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Review

Heart targeted nanoliposomal/nanoparticles drug delivery: An updated review

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ABSTRACT

Nanoliposomes are type of nano-sized vesicles made of bi-layered phospholipid membranes with an aqueous interior. They have been demonstrated to deliver several materials like low molecular weight drugs, imaging agents, peptides, proteins, and nucleic acids. Nanoliposomes have been demonstrated to slowly release an encapsulated drug, thereby leading to sustained exposure to target region and improved efficacy. This ability of nano-liposomes can be harnessed to deliver therapeutic agents precisely to the infarcted heart. Accordingly, this article will review recent developments in the application of nano liposomes and nanoparticles as drug delivery systems to treat cardiovascular related disorders such as atherosclerosis, restenosis and myocardial infarction.

Contents

1. Introduction

The use of nano-technology in providing treatment and therapy to cardiovascular diseases (CVDs) might be the answer to current challenges in CVDs. Kong, in his report says nano-technology helps to improve detection and therapy by advancing the ex-vivo and in-vivo detection and imaging of biomarkers, in addition will upgrade the delivery of drugs and tissue regeneration [1] (Fig. 1).

Nanoliposomes are type of nano sized nano-vesicles made of bilayered phospholipid membranes with an aqueous interior (Fig. 2) [2].

Nano-liposomes have been demonstrated to deliver several materials like low molecular weight drugs, imaging agents, peptides, proteins, and nucleic acids [3–7]. Nanoliposomes have been demonstrated to slowly release an encapsulated drug, thereby leading to sustained exposure to target region and improved efficacy. Most importantly nano-liposomes have been used effectively as both passive targeting and active targeting delivery routes [8]. As an active targeting route, it is loaded with

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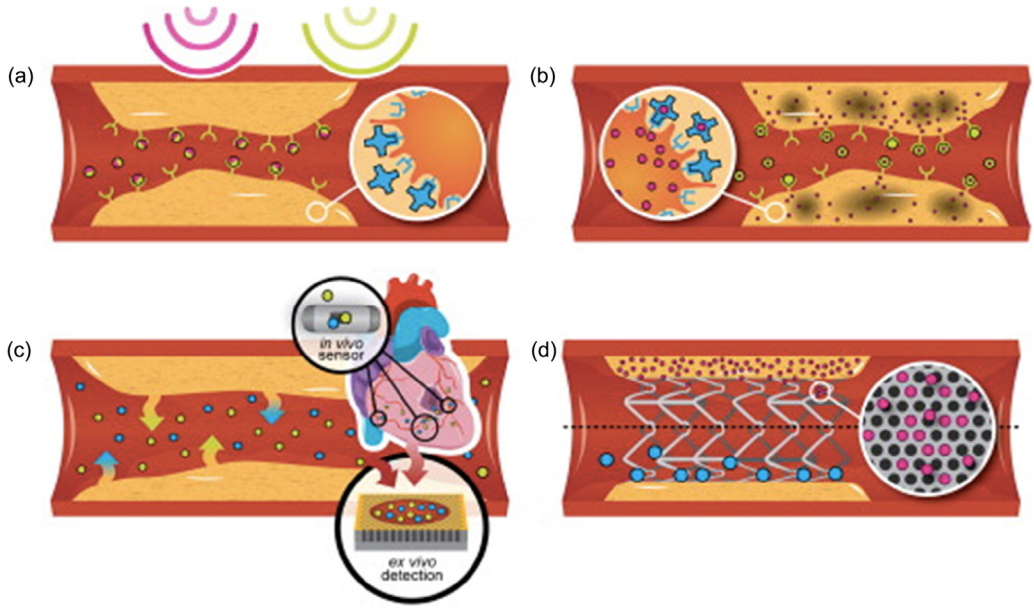

Fig. 1. Nanotechnology approaches for the advanced diagnosis and treatment of CVDs (schematic): Nanoparticles for (A) multimodal image contrast and (B) improved treatment of CVDs can be targeted to immune cells or specific ligands on the inflamed endothelium of the atherosclerotic plaque; (C) *in-vivo* sensors implanted in the pericardial region or on one of the main blood vessels and techniques for *ex-vivo*detection of biomarkers; (D) nanostructured drug/nanoparticle-eluting stents.

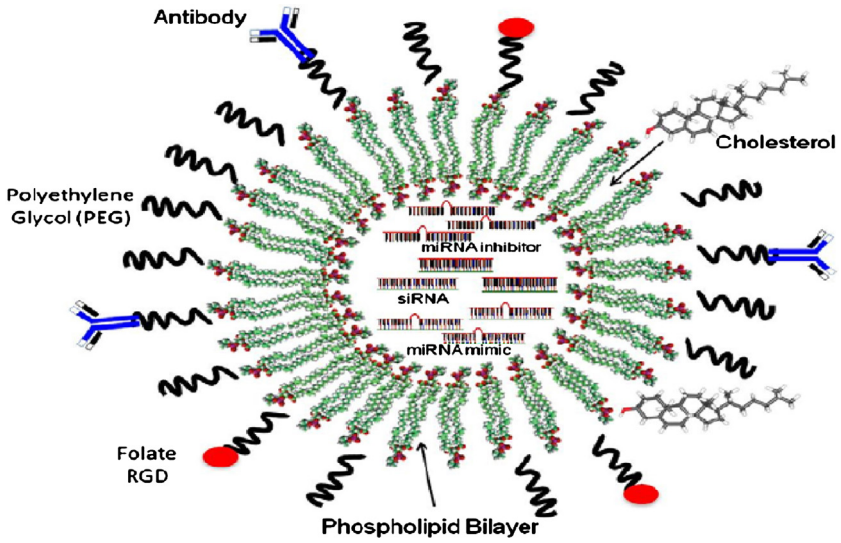

Fig. 2. Showing a diagrammatic representation of nano-liposome application in drug delivery.

bio-materials, antibody, ligands to be precisely delivered to the targeted organs or tissues, and release drug for a prolonged period of time, so that the healthy cells are not affected and only the unhealthy or infarcted cells are affected [9]. In this review, we will extensively give a summary of recent developments in nanotechnology for the detection and therapy of cardiovascular diseases (CVD) focusing on nanoparticles and nano-liposomes. Over the years liposomes have been used as a nano-carriers with different surface characteristics and have been investigated as therapeutic and theranostic agents for restenosis. Other examples of these classes are given in Table 1.

The treatment of infarcted heart through experimental studies has involved the delivering growth factors, cytokines and drugs to the infarcted cardiac cells [10] and they have been basically delivered via two ways namely direct injection, or by injecting biomolecule-loaded nano-particles/nanoliposomes or gels to the left ventricle (LV) [11,12]. However, the efficiency of these two basic methods may be decreased due to lack of retention of the factors or micro particles in the desired area. As such there is a need to develop an approach to deliver a biomaterial that will precisely deliver these bio-molecules into the infarcted area [13,14]. Fig. 3 shows a model of drug delivery by nanoliposomes.

1.1. Mode of action of liposomal-cell interactions

There are different ways by which a drug loaded on a liposome is delivered when a liposome interacts with a cell. Firstly, the cell membrane can be responsible for the inward absorption of the liposomes and lipases enzyme degrades the carriers' bilayer membrane. Secondly, the release of the liposome content as a result of its fusion with the plasma membrane of the target cells. Thirdly, it's a kind of receptor-mediated endocytosis. This process

Table 1
Showing different forms of liposomes and its application.

Nanocarriers	Example of agent	Experimental model	Outcomes	Refs.
	Bisphosphonates (clodronate, alendronate)	Injured carotid artery in rats	Macrophage depletion, reduced inflammation	[62]
Cationic liposomes	Chloramphenicol acetyl transferase (CAT) encoding gene.	Balloon-injured artery in Yorkshire pigs, local delivery	Increased expression of CAT	[63]
	Vascular endothelial growth factor (VEGF) encoding viral vector	Clinical trial, patients with 60–99% stenosis in major arteries, local delivery through catheter	Significant improvement in myocardial perfusion	[64]
Perfluorocarbon nanoparticles	Surface bound streptokinase, α3β integrins, others	Human plasma clots, hyperlipidemic animals	*In-vitro*fibrinolysis, theranostic *in vivo*	[65]
Polyelectrolyte nanoparticles (RNA or polyvinyl sulfate with polyethylene imine/DNA complex)	Gene encoding for urokinase plasminogen activator	Rat carotid artery	High transfection efficiency	[66]
Polymeric (PLA or PLGA) nanoparticles	AG-1295 and AGL-2043	Balloon-injured carotid artery in rats	Inhibition of restenosis	[67]

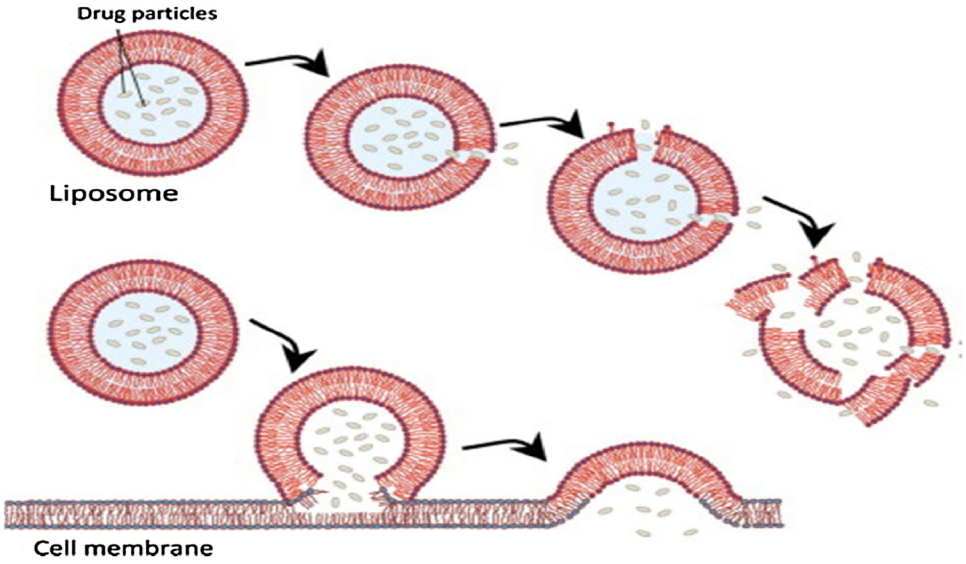

Fig. 3. Showing diagrammatic representation of drug delivery by liposomes.

only involves vesicles and liposomes of a maximum diameter of 150 nm that are phagocytosed by cells like macrophages, monocytes, and Kupffer cells Fig. 4 [15]. Furthermore, the mode of action and level of liposome–cell interaction is strongly determined by the nature and density of the charge of the liposomes surface, however changes in the lipid composition can lead to the modification of the above-mentioned parameters.

1.2. Mode of action of liposomal drug interactions

The delivery of the encapsulated drug is strongly determined by the nature of the lipid bilayer, the size of the drug molecules and importantly their interactions with the lipid membrane. The encapsulation efficiency of a loaded drug in a liposome depends on its polarity and partition coefficient. If the loaded drug is hydrophobic in nature, it resides in the acyl hydro- carbon chain of the liposome, and hence encapsulation is dependent on the properties of the acyl chains of the liposome. However if the loaded drug is polar, its likely to be localize in the aqueous core or adjacent to the water–lipid interface, very close to the polar head groups of the liposome [16]

The advantages of drug delivery using a nanoliposomes and liposomes are because of greater solubility of the intended drug, increased half-life, and selective delivery to the site of action, enhanced therapeutic index, and resistance against chemotherapeutics. When a drug is loaded into liposomes, it assumes the liposome pharmacokinetics until it is delivered. As a result, liposomes alters both the tissue distribution and the rate of clearance of the loaded drug [17]. The pharmacokinetics of drugs loaded on a nano-liposome depends on the physicochemical characteristics of the nano-liposomes like lipid composition, size, membrane lipid packing, steric stabilization, surface charge, dose, and route of administration.

1.3. Molecular mode of action of nano-liposomal drug interactions

There are two possible different mechanisms to explain how nano-liposomes are internalized by cells in vivo: (i) integral nano-liposomes up- take by cells, followed by intracellular drug release, or (ii), the nano-liposomal loaded drug is released into the tumor and taken up by the cells via interstitial fluid.

Furthermore factors leading to effective release of nano-liposomal loaded drug have been said to include collapse or partial collapse of the ammonium sulfate gradient and/or the destabilization of nano-liposomes by phospholipases that hydrolyze the liposome phospholipids, thereby enabling faster release of the nano-liposome loaded drug [18]. However, it should be noted that there are still some major oppositions to the phospholipase-related drug release mode of action, as there is no proven drug release in vivo from Stealth cisplatin, an identical drug delivery system to nano-liposomal. Secondly, the presence of cholesterol in the liposome membrane inhibits severely phospholipase activity

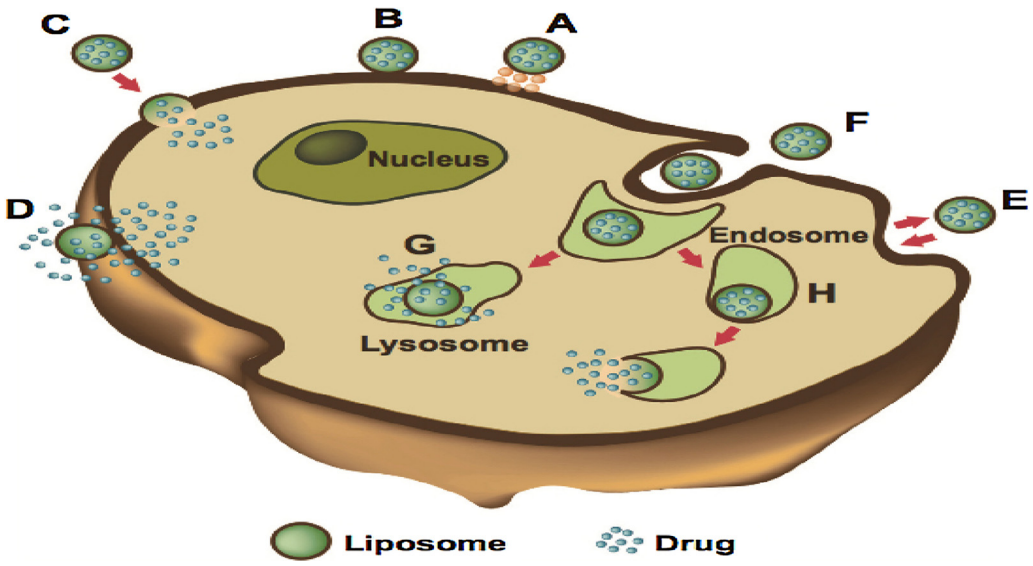

Fig. 4. Liposome–cell interaction.Notes: Liposomes loaded with a drug interact with the cell, binding to the surface through receptors (A). Absorption onto the plasma membrane can also occur by electrostatic interactions (B). The delivery of the cargo into the cell cytoplasm can take place through different modes. Lipid nanocarriers fuse with the plasma membrane and discharge drugs into the cell (C). After the interaction with the cell, the structure of the liposome bilayer can be affected and the cargo is released (D). exchange of carrier-lipid components with the cell membrane can also occur (E). Liposomes internalized by endocytosis (F) can have different fates depending on physicochemical characteristics. endosomes fuse with lysosomes (G): in this case, the low pH induces the degradation of the liposome membrane and the drug is released. endosomes follow another route (H): liposomes release their cargo after fusion or the destabilization of the endocytic vesicle. This figure was culled from [61].

[18]. Conclusively the collapse of the ammonium sulfate gradient might be the only available explanation to how nano-liposomes deliver its loaded drugs in vivo. However it's yet unproven and its proof still requires both clinical and non-clinical extensive investigations.

1.4. Nano-liposome drug delivery to infarcted heart

Several researchers have reported the efficacy of targeted nano-liposomes, as they maybe injected intravenously (IV), to circulate within several body organs example been in infarcted heart where they have been used to precisely target macrophages [19] and blood vessels [20] while some researchers have successfully designed a nanoparticulate system based on liposomes principle that could specifically target cardiac cells (Fig. 5).

Dvir et al. recently investigated and reported the potential of the angiotensin II type 1 (AT1) nano-liposomes to bind cardiac cells. The AT1 particles exhibited superior and efficient targeting capability (Fig. 6A and B). Furthermore, the cells were subjected to 48 h of hypoxia, the proportion of targeted cells rose from 52% to more than 83% ($p = 0.007$) (Fig. 5C and E). Finally, he reported that the amounts of AT1 nano- liposomes amassed in the infarcted heart after day 1, 4, and 7 were 48, 39, and 27% respectively of the total amount accumulated in all organs studied. Dvir et al. concluded that nano-liposomes would precisely target an injured or unhealthy health but not the healthy heart, proposing that this finding can form the backbone for drug delivery to a heart after MI. Furthermore; he stated that angiotensin II type 1 (AT1) targeting improves the accuracy of delivery to the injured myocardium. He concluded that both methods could be used to decrease systemic toxicity of delivered drugs, thereby increasing local therapeutic effect [21]

In addition to Dvir and colleague findings, they also reported the efficacy of AT1 nanoparticles to precisely target the infarcted heart in mice in which MIs were induced via ligation of the left descending coronary artery. Fluorescently labeled nano liposomes

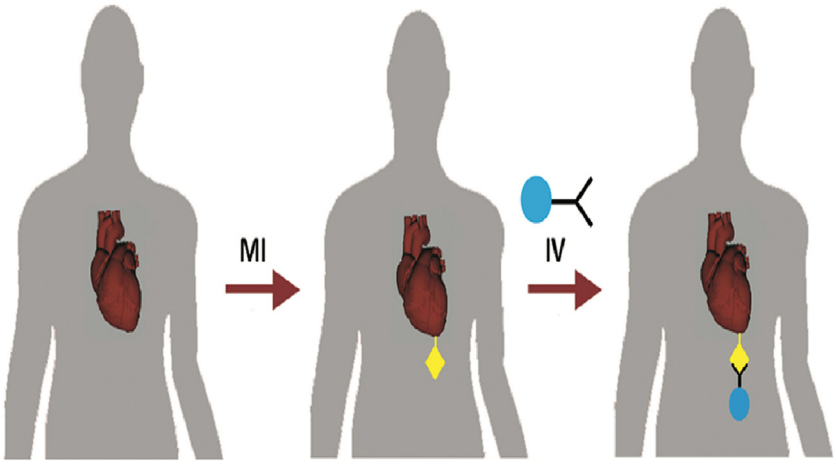

Fig. 5. Concept schematic. After myocardial infarction, the AT1 receptor is overexpressed in the LV. Nanoparticles conjugated with a ligand specific for the AT1 receptor are injected intravenously. After circulating in the body the particles specifically target the LV, where they can release therapeutic agents. This figure was re-produced from [21].

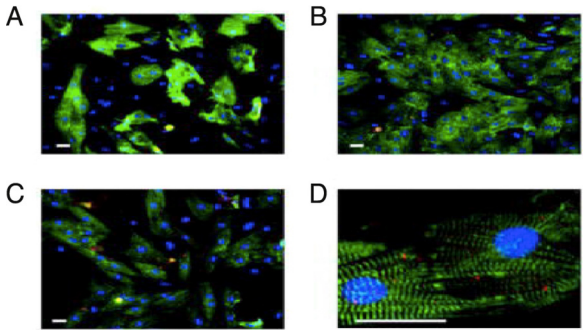

Fig. 6. Cardiac cell targeting in vitro. (A) Targeting cardiac cells with nanoparticles conjugated with nonspecific scrambled peptide as a targeter. (B) Targeting with AT1 nanoparticles. (C) Cardiac cells cultured under hypoxic conditions targeted by AT1 nanoparticles. (D) Higher magnification of C reveals multiple particles binding to each cell. Sarcomeric actinin (green), nuclei (blue), and nanoparticles (red).

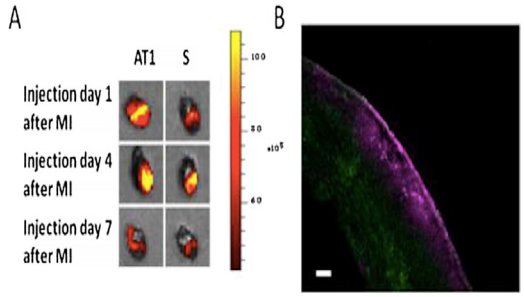

Fig. 7. Targeting the infarcted myocardium. (A) IVIS images of hearts injected with AT1 or scrambled (S) nanoparticles 1, 4, and 7 days after infarction. The hearts were isolated 24 h post injection and imaged. LV is located in the lower right side of each image. (B) Accumulation of AT1 nanoparticles injected one day post infarction in the LV of the infarcted heart. Nanoparticles, red; tissue autofluorescence, green.

were injected into the right jugular vein day 1, 4, and 7 after MI. It was concluded via in vivo imaging system (IVIS) that nano liposomes particles amassed predominantly in the left ventricle. To further validate the presence of the nano-liposomes particles, thin sections of the LV wall after MI was observed (Fig. 7A and B).

Katherine and co-worker demonstrated the therapeutic efficacy of celecoxib nanoparticles in ischemic tissue, which was experimentally carried in mice with the ligation of the left anterior descending artery (LAD) that lead to continuous waves of heart attack accompanied with ischemia of the cardiac muscles. 10 of the mice were treated administered with celecoxib nanoparticles in the hydrogel while others were administered drug-free vehicle control in the hydrogel.

After 4 weeks, parameters like vital signs, heart function, myocardium structural changes, heart volume, and infarct perfusion were monitored and recorded at two and four- week time points after ligation [22]. Katherine and co-worker reported that 60% of the mice survived in the control group, while 100% survival rate was recorded in the treated group, which was evident as there was angiogenesis in the infarcted area (Fig. 8A) at both second and fourth week of recorded time points. They also reported evidences of no heart failure and poor cardiac muscle contractility (Fig. 8B) in the treated group and through echocardiography there was insignificant changes observed in the functions of the left ventricle (Figs. 8C) [23–28].

1.5. Application of nano-liposomes to imaging cardiovascular disorders

Imaging and therapy of atherosclerosis, restenosis have been the few areas of cardiovascular research to witness the application of nanotechnology in the identification and characterization of the early stages of some diseases. Nano technology like fluorescent, radioactive, paramagnetic, super-paramagnetic, electron-dense and light-scattering particles have been applied to cardiovascular imaging (Table 2).

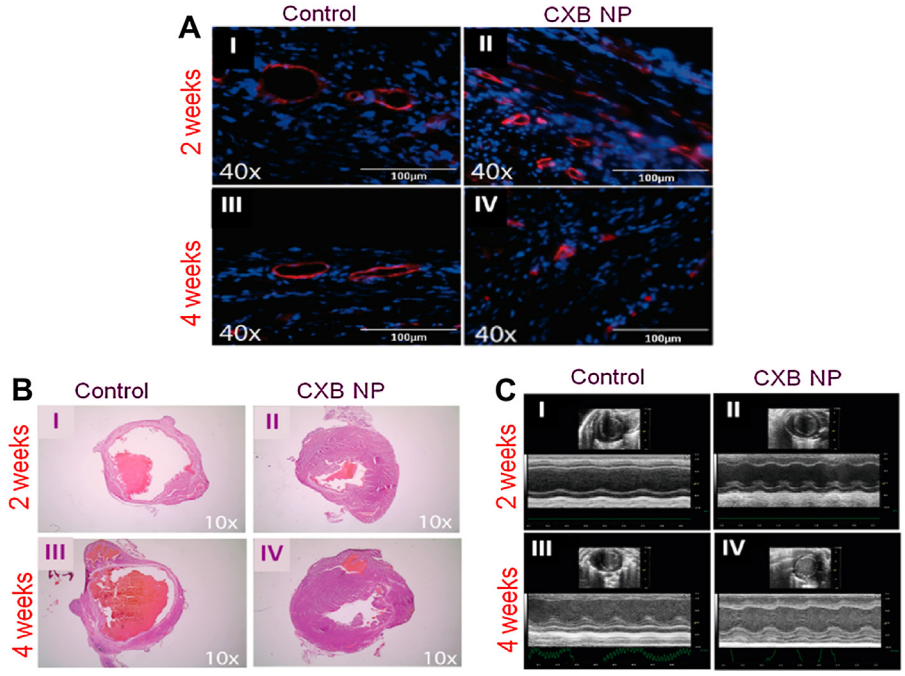

Fig. 8. Treatment efficacy in mice with permanent LAD ligation 2 and 4 weeks postinjection. (A) CD31 staining of blood vessels at the infarction area. Red color indicates blood vessels; blue is cell nuclei. (B) Myocardium morphology, H&E stained. (C) M-mode echocardiography. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 2
Showing various application of nanoparticles to imaging of cardiovascular system.

Category	Agent (examples)	Imaging techniques	Refs.
Fluorescent	Quantum dots	Fluorescence tomography	[68]
Radioactive	FCLO,In nanoparticles	PET, SPECT	[69]
Paramagnetic	Gd-DTPA	MRI	[70]
Superparamagnetic	Ironoxide nanoparticles	MRI	[71]
Electron-dense	Gold or I-based nanoparticles	CT	[72,73]
Light-scattering	Gold nanoshells	Optical coherent tomography	[74]
Photoacoustic	Colloidal nanobeacons	Photoacoustic tomography PET, MRI, NIRF	[75]
Multimodal	Copper-CLIO Perfluorocarbon nanoparticles	MRI, Molecular imaging	[65]

Abbreviations: SPECT: single photon emission computed tomography, PET: positron emission tomography, MRI: Magnetic resonance Imaging, NIRF: near infrared fluorescence, DPTA: diethylenetriaminepentacetate, CT: Computed topography.

Table 3
Showing various applications of nano-liposomes in the detection of CV related diseases.

Sensor targets	Technology	Applications	Refs.
K^+, H^+ ions	Field effect transistor (FET)	Myocardial ischemia	[29]
Na^+ ions	Fluorescent nano-liposomes sensors	QT syndrome, heart failure	[30]
Nitric oxide	Single-walled carbon nanotube (SWNT)	Hypertension Ischemia/reperfusion	[76]
oxLDL Cholesterol	Porphyrinic nano-liposome sensor	Acute heart attack	[37]
Blood pressure	In_2O_3 nanowire-based FET Piezoelectric-BioMEMS Chip-embedded flexible packaging (CEFP)	Pressure monitoring, Myocardial infarction Stenosis in heart bypass Grafts	[77]
Blood flow	Piezoelectric-BioMEMS		[78]

Furthermore, nano particles have been demonstrated to be used as a nano sensors for in-situ rapid detection of K^+, H^+, Na^+ and Ca^{2+} ions, as the activities of these ions have an important role to play as a potential indicators of acute myocardial infarction (AMI) [29]. Ji and co-worker reported the fabrication of flexible nano-electrode sensors for K^+ to detect the mechanism of ischemic heart disease [30–35]. In addition, Errachid and colleagues also demonstrated a multi-nanosensor silicon needle used for the detection of myocardial ischemia during cardiac surgery [36]. It should be noted that heart failure have been linked to changes in the sodium-channel function as such functionalized nano-particles have been demonstrated to detect Ca^{2+} ions in relation to CVDs [37]. Table 3 [38–41] shows important nano particles used as nanosensors for the detection of bio-molecules involved in cardiovascular system [42–45]. Cholesterol and low-density lipoprotein are labeled as a biomarker for acute heart attack in patients with coronary artery disease (CAD) have been demonstrated to be detected by a In_2O_3 nanowire-based FET sensors [46–50].

2. Conclusion

CVDs are one of leading cause of morbidity and mortality in the world. We gave an overview on the current applications of nano-liposomes and nanoparticles in detecting and treatment of cardiovascular diseases, however more research studies and clinical trials are needed to fabricate and develop efficient nanoliposomes with reduced side effects to deliver drugs to myocardial infarction and other CVDs [51–56]. In conclusion, we envisage that nano-liposomes in combination with appropriate drug delivery system can be used to achieve a long-term cardiac repair, and such knowledge may be inculcated into clinical trials by utilizing several potential delivery routes [57–60].

Conflict of interest statement

The authors have no conflicts of interest in regard to this research or its funding.

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