [6] confirmed that Pitavastatin nanoparticles eluting stent has the same efficiency as sirolimus eluting stent in reducing in stent restenosis, but it can accelerate endothelial healing (Figure 1).

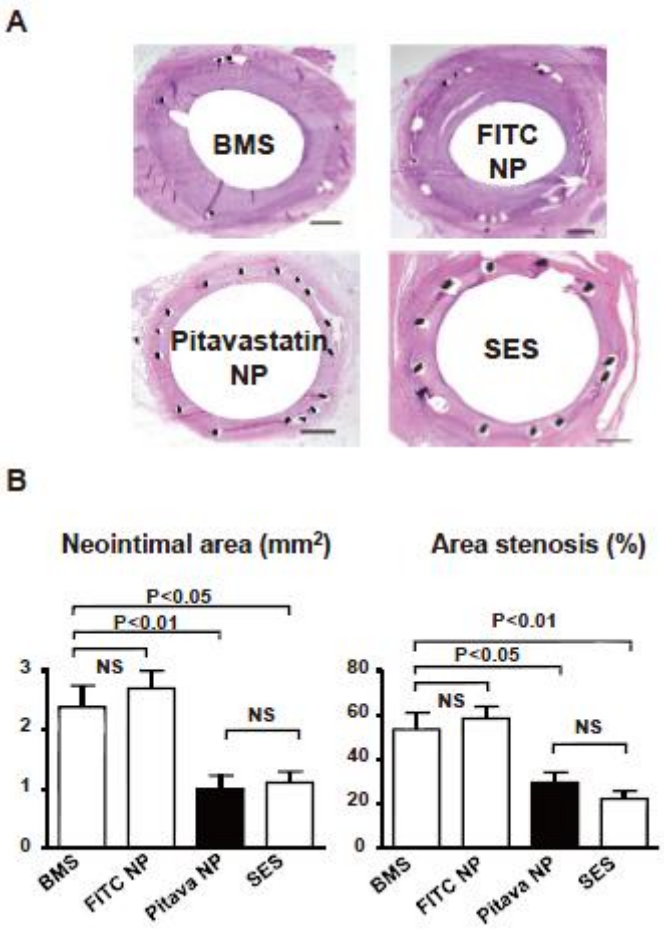

Figure 1. Histopathological analysis of in-stent neointima formation four weeks after stent implantation. Reproduced/Adapted with permission.

4.2. Application of nanoparticles in hypertension

The diagnosis of hypertension is usually based on measuring systolic and diastolic blood pressure, but in the early stages of hypertension, there are usually no obvious symptoms and it is difficult to detect. Therefore, the diagnosis of hypertension is usually after the occurrence of severe organ damage, which is already too late. Multiple physiological indicators have been reported to be associated with the occurrence of hypertension, and combined with nanotechnology, they can be used as indicators for early diagnosis of hypertension [7]. Sun et al. [8] used reduced Graphite oxide conjugated Fe_3O_4 nanoparticles to modify the surface of the electrochemical immunosensor in turn. At the same time, gold nanoparticles and anticortisol antibodies were covered on the

glassy carbon electrode to detect the total amount of cortisol in plasma through competitive binding antibody sites. The results showed that the amount of cortisol in human plasma samples was in the range of 1 to 1000 ng/mL. Similarly, some other physiological indicators, such as NO concentration, Galactose Lectin -3, leptin, sodium ion, growth hormone, inflammatory factors, etc., can be quickly detected by nano sensors to achieve early diagnosis of hypertension.

At present, most of the main antihypertensive drugs in clinic have some defects, such as poor water solubility, low bioavailability, short half-life, etc. The research shows that when Olmesartan is prepared into a nano emulsion system, compared with the conventional dose, the blood concentration of olmesartan increases by 2. 5% Eight times, the antihypertensive effect is better, the maintenance time is longer, and the dosage is reduced by nearly three times [9]. In addition, A research [48] used a new platform based on hydrogel/glass mixed nanoparticles to prepare NO controlled release nanoparticles. At the same time, nanoparticles can be used as a system for delivering small interfering RNA to prevent nucleic acid Endonuclease and Exonuclease in blood, serum and cells from degrading small interfering RNA (Figure 2). Cationic liposomes made from (2,3-dioloyl-propyl) trimethylammonium chloride can be administered intravenously to reduce β 1. The expression of adrenergic receptors can control blood pressure for 12 days [49]. Therefore, some oral drug management systems based on nanoparticles have become alternative strategies for antihypertensive drugs.

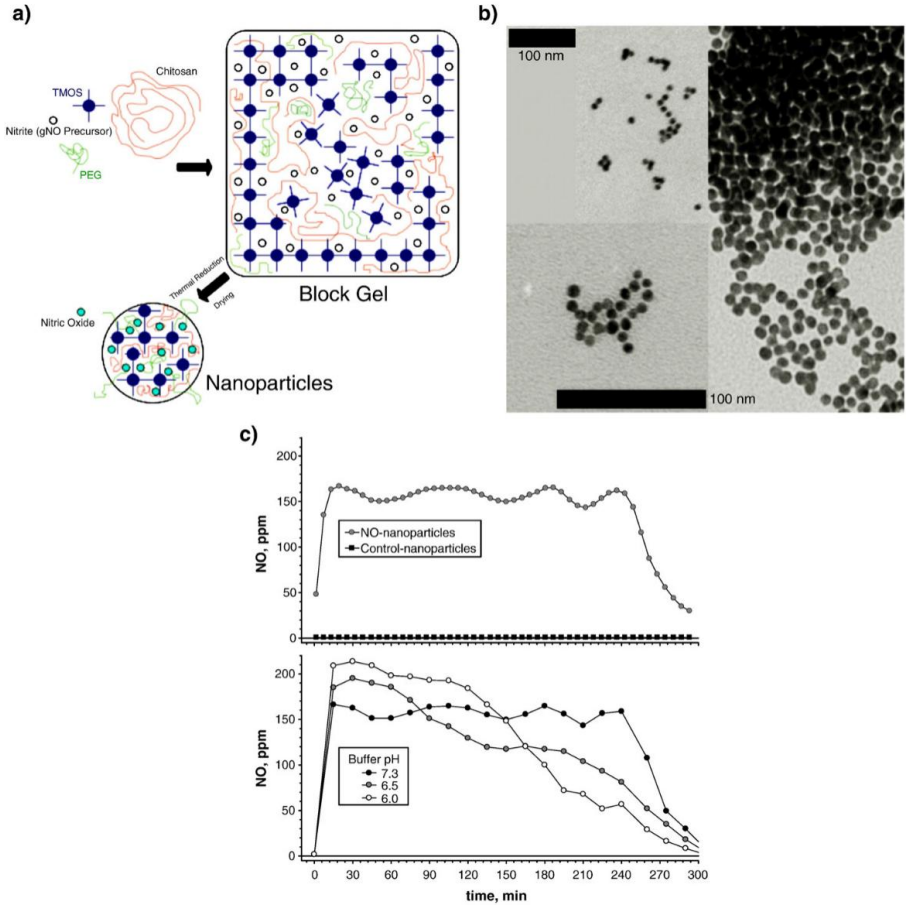

Figure 2. NO-releasing nanoparticle synthesis and morphology. (a) Schematic of NO-releasing nanoparticle synthesis. The various components are prepared and combined to form a block gel consisting of a silica hydrogel matrix encompassing the other ingredients. The block gel is dried and the nitrite precursor converted to NO via thermal reduction, resulting in the formation of the nanoparticles. (b) TEM of NO-releasing nanoparticles. The scale bars represent 100 nm, the bottom one representing the lower left and right panes and the upper one for the upper left image. (c) NO gas levels were measured using a chemiluminescent NO analyzer. Upper panel, 1 mg of NO-np or control-np at 7.4 pH. Lower panel, 1 mg of NOnp at 6.0, 6.5, and 7.3 pH. Reproduced/Adapted with permission.

4.3. Application of nanoparticles in the treatment of Atrial fibrillation

Atrial fibrillation significantly affects the incidence rate of stroke and has a high mortality rate [50]. Radiofrequency catheter ablation has become the main treatment for drug-resistant Atrial fibrillation. Previous animal experiments have proved that atrial Nerve plexus (GP) plays an important role in the occurrence and maintenance of Atrial fibrillation, and clinical evidence also shows that ablation of major GP can increase the success rate of standard Pulmonary vein separation in the treatment of Atrial fibrillation [51]. A research [52] proposed a novel ablation strategy using functionalized magnetic nanoparticles (MNPs) (Figure 3). A technique using Superparamagnetism Fe_3O_4 nanoparticles is described. When in vivo, the nanoparticles coated with thermal response polymer hydrogel release the nerve poison contained in them at body temperature, and act on the corresponding Nerve plexus to achieve the purpose of nerve ablation. The results showed that when MNP was directly injected into 6 dogs of right anterior GP, the Sinus rhythm slowing response induced by high-frequency stimulation was significantly inhibited, and the minimum voltage of Atrial fibrillation induced by high-frequency stimulation was significantly increased. In the other four dogs, MNP was injected into the left circumflex branch of the coronary artery supplying the right lower GP, and MNP was attracted to the right lower GP through a magnet sutured on the epicardial surface, which inhibited the function of the right lower GP and reduced the ventricular rate. These results indicate that targeted drug delivery based on nanotechnology may have broad prospects in the treatment of Atrial fibrillation.

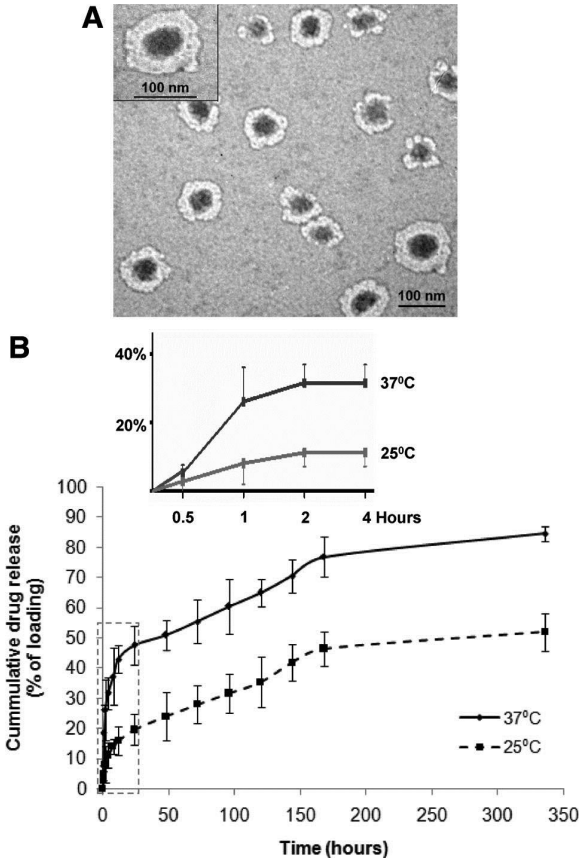

Figure 3. Physical properties of the MNP. A, Transmission electron micrograph of pNIPA-AAm–coated MNPs. Each magnetic core (dark center) was surrounded by a polymeric shell layer (white layer surrounding the dark core). B, In vitro release profiles of NIPA-M from pNIPA-AAm–coated MNPs at 25°C and 37°C. Curves represent the cumulative percent releases of NIPA-M over 336 hours at 25°C and 37°C. Inset, Release kinetics in the first 4 hours indicated by the dotted box in B. Reproduced/Adapted with permission.

4.4. Application of nanoparticles in the treatment of acute myocardial infarction

After acute myocardial infarction, due to the low proliferation and limited self-repair ability of cardiomyocytes, the cardiac function will decline and cannot be restored as before, and the conventional restoration of myocardial blood supply cannot repair the apoptotic cardiomyocytes. Therefore, Stem-cell therapy has become a new therapeutic method [19]. Because of its unique magnetism and good biocompatibility, iron oxide superparamagnetism nanoparticles can be used to guide and monitor the therapeutic effect of stem cells on acute myocardial infarction. It has been recognized as one of the most promising stem cell markers [20]. In addition, a research [21] used chitosan alginate nanoparticles to target the delivery of placental growth factor, which can achieve the goal of continuously releasing placental growth factor and improving cardiac function in acute myocardial infarction sites.

A research [22] have proposed that polylactide glycolic acid copolymer nanoparticles doped with Irbesartan can inhibit the recruitment of inflammatory Monocyte, which is helpful to reduce myocardial ischemia reperfusion injury, further reduce infarct size and improve left ventricular remodeling. A research [23] designed a kind of silica nanoparticles containing adenosine (prototype heart protective agent) to reduce the infarct area, and reduce Hypotension and heart rate slowdown caused by the use of adenosine throughout the body (Figure 4).

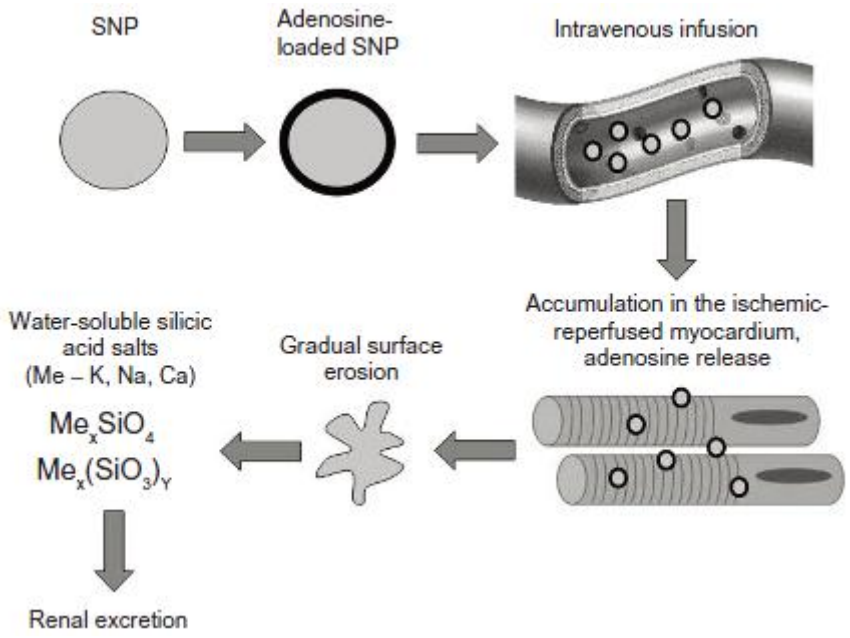

Figure 4. Proposed algorithm of passive heart targeting with silica nanoparticles. Reproduced/Adapted with permission.

4.5 Application of nanoparticles in the treatment of Atherosclerosis

In recent years, non stimulation responsive nanoparticles used in the treatment of Atherosclerosis are mainly polymer materials such as polylactic acid Glycolic acid copolymer (PLGA), Cyclodextrin and chitosan [26] (Figure 5). PLGA has good biocompatibility and is often used as a carrier for drug delivery. Katsuki et al [27] loaded Pitavastatin into PLGA particles, and the results showed that compared with free Pitavastatin, the nanoparticles could significantly inhibit plaque rupture. Guo et al. [28] prepared conjugated Luminol β — Cyclodextrin nanoparticles, which have intrinsic anti-inflammatory activity, can significantly inhibit the inflammatory reaction mediated by macrophages and neutrophils, showing good therapeutic effect. Kim et al. [29] reported a study based on 2-hydroxypropyl – β-Self assembled core-shell nanoparticles of Cyclodextrin and statin, 2-hydroxypropyl

– β-Cyclodextrin can accelerate the removal of cholesterol from plaque, and use host guest affinity to drive the exchange of Cyclodextrin internal drug statin and plaque cholesterol. Research has shown that the levels of cholesterol and macrophages in plaques significantly decrease after injection of the nanoparticles, which can effectively slow down the occurrence of plaques. Wang et al. [30] covalently coupled Superoxide dismutase mimetic agent with pinyl phenylboronic acid to β-On cyclodextrin, a kind of broad-spectrum ROS scavenging nanoparticles (TPCD) has been developed. After TPCD is engulfed by macrophages and vascular smooth muscle cells, it can effectively eliminate excessive ROS in cells, and significantly reduce inflammation and apoptosis caused by ROS [32-44]. After intravenous injection of TPCD, it can effectively reduce the macrophage infiltration and the expression of Matrix metalloproteinase 9 in the plaque, thus increasing the stability of the plaque. Nguyen et al. [45] loaded miRNAs into chitosan nanoparticles through ion interactions, delivering exogenous miR-206 and miR-223 to macrophages. miRNAs can reduce the expression of ABCA1, thereby promoting reverse cholesterol transport.

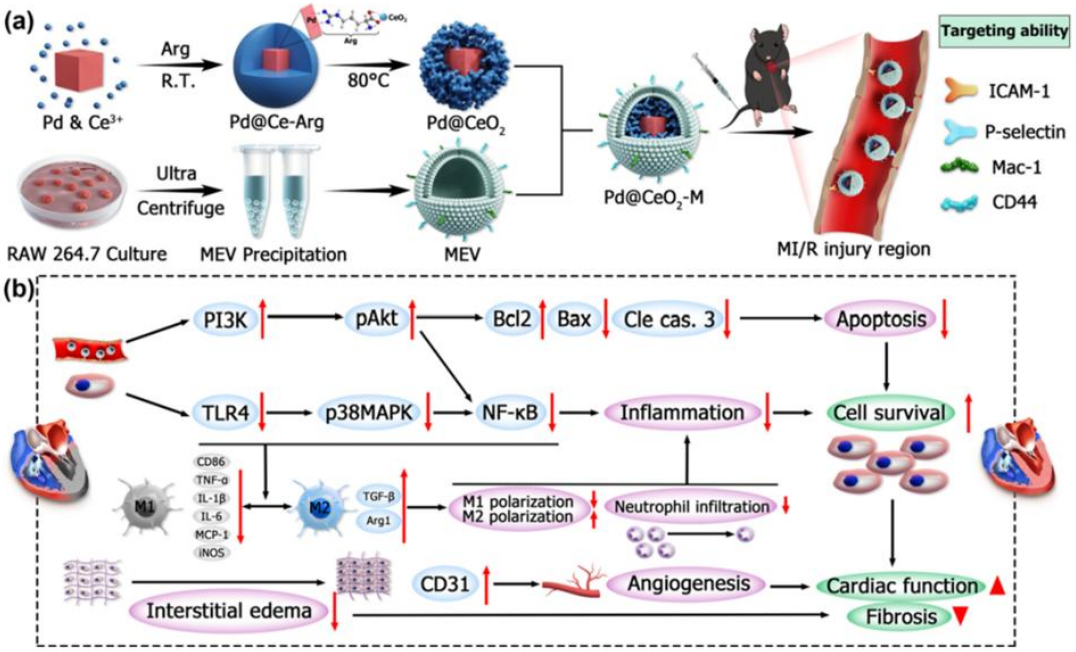

Figure 5. Pd@CeO_2-M The system is composed of Pd@CeO_2 Heterogeneous structures are composed of extracellular vesicles (MEVs) derived from external macrophages, and the expression of Mac-1 and CD44 on the surface helps to adsorb to inflammatory endothelial cells, effectively enriching damaged cells in the damaged cardiac microenvironment, thereby achieving inflammation targeting ability and alleviating MI/R injury. Reproduced/Adapted with permission.

In order to further enhance the targeting of nanoparticles, researchers developed intelligent response nanoparticles by using the special microenvironment (endogenous stimulus) or exogenous stimulus (such as light, ultrasound, and magnetism) at the plaque site [46]. Intelligent response nanoparticles based on endogenous stimuli mainly utilize the high ROS and low pH characteristics of plaque sites to regulate drug release, thereby reducing the concentration of nanoparticles in normal tissues [47]. Wu et al. [48] prepared polyethylene glycol and poly (propylene sulfide) (PEG-PPS) nano micelles containing Andrographolide. In vitro experiments showed that PEG-PPS had a good response to ROS. Oil red O staining showed that the nano micelles were more effective than free Andrographolide in inhibiting Atherosclerosis in the aortic root. Ma et al. [34] combined two-photon aggregation induced luminescence of active fluorescent groups (TP) with β-Cyclodextrin is connected by ROS

response bond, and then Prednisolone is loaded into the cavity by Supermolecule interaction. Finally, it is wrapped with ROS sensitive nano micelles (PMM) to construct diagnosis and treatment integrated nanoparticles (TPCDP @ PMM). TP can overcome the problems of aggregation induced quenching and shallow imaging depth faced by traditional fluorescent groups, and track the aggregation of TPCDP @ PMM in vivo, And perform fluorescence imaging on plaques. When TPCDP @ PMM reaches the plaque site, under the action of ROS and lipids, PMM disintegrates, and TP reacts with β — Cyclodextrin is separated to achieve dual therapeutic effects of anti-inflammation and lipid clearance. In addition, utilizing multiple stimuli for response can further improve drug release efficiency. In 2017, Dou et al. [49] compared β-Cyclodextrin chemically modified and encapsulated Sirolimus (RAP) self-assembled into acid and ROS sensitive non pro-inflammatory nanomaterials. Compared with nonresponsive nanomaterials, dual responsive nanoparticles can release drugs more effectively and achieve more excellent therapeutic effects. In the nanotherapy of Atherosclerosis, exogenous stimulation is usually light. Light stimulation, especially near-infrared lasers with wavelengths ranging from 950 to 1700 nm, can penetrate deep into biological tissues for PTT or PDT treatment of plaque sites, but most nanoparticles modify ligands or undergo local injection. It is noteworthy that Kharlamov et al. [50] carried out the PTT clinical experiment of Atherosclerosis with the patch coated with silicon gold nanoparticles. Although the aforementioned nanomedicines have shown better efficacy and fewer side effects, some studies suggest that only 0.7% of the administered nanoparticles can deliver to the targeted lesion tissue in passive targeting. Therefore, it is necessary to improve the design of nanoparticles to improve delivery efficiency [51].

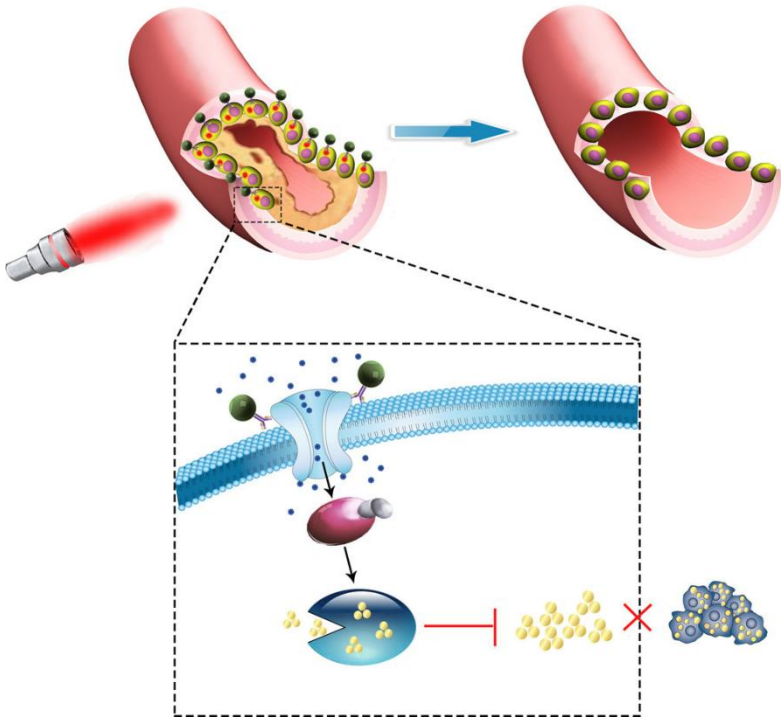

Figure 6. Illustration of CuS-TRPV1 switch for photothermal activation of TRPV1 signaling to attenuate atherosclerosis. Reproduced/Adapted with permission. Reproduced/Adapted with permission.

The most commonly used ligands for active targeting of nanoparticles through ligand modification include antibodies, peptides, polymers, etc. Antibodies can serve as targeted ligands for nanoparticles due to their strong specificity, high affinity, and good stability. Gao et al. [37] assembled specific antibodies targeting TRPV1 with CuS nanoparticles to form a photothermal switch (CuS TRPV1) (Figure 6). By activating the TRPV1 channel of VSMCs with near-infrared lasers, Ca2+influx occurred in VSMCs, activating the autophagy pathway. At the same time, CuS

TRPV1 can perform photoacoustic imaging of plaque sites, Accurately control the TRPV1 channel, thereby significantly reducing lipid accumulation. However, the volume of antibodies is relatively large, about 10-15 nm, making it difficult to attach multiple molecules to a single nanoparticle. Therefore, a large number of peptide ligands with different lengths and amino acid sequences have become a more common choice for improving the targeting of nanoparticles [52]. Unlike antibodies, peptide ligands are small enough, typically composed of 250 amino acids, to be loaded into a shallow or hydrophobic binding pocket without affecting their specificity or affinity, and have low immunogenicity and are easy to manufacture and handle [53]. Chin et al. [54] prepared peptide amphiphilic micelles, which can target the Chemokine receptor 2 (CCR2) of synthetic vascular smooth muscle cells, deliver miR-145 to the plaque site, and slow down the progress of plaque by regulating the phenotype conversion of vascular smooth muscle cells. Gao et al. [55] showed that the stabilizer 2 specific peptide ligand (S_2P) can effectively improve the targeting and plaque penetration ability of nanoparticles. Kim et al. [56] utilized the temperature dependent volume expansion characteristics of proteins in aqueous solutions to load the broad-spectrum anti-inflammatory factor IL-10 into Planck nanocarriers, and coupled it to nanoparticles through the cRGD targeted peptide thiol group and Planck's amino reaction, effectively extending the half-life of protein drugs, Moreover, the interaction between cRGD targeting peptide and Integrin can deliver it to Atherosclerosis plaque, significantly increasing the drug concentration at the plaque site, and realizing the problem of difficult protein drug delivery.

Recently, Li et al. [57] synthesized Cyclodextrin derived pH responsive nanoparticles (AAM NP) and further modified them with the peptide ligand cRGDfK of Integrin (Figure 7), which can effectively deliver anti miR33 to macrophages and significantly enhance the therapeutic effect of AAM NP. Collagen IV is abundant in the plaque site, therefore, Fredman et al. [58] synthesized collagen IV targeted peptide nanoparticles to improve the accumulation of nanoparticles in the plaque site. However, some studies suggest that in the early stage of atherosclerosis, targeting based on cRGD peptide is more effective than collagen Ⅳ peptide [59]. In addition, polymers can also be used as ligands, among which hyaluronic acid is the most widely used in Atherosclerosis. Hyaluronic acid is a polysaccharide with anti-inflammatory activity that can specifically interact with CD44 and Stabilin-2 receptors expressed in inflammatory cells and endothelial cells, and has good biocompatibility [60-67]. In 2020, Hos Saini et al. [68] coupled Atorvastatin and hyaluronic acid to form an amphiphilic polymer, which was self-assembled into nanoparticles in aqueous solution. Using the specific combination of hyaluronic acid and CD44, Atorvastatin was delivered to macrophages. After one week of treatment, the inflammation of the plaque was significantly reduced.

In addition, Glucan sulfate can be used as a target ligand for Class A scavenger receptor (SR-A), with a large amount of negative charges and good biological safety. A research [69] designed a SR-A targeted multi-modal and multi-functional nanoparticles, which can achieve specific diagnosis and Targeted therapy of vulnerable plaque (Figure 8). It uses double emulsion solvent evaporation method to embed Fe_3O_4 in the shell film of nanoparticles, Perfluorohexane encapsulated in the core, and finally uses the electrostatic effect to adsorb Glucan sulfate on the nanoparticles. Under low energy focused ultrasound irradiation, nanoparticles undergo phase transition, enabling ultrasound imaging while inducing macrophage apoptosis and alleviating plaque burden. In addition, loaded Fe_3O_4 can perform magnetic resonance imaging (MRI) on plaques, making up for the shortcomings of ultrasound imaging and accurately evaluating vulnerable plaques. The unique four legged cone needle PdH can effectively treat Atherosclerosis through combination of reactive oxygen species (ROS) clearance, hydrogen anti-inflammatory and autophagy activation (Figure 9).

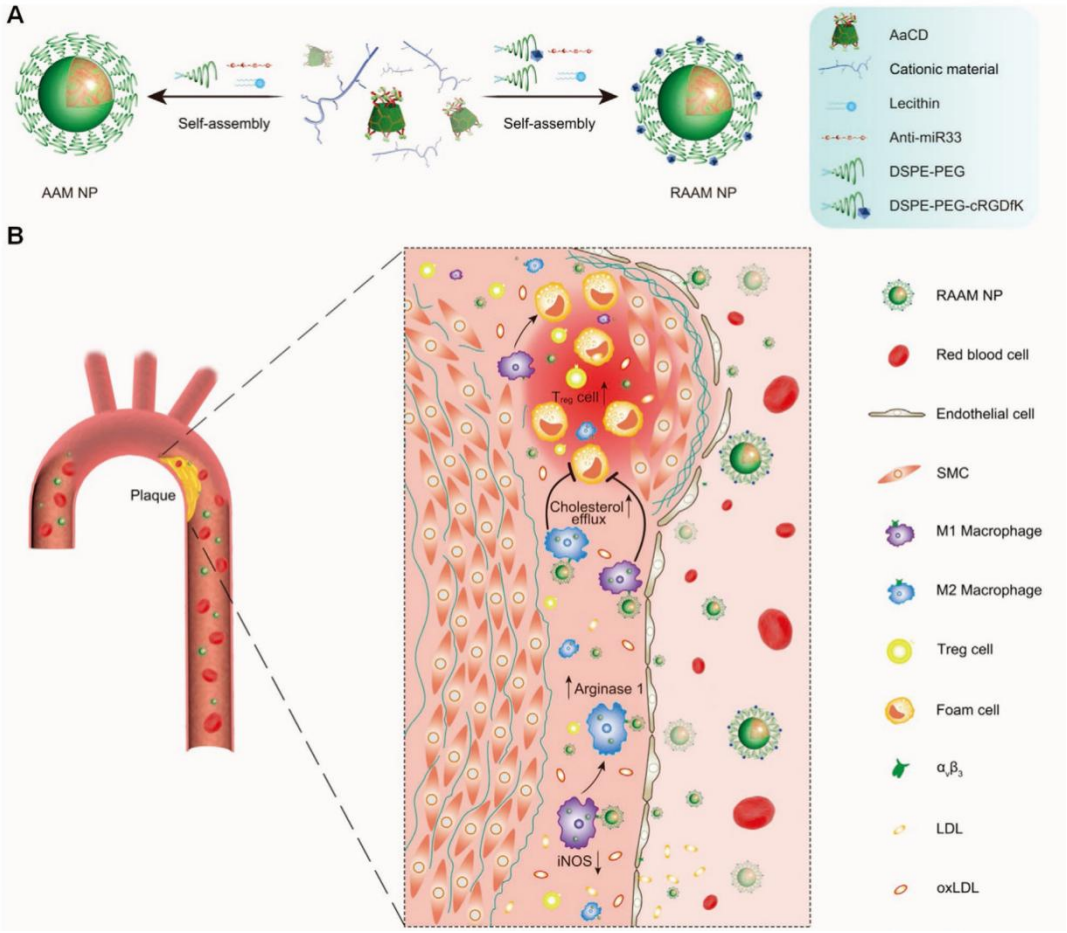

Figure 7. Schematic illustration of the composition and engineering of pH-responsive anti-miR33 nanotherapies for targeted treatment of atherosclerosis. A) The composition and preparation of designed anti-miR33 nanotherapies AAM and RAAM. AAM, a pH-responsive anti-miR33 nanotherapy; RAAM, a pH-responsive cRGDfK-targeting anti-miR33 nanotherapy. B) Sketch showing targeted treatment of atherosclerosis with the active targeting nanotherapy RAAM by simultaneously regulating reverse cholesterol transport and lesional immune responses. Reproduced/Adapted with permission.

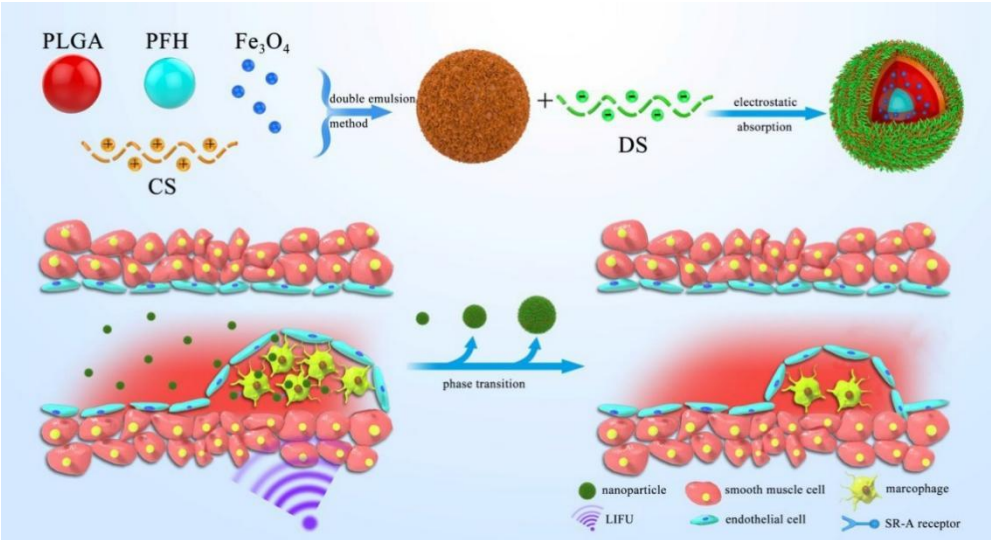

Figure 8. Schematic diagram of the preparation of the Fe-PFH-PLGA/CSDS NPs and the NPs targeting SR-A expressed on macrophage surfaces and endocytosed by macrophages, followed by cell damage due to phase transition under LIFU irradiation. Reproduced/Adapted with permission.

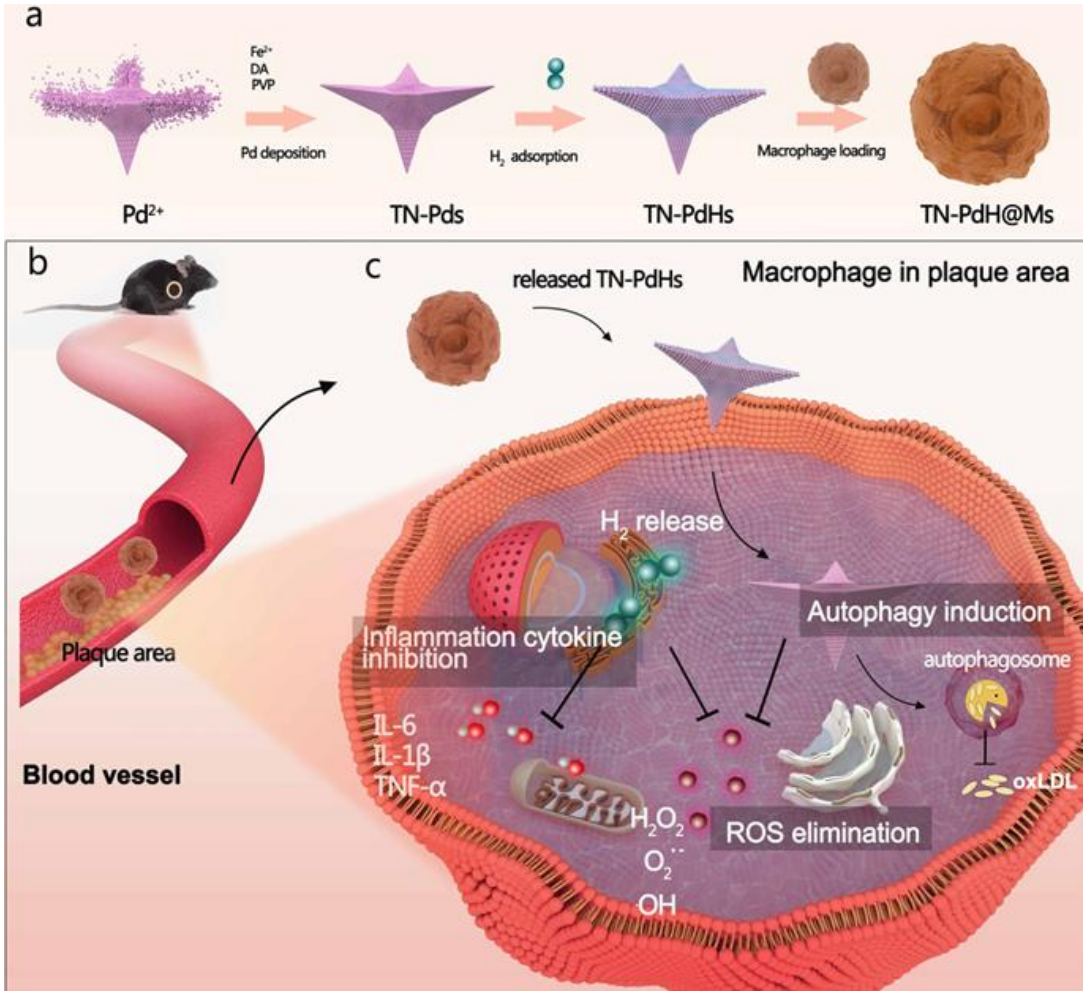

Figure 9. The unique four legged cone needle PdH can effectively treat Atherosclerosis through combination of reactive oxygen species (ROS) clearance, hydrogen anti-inflammatory and autophagy activation. Reproduced/Adapted with permission.

4.6. The role of nanoparticles in other CVDs

As a new drug delivery platform, nanoparticles also perform well in many other CVDs. Nanoparticles can target delivery of thrombolytic drugs, such as tissue type Plasmin activator, which can play a role in rapid recanalization of occluded blood vessels, and can improve the low efficiency of systemic drug use and significantly reduce bleeding and other complications [70]. As a drug release platform for perivascular drug delivery, nanoparticles have stimulated nanomedicine research on inhibiting vascular intimal hyperplasia after the treatment of Atherosclerosis with open vascular reconstruction, such as the application in the anti-proliferation of saphenous vein bridge intima [71].

5. Summary and Outlook

Nanomaterials as drug carriers and targeted contrast agents for molecular imaging have broad research prospects in the treatment and diagnosis of cardiovascular diseases. However, this field is still in the early stages of research. Although some very promising methods have been designed, most of them are still in the preclinical research stage or in vitro proof of method concepts. In order to minimize the recognition of non-specific tissues and enhance targeting, optimizing the performance of nanoparticles still poses significant challenges.

Although the theoretical results of molecular imaging and Targeted therapy have been proved favorably, the final application of these nanosystems must be based on clinical trials. Due to their inherent complexity, the clinical transformation of these new nanotechnology technologies poses great challenges. Like clinical trials of any new pharmacological active agent, nanomaterials will also require toxicity, pharmacokinetics, and biological distribution evaluation studies.

Conflict of interest

All the authors claim that the manuscript is completely original. The authors also declare no conflict of interest.

Author contributions

Conceptualization: Qiang Xie, Hongmei Yang; Investigation: Wenjie Shi; Methodology: Hongmei Yang; Writing–original draft: Qiang Xie; Writing–review & editing: Wenjie Shi.

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