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Innovative approaches in atherosclerosis treatment: A comprehensive review of nanomedicine and herbal medicine strategies

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Abstract

CVD or cardiovascular disorders are one of the major factors causing significant increases in mortality worldwide. One of the major infections in the heart's blood vessels is atherosclerosis, which is mainly caused by the deposition of fats, high blood pressure, and diabetics. The use of synthetic medicine can cure cardiovascular disorders. Although some side effects have been observed using synthetic medicine. With the recent advances in technology especially biotechnology, the scientific community now looking for new and useful treatment methods, among them Nanomedicine and herbal medicine are some of the significant approaches for the cure of cardiovascular disorders. In this study, we reviewed the current status of Nanomedicine and herbal medicine approaches for the treatment of atherosclerosis. Several studies have demonstrated that treatment has a major impact on the management of atherosclerosis and other related cardiovascular issues. Furthermore, this study concluded how the nanoparticle with macrophage target could be delivered for the treatment of a wide range of atherosclerotic disorders. A more precise solution and cure for inflammation and control of atherosclerotic plaque could be obtained by the suppression of pro-atherogenic macrophage with the nanoparticle. Hence, we suggested the use of Nanomedicine therapeutic approaches for the cure and treatment of atherosclerosis and other cardiovascular problems could be a significant solution, although more clinical trials are needed on the Nanomedicine approaches in CVD.

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Introduction

Cardiovascular disorders are the major cause of mortality worldwide. Myocardial infection can lead to atherosclerosis and is the major cause of atherosclerosis (Li *et al.*, 2020). Recent studies showed that about 12 million deaths worldwide are occurring due to atherosclerosis and the percentage will rise at the end of 2030, the major causes investigated are myocardial infection, and coronary disorders (Vogel *et al.,* 2021). The early treatment of cardiac ischemia can be significant in stopping atherosclerosis, cell damage, necrosis, and other cardiac infections (Li *et al.*, 2020). Studies at the molecular and cellular level suggested that atherosclerosis and other cardiac problems lead to heart failure (Fig. 1) (Zhao *et al.,* 2023). The disorder in endothelium tissue in large and average size particles can cause the formation of atherosclerotic plaque in lesion-prone regions. The major risk factors for plaque formation are alcohol, smoking, hypertension, obesity, hyperlipidemia, and diabetes (Stangret *et al.,* 2023). Endothelium disorders are a pathophysiological factor enhancing the deposition of fats, expression of adhesions molecules, and chemotactic molecules which are deposited and buildup in arteries (Stangret *et al.,* 2023). Successively differentiation of monocytes into macrophages, which further form foam cells by phagocytosis apolipoprotein B consists of low-density lipoproteins (Deng *et al.,* 2023). In the vessel wall, the immune cells and lipoprotein constitute the principal stage of atherosclerosis development. Together lipoprotein and immune cells either help in inflammation or result in the evolution of plaque, cell death and neovascularization over a long period or maybe long decades (Lampsas *et al.,* 2023). The major issue related to atherosclerosis is the deposition of fats in arteries which leads to blood clots. The CVDs terms are collectively used for the problem and issues in the heart and blood vessels which can damage organs like the kidney, brain, heart and eyes (Zakir *et al.,* 2023; Hamada, 2023; Asiwe and Oritsemuelebi, 2023).

The recent research conducted on CVD and a report from WHO shows that CVD is one of the leading causes of mortality worldwide. The death ratio around the globe with CVD is calculated at about 18 million people per year. Heart attack and stroke score higher in patients with CVD and one third of these deaths were observed before the age of 70 (Holt *et al.,* 2023). The current treatment available for the cure of CVD is mostly surgery, traditional medicine, diet plan and physical activity, although medication and surgery become a burden on patients (Perone *et al.,* 2023; Tanveer *et al.,* 2023; Fallows, 2023). Furthermore, the current treatments have reduced the mortality rate but they have some limitations. Prolonged treatment like using medication when the symptoms are more chronic due to inflammation and damage of tissue for a long time can affect the liver and other problems (Li *et al.,* 2023; Thu *et al.,* 2023; Farid *et al.,* 2023). Additionally, these medications inherent some limitations like poor water solubility, drug resistance and poor biological pathways (De Rubis *et al.,* 2023; Tiwari *et al.,* 2023; Veerapandian *et al.,* 2023). Moreover, patients with chronic cardio problems need some surgical procedure, although surgical techniques may cause inflammation, a long time for recovery and other factors which are huge burdens. Hence the advancements in surgical procedures have significantly decreased the mortality and increased chances of recovery and treatment but still, the cost is a burden on patients. Hence novel therapeutic techniques like Nanomedicine could reduce the risk of surgery and the burden on patients.

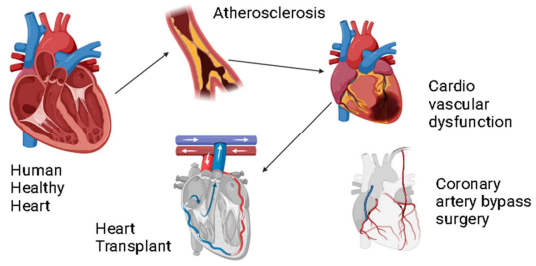

Fig. 1. Human healthy heart, atherosclerosis is the deposition of fats in blood vessels of the heart which leads to heart failure. The possible therapeutic techniques are a transplant, bypass surgery and medicine but these techniques have some limitations.

Table 1. The information in this table was taken from Hu *et al.* (2015)

Drug type	Loaded drug	Nanoplatforms	Disorders	Mechanism of action	Surface modifications	Model of use/Animal	Administration route
Statins	Atorvastatin	HA-ATV-NP	Atherosclerosis	Suppression of inflammation	Hyaluronan proteins derived from macrophages membrane	*in vitro*; *in vivo*, ApoE-/- mice	Intravenous injection
	Atorvastatin	Oxi-COS/ MM-AT-nps	Atherosclerosis	Suppression of inflammation		*in vitro*; *in vivo*, ApoE-/- mice	Intravenous injection
Rapamycin	Rapamycin	PFN1-CD-mnps	Atherosclerosis	Suppression of inflammation	Profilin-1 antibody membrane	*in vitro*; *in vivo*, ApoE-/- mice	Intravenous injection
	Rapamycin	liposome	Atherosclerosis	Suppression of inflammation	Protein from leukocytes	*in vitro*; *in vivo*, ApoE-/- mice	Retro-orbital injection
Traditional Chinese medicine	Sal B, PNS	RGD-S/P-lpns	AMI		RGD peptide ligand	*in vivo*, SD rats receiving experimental MI	Intravenous injection
Small molecule agonists/ inhibitors	SMI 6877002	rHDL NPs	Atherosclerosis	Inhibition of monocyte recruitment; suppression of plaque inflammation	ApoA-I	*in vitro*; *in vivo*, ApoE-/- mice, cynomolgus monkeys	Intravenous injection
Small molecule agonists/ inhibitors	SNO	SNO-HDL NPs	Atherosclerosis		ApoA-I	*in vitro*; *in vivo*, ApoE-/- mice	Intravenous injection
siRNA	siCamk2g	G0-C14 PLGA NPs	Atherosclerosis	Promotion of efferocytosis	S2P peptide (CRTLTVRKC)	*in vitro*; *in vivo*, Ldlr-/- mice	Intravenous injection
miRNA	miR-145	PAM	Atherosclerosis	Promotion of the contractile VSMC phenotype	MCP1/CCL2	*in vitro*; *in vivo*, ApoE-/- mice	Intravenous injection
miRNA switches	miRNA switches	mRNA-p5RHH nanoparticle	Restenosis	Specific inhibition of the VSMCs and inflammatory cells		*in vitro*; *in vivo*, C57BL6/J mice undergoing femoral artery wire injury	Intravenous injection

The detail of possible approaches for the targeted delivery of nanomedicine to the targeted tissue, and blood vessels in cardiovascular diseases

The current research conducted on Nanomedicine was extensively carried out for the treatment and cure of cancer, diabetics and cardiovascular problems (Setia *et al.,* 2023; Ansari *et al.,* 2023; Khan *et al.,* 2023; Shariati *et al.,* 2023; Haleem *et al.,* 2023). Nanotechnology is currently time massively developed, with scientists designing nanomedicine drugs in a particular scale 10-9m size scale. The designing scale of nanomedicine is based on the human body's biological mechanisms which allow the medicine to cross natural barriers attached to the DNA or protein and reach the targeted area within the blood, tissue or organs and cells. The nanotherapeutics targeted drug treatments are currently applied in health sciences using nanomedicine (Farooq *et al.,* 2023; Shree *et al.,* 2024). Further nanomedicine is also used massively in medical imaging, diagnostics, vaccine and regenerative medicine (Altyar *et al.,* 2023; Nosrati and Nosrati, 2023; Samuel *et al.,* 2023; Arshad *et al.,* 2023; Vijayalakshmi *et al.,* 2023; Widjaja *et al.,* 2023; Baruah *et al.,* 2024; Eskandar, 2023). The nanomedicine used in therapeutic approaches increases the efficiency of drugs and reduces the side effects, although the development of nanomedicine for cardiovascular disorders is still challenging for medical scientists. The challenge is in the delivery to targeted blood vessels or tissue due to complications wide range of lesson areas same vascular disorder. Hence development of a more accurate nanomedicine and delivery system is a significant approach to the cure and control of CVD. The development of suitable approaches for targeted drug delivery will be able to cure and control the CVD (Table 1).

Currently used treatment techniques

The management and cure of atherosclerosis consist of pharmacological and surgical techniques, the surgical procedure is applied during chronic heart infection or CVD. In surgical techniques, angioplasty, placement of a stent, bypass surgery of coronary artery, endarterectomy etc. are applied to follow-up the normal blood flow (Perera, 2023). This procedure is applied when the artery is ruptured or tissue is damaged (Perera, 2023). Pharmacological approaches are applied in heart infection for the controlling of blood lipids, blood pressure, development of thrombus and many more factors. Small drugs

molecule is widely used in clinical approaches during CVD like statins, aspirin, clopidogrel, warfarin, heparin, beta-blockers etc. for lipid lowering, blood pressure normality and angiotensin etc. although these drugs have some limitations like water solubility, first pass effect, drugs side effect and bioavailability as low as 30% (Famta *et al.,* 2023). A common diagnostic application of CVD in clinical application is arteriography which consists of computed tomography (CT), MRI (magnetic resonance imaging), positron emission tomography (PET) and the singlephoton emission tomography (SPECT) during imaging contrast agents play a vital role. Mostly agents such as gadolinium diethylenetriamine Penta acetic acid are used but the agent has a short retention time weak signal and toxic effects and they are not able to detect specific regions or tissue (Akbas *et al.,* 2023). Imaging technologies provide significant information about atherosclerosis although these are unable to detect the threat of artery plaque rapture (Florek *et al.,* 2023). Collectively all the available therapeutic procedure provides significant applications for atherosclerosis and other cardio problems but it requires further advancement to develop novel approaches which are very effective.

Active targeting of macrophages

In the formation and progression of atherosclerosis macrophages and monocytes play a key role. Hence these cells are significantly considered to be used for therapeutic purposes of atherosclerosis. At the site of atherosclerosis plaques, the phagocytic activities of macrophages increase and make a good response to plaques (Shen *et al.,* 2023). Different methods for the targeting of macrophages involved in inflammation can provide significant results, like MRI of plaques of atherosclerosis in the mouse model (ApoE) through nor targeted Iron oxide nanoparticle has been used to target plaques (Yan *et al.,* 2024). The nanoparticle consists of polysaccharide hyaluronic acid conjugated with iron oxide been developed which is used for the targeting of CD44 macrophage receptors in a rabbit model for the in vivo image of atherosclerosis plaques using 3.75 μ mol Fe/kg injection (Wu *et al.,* 2023).

Materials used in nanostructured are also fabricated to restrict the activity of biomolecules, working as nanobiosensors which investigate the stages and biomarkers in specific diseases like triglyceride and glucose nanosensors (Salarizadeh *et al.,* 2023). Hence more devices and equipment are manufactured to study diabetics, e.g. devices which contain nanoelectronics are wearable or implanted on the body and detect real time physiological changes (Shoaib *et al.,* 2023). Further, the advancements in nanomedicine and nanotechnology revolved around many significant milestones in medicine and surgery especially in CVD. The properties of nanomedicine include small sizes like 1-100nm and prolonged circulation in blood (Li *et al.,* 2023). Moreover, quickly digestible and solubility also give significant insight into the nanomedicine compared to traditional therapy like fenofibrate nanomedicine available in the market used to manage cholesterol and triglyceride levels in patients with ameliorative drug solubility and lower absorption (Wang *et al.,* 2023). Nanoparticle ideal size distributions give significant properties to the drugs to pass smoothly in blood vessels without any physiological barriers. Nanomedicine has also desirable characteristics like considerable surface area which allow it to easily pass and absorb blood. In atherosclerosis, nanoparticles pass easily to interstitial tissue (Sobańska *et al.,* 2023).

The remarkable properties of nanoparticles provide more possibilities for targeted therapy, imaging, improving pharmacokinetics, diagnosis and treatment of atherosclerosis as compared to other drugs and therapies (Thapa *et al.,* 2023). In a recent study a nanoparticle designed with transitional materials perfluorohexane and dextran sulfate which targeted A scavenger receptor (SR-A) and was used as a therapeutic target for the treatment of atherosclerotic plaque (Cheng *et al.,* 2023). In the experiment active accumulation of nanoparticles was achieved at the position of SR-A receptor expressed macrophages in ultrasound imaging procedure in atherosclerotic plaque. Hence the overall performance of nanomedicine management in CVD

treatment showed significant outcomes (Saeed *et al.,* 2023). Many recent studies have been conducted to investigate the development and enhancement of nanomedicine approaches in the treatment of CVD (Shariati *et al.,* 2023). In a recent review article, the latest advances in nanomedicine have been explained with their applications in atherosclerosis and CVDs treatment and diagnosis (Fig. 2 and Table 1). The study has also revolved around the current approaches of nanomedicine for the treatment and diagnosis of CVD in both clinical and preclinical trials.

Fig. 2. Morphology of *Salvia miltiorrhiza*

Currently used nanomedicine therapeutic applications

Recent advances in nanomedicine-based therapeutic approaches have been extensively used for the treatment of CVD. In reality, the nanomedicine approaches provide interesting and significant applications for the cure of atherosclerosis like nanomedicine being phagocytosed by macrophages in atherosclerotic plaque hence, therefore, this must be targeted to deliver drugs with the help of macrophages at atherosclerotic plaque site (He *et al.,* 2023). The most advanced therapeutic nanomedicine approaches are explained below.

Cellular receptor targeting nanomedicine therapy

There are two major ways to target white blood cells with nanomedicine, one is to target receptors and the second is to modify biological mechanisms inside the cell. In the first option the receptor on leukocytes guides them through the vascular wall, and the injured organs secret specific chemicals like cytokines or chemokines which attract the circulating leukocytes, this process occurs due to the expression of adhesion molecules which migrate the leukocytes such molecules are selectins and integrins (Chehelgerdi *et al.,* 2023). The integrins surrounded by the extracellular matrix is binding with some components in the extracellular matrix. The blocking of selectin and integrins could be useful approaches for the infiltration of additional immune cells which could further damage the organs by causing more inflammation. The αvβ3 integrins also play a key role in other methods used for the cure of atherosclerosis like angiogenesis. The expression of αvβ3 integrin is upregulated by several proangiogenic factors on ECs (Jing *et al.,* 2023). For the delivery of integrin αvβ3 to targeted cells where atherosclerotic plaque occurs using cRGDfk peptide coating to nanoparticles (Najberg *et al.,* 2020). The other receptors like stabilin-2 could be targeted using nanoparticles, this receptor is involved in cell adhesion and angiogenesis. The stebilin-2 binds and clears ligands such as hyaluronic acid and heparin (Chen *et al.,* 2021). The surface expression of stabilin-2 in atherosclerotic plaque has been increased by macrophages and ECs (Beldman *et al.,* 2019). Hence HA coating nanoparticle delivery is used to visualise the atherosclerotic plaque binding with effected endothelium and macrophages (Yue *et al.,* 2018). The HA is also a ligand for other receptors like CD44 (Krolikoski *et al.,* 2019). The CD44 receptor is mostly involved in the activation of vascular and immune cells and also the adhesion of leukocytes to the endothelium cells, hence promoting the pro-inflammatory mediator production and is known as pro-atherogenic response (Mauersberger *et al.,* 2022; Chen *et al.,* 2023). Additionally, inhibiting this receptor led to reducing the recruitment of leukocytes and activation of vSMC (Munjal and Khandia, 2020). Hence nanoparticle coating with HA could be a significant approach for targeting atherosclerotic plaque and use as a treatment for CVDs.

Cellular processes targeting

Intervening with the cellular process is mostly considered as the second level of manipulation of immune cells. vSMC proliferation and death are the key processes in atherosclerosis, which lead to

necrotic core and thinning of fibrotic cap and calcification (Basatemur *et al.,* 2019). Various nanoparticle was designed to target these processes like rapamycin was covered on gel like NPs. The result of using these nanoparticles showed 20% reduction in human vSMC proliferation in vitro compared to regular free rapamycin (Chen *et al.,* 2021). The test of these nanoparticles was conducted in rats in vivo by infusion to the left carotid artery after vascular injury. The concentration of rapamycin in the carotid artery was found stable for 2 weeks and was not detected in the opposite carotid, hence it showed the targeted delivery to localized point. Hence in the treated rats' decrees of hyperplasia and increased reendothelization of the injured artery. Thus, the research conducted showed that these NPs could significant approaches for the cure and treatment of CVDs by targeting the cellular processes and inflammation inside cells or tissue. Meneghini *et al.* experimented on rats with atherosclerosis by injection Nanoparticles Coated with Docetaxel (DTX) which are lipid-based intravenously (Meneghini *et al.,* 2019). Using LDE-DTX significantly lowers the pro-inflammatory markers like IL-6, NK-kB, IL-1β and TNF- α. Further, it may be possible to lower the inflammation in the atherosclerotic plaque area. Moreover, LDE-DTX also lowers the expression of C-C motifs (Chemokine) CCL2 (Ligand 2) which are responsible for monocyte infiltration and CD68 macrophage marker. Hence LDE-DTX also significantly decreased the leukocyte infiltration. A recent study showed that encapsulated dexamethasone is also used to treat liver disorders (Li *et al.,* 2021). To avoid inflammatory activation, siRNAs were used to activate transcription factors by targeting immune cells (Veiga *et al.,* 2019). Tao *et al.* (2020) performed a study and demonstrated that targeting the calmodulin-dependent protein kinase pathway by siRNAs in mice showed significant results. Hence targeting this pathway by siRNA could stop arteriosclerosis. The findings of these studies showed a significant way to design nanoparticles which could be used to treat and control CVDs by targeting cellular processes.

Using nanoparticles to target lipid level

Targeting lipid levels using NPs is a key strategy to combat CVDs caused by high cholesterol or fat levels. Reduction of LDL plasma level the significant target is PCSK9. Classical strategies consist of targeting PCSK9 is inhibited with monoclonal antibodies which reduce the level of LDL by expression of LDL receptor in Plasma. The other approach is to inhibit PCSK9 with siRNAs so designing nanoparticles contain with siRNAs and target PCSK9. Fitzgerald *et al.* (2017) performed a study and the result showed the efficacy of ALN-PCS is a siRNAs that is used to target the expression of PCSK9 in healthy individuals who are not using any drugs. The drugs were delivered with Lipid NPS. The results of NPS in volunteers showed significant results by reducing LDL level by 70% compared to using other drugs which showed 40% decrease in LDL level. Hence it showed the significance of the NPs using it for future cure and treatment of CVDs (Hu *et al.,* 2023).

Currently, the European Union has approved the use of nanoparticles in medications for adult patients dealing with high levels of cholesterol or lipids. (Mohamed *et al.,* 2023). Designing LDL nanoparticles could be also a significant medicine due to it is accumulation inside atherosclerotic plaque (Zhu *et al.,* 2023). Using this approach to targeting the LDL-accumulating macrophages in atherosclerotic plaque could be significant, although currently some fluorescent biomarkers developed have been used for imaging (Yue *et al.,* 201873). Hence this treatment procedure could be significant for the treatment of CVDs but more research is needed to be carried out.

Routs for administration of nanomedicine for the treatment of atherosclerosis

The targeted delivery of nanoparticles is one of the important discussions, hence several approaches like intervenes (IV) administration are commonly used. Although oral administration is also formulated like rosuvastatin nanomedicine was formulated which is coated with solid lipid nanoparticles and delivered orally, these drugs have good bioavailability as well as lowering plasma LDL levels compared with other

drugs (Lin *et al.,* 2017). Nanoparticle design through self-assembly loaded with RAP and orally administrated in a recent study, the particle contains cationic polymer polyethyleneimine. The nanoparticle is capsulated with yeast microcapsules obtained from Saccharomyces cerevisiae (Paramera *et al.,* 2023). The yeast capsule is absorbed by M cells where it engages lymphoid follicles in the gut (Yang *et al.,* 2023). Hence the macrophages and monocytes absorb it and transfer it to the atherosclerotic plaque. Furthermore, other drugs like ursodeoxycholic acid and sulindac to atherosclerotic plaque with RAP nanoparticles are also delivered. Using oral administration of these nanoparticles instead of IV injection could be the significant approach for future clinical studies.

Another way of administration of nanomedicine to atherosclerotic plaque is intraperitoneal injection (Zhang *et al.,* 2023). The delivery of nanomedicine to atherosclerotic plaque using IV or IP injection was reported by Jung and co-workers (Jung *et al.,* 2023). Although the same nanoparticles for HDL treatment were also reported in the same study using IV injection, the delivery of nanoparticles depends on size and charge. Injection of subcutaneous hydrogel has been studied for the targeted delivery of anti-inflammatory nanoparticles (Nazir and Munawar, 2024). Subcutaneous nanoparticles containing insulin like growth factor were delivered into a mouse model which showed inhibition of atherosclerosis (Min *et al.,* 2023). Generally, nanoparticles were designed for targeting the atherosclerosis using IV injection method although other routes are also investigated to take advantage of the ability of macrophages to take the particle and deliver it to atherosclerotic plaques.

Nanoparticle clinical trials

The important aspect of nanomedicine is used to treat and cure the illness, although the formulation of nanoparticles is necessary to test it in clinical trials. Because the solubility, delivery and toxicity must be checked like nanomedicine coated with abandoned drug wortmannin (Wtmn) was designed to inhibit the activity of phosphatidylinositol 3' kinases (PI3Ks) and phosphatidylinositol 3' kinases like kinases (PIKKs). The results of the drugs in free clinical trials were significant but in clinical studies, the drugs showed certain limitations like lower solubility, less stability and high toxicity. Polymer Nanoparticle formulated Wtmn showed results which overcome these negative aspects (Pardeshi *et al.,* 2023). Hence clinical analysis of these drugs could be significant for future drug delivery to the targeted tissue or organs. The overview of nanomedicine with completed clinical trials and nanoparticles used for the treatment of CVDs is shown in Table 1. The use of nanomedicine has been used in many fields among them few are used for CVDs. Research on nanomedicine clinical trials showed significant outcomes of their use for the treatment. The liposome nanocapsule formulated with prednisolone phosphate drug used in a recent study showed significant outcomes in treatment, however, the drugs did not show significant outcomes in inflammation (Wang *et al.,* 2023). Hence these studies showed significant results of nanoparticles used for the treatment instead of existing medicine however more research is needed. In another study, liposomal nanocapsule formulated with prostaglandin E1 was used in a patient as an additional therapy with surgery in acute lower limb ischemia (ALLI) (Srivastav *et al.,* 2023). The results of the study showed significant outcomes in the patients compared with the control sample.

In a patient with multivessel disease nanomedicine formulated with albumin bound with paclitaxel was intravenously injected (Chen *et al.,* 2023). The results showed that dosages below 70mg/m2 were optimal in these patients. Collectively the current used of nanomedicine and the clinical trials are still carried out and provide more advantages. This trial could be very significant for future pharmaceutical and clinical practices and will provide tremendous approaches for the cure and treatment of CVDs and other disorders (Table 2).

Table 2. Overview of completed clinical trials which include nanomedicine for CVDs

Nanocarrier	Drug	Phase	Effects/Outcome	Reference
Liposomal	ALN-PCS	Phase I	70% decrease in PCSK9 levels and 40% reduction of LDL cholesterol.	(Tao *et al.,* 2020)
Liposomal	Prednisolone phosphate	Phase I/II	Liposomal encapsulation improved the half-life of the drug and successful delivery to plaque macrophages was achieved. However, no anti-inflammatory effects have been observed.	(Karve *et al.,* 2012)
Liposomal	Prostaglandin E1 (PGE1)	Not specified	Patients with acute lower limb ischemia (ALLI) who received PGE1 had significantly fewer adverse events.	(Van der Valk *et al.,* 2015)
Albumin-bound	Abraxane/ Paclitaxel	Phase I	The safety and optimal dose of Paclitaxel was tested in patients with multivessel disease. Dosages below 70 mg/m^2 were tolerated by the patients and no adverse events were noted.	(Li *et al.,* 2013)
Silica gold and silica gold iron-bearing	-	Not applicable	Patients with atherosclerotic lesions received either silica gold NPs in an on-artery patch (Nano); silica gold iron-bearing NPs with targeted microbubbles and stem cells via a magnetic navigation system (Ferro); or a stent (Control). In both experimental groups, the total atheroma volume was reduced up to 60 mm^3 with a high level of safety. A five-year follow-up showed a higher safety and better mortality rate in the Nano group compared to the Ferro and Control.	(Margolis *et al.,* 2007; Kharlamov *et al.,* 2015)
Iron oxide-bearing	-	Not applicable	After acute MI, NPs of iron oxide were injected intravenously into patients and detected via magnetic resonance imaging. These NPs were taken up in the infarcted and remote myocardium, thus highlighting the method's potential to be used to assess cellular myocardial inflammation and left ventricular remodeling.	(Alam *et al.,* 2012)

The application of herbal medicine in the treatment of atherosclerosis

Human beings use natural products obtained from plants, fungi, animals and other organisms for the treatment and cure of CVDs and other disorders for a long time. Currently, the research is significantly conducted to study the effect of herbal medicine and used as an alternative approach for the treatment. The use of herb medicine has significantly increased and many studies showed significant results of using herbal medicine for the cure and treatment of atherosclerosis and other associative disorders of the heart. However, the mechanism and action of these herbal medicines have been studied recently using lab approaches and lab models for anti-atherosclerosis (Zhao *et al.*, 2023; Li *et al.,* 2024; Wang *et al.,* 2024). Further, extensive analysis of these plants is also carried out and extensive study is conducted on their mechanism and action during treatment of atherosclerosis (Pena-Jorquera *et al.,* 2023; Alamri and ul Qamar, 2023). Hence in this study, we investigated the current status of medicinal herbs used for the cure of CVDs**.**

Medicinal herbs used for lowering blood lipid level

High blood lipid level is considered one of the major risk factors of atherosclerosis, many studies showed that hypercholesterolemia and hypertriglyceridemia are the leading risk factors causing heart problems and especially atherosclerosis (Roeters van Lennep *et al.,* 2023; Li *et al.,* 2023; Dorobantu *et al.,* 2023; Gerasimova *et al.,* 2023). Hence previous research on LDL and associated proteins like apolipoprotein B-100 showed that these factors promote the development of atherosclerosis (Di Fusco *et al.,* 2023). However, studies on herbal medicine used for the treatment of atherosclerosis show these products lowering blood lipid levels (Table 3).

Table 3. Lowering lipids in the blood by medicinal herbs

Compounds/extracts	Herbs	Targets or indicator	References
Tribulus terrestris extract	*Tribulus terrestris*	Serum TC, TG, LDL-C, HDL-C	(Tuncer *et al.,* 2009)
Aqueous extract of *Ocimum basilicum*	*Ocimum basilicum*	Serum TC, TG, LDL-C, HDL-C	(Amrani *et al.,* 2006)
Salvianolic acid B	*Salvia miltiorrhiza*	CD36	(Bao *et al.,* 2012)
Ethanol extract of *Cynanchum wilfordii*	*Cynanchum wilfordii*	TG, LDL-C, HDL-C	(Choi *et al.,* 2012)
Ethanol extract of *Terminalia arjuna*	*Terminalia arjuna*	TC, TG, LDL-C, HDL-C	(Subramaniam *et al.,* 2011)
Polysaccharide from *polygonatum sibiricum*	*Polygonatum sibiricum*	TC, LDL-C, Lp(a)	(Nader *et al.,* 2010)
Marrubium extract	*Marrubium vulgare*	TC, TG, LDL-C	(Ibrahim *et al.,* 2016)
Panax notoginseng saponins	*Panax notoginseng*	TC, TG, LDL-C, HDL-C	(Zhang *et al.,* 2013)
Propolis, thymoquinone	*Nigella Sativa*	TC, TG, LDL-C, HDL-C	(Khoshandam *et al.,* 2023)
Celastrus orbiculatus extract	*Celastrus orbiculatus*	TC, non-HDL-C, TG, apoB100, apoE, HDL-C, LDL-R, SR-B1, CYP7A1, HMGCR	(Elbouny *et al.,* 2023)
Sweritamarin	*Enicostemma littorale*	TC, TG, LDL-C	(Guo *et al.,* 2023)

In New Zealand experiment on rabbits was carried out, first, the rabbit was fed with high lipid diet and then an extract of Tribulus terrestris was given the results showed significant decrease in blood cholesterol level like TC, HDL, LDL and TG compared the results with control (Hazra *et al.,* 2023). In other studies, extracts of *Ocimum baslicum* were used in rats with higher lipids, the results showed significant outcomes by decreasing the level of TC, TG and LDL while HDL was higher in those rats which were only treated with triton (Kanmaz *et al.,* 2023). Extracts from dried roots of *Salvia miltiorrhiza* have been used for long time for the treatment of CVDs. The extract of this plant contains Salvianolic acid B is one of the important bioactive molecules that showed inhibition of CD36 mediated lipid it binds with CD36 and confirms its physical interaction with this receptor (Gong *et al.,* 2023). Using *Cynanchum wilfordii* extract reduced the TG and LDL levels in rats with high lipid diet (Kim and Jeong, 2023). The extract of *Terminalia arjuna* used in rabbits fed with high lipid diet showed significant results by lowering the TC, TG and LDL levels (Palanivelu *et al.,* 2023). The polysaccharide extract from *Polygonatum sibiricum* showed hypolipidemic activates on TC, LDL and Lipoprotein but not on HDL and TG in rabbits with high lipid diet (Xue *et al.,* 2023). The extract marrubium vulgare decreased the blood lipid level further more extracts of this plant like petroleum ether, chloroform methanol soluble fraction and ethyl acetate were also investigated. Among these extracts, soluble fraction showed a significant outcome by lowering blood lipid level while petroleum ether lower LDL and TG level. Polar fractions like methanol and ethyl acetate influenced LDL and HDL ratio and atherogenic index (Amirullah *et al.,* 2023). Extract Saponins from panax notoginseng also showed significant results by lowering the level of apolipoprotein E in rats further reduced the level of TC, LDL, HDL and TG in mice (Wang *et al.,* 2024). Extract propolis and thymoquinone of Nigella sativa seed oil showed significant results in the inhibition of atherosclerotic plaque formation in rabbits feed with heavy cholesterol diet and also decreased the level of TC, LDL and TG while increased the HDL-C level (Abo-Neima *et al.,* 2023).

Extract from Celastrus orbiculatus showed significant decreased in TC, non-HDL-C, TG and ApoB-100 and apo-E blood level. Further mRNA level of LDL receptor and Scavenger receptor SR-B1, CYP7A1 cholesterol 7α- hydroxylase A1 and 3-Hydroxy-3-methyl-glutaryl-coenzyme were upregulated by *C. orbiculatus*. Further this extract also decreased the lipid deposition in the artery wall (Hou *et al.,* 2023). In hyperlipidemic rat the extract of Enicostemma littorale namely swertiamarin was injected and the results showed significant outcome by decreasing the level of TC, TG and LDL-C (Ji *et al.,* 2023).

Extract of Pueraria mirfica showed remarkable result lower down the TC, TG and LDL-C level in a woman (Yusof *et al.,* 2023).

Extract from mulberry the fruit of *Morus alba* L is used as an herbal medicine in many disorders like antioxidant, anti-tumor and anti-inflammation (Ma *et al.,* 2023). Anthocyanins were used by Liu *et al.* (Liu *et al.,* 2020) in a study and the results showed significant decrease in LDL level, hence it showed that Anthocyanins could be used as antioxidant of LDL. Collectively these findings showed that natural products or herbal medicine could be a significant treatment for atherosclerosis and associated heart disorders.

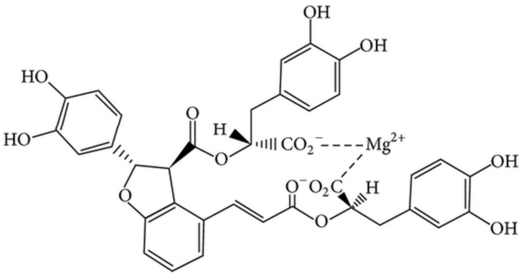

Fig. 3. Salvianolic acid B-Major water-soluble compounds derived from *Salvia miltiorrhiza*

Slavonic Acid as medicine for the treatment of CVDs

The salvia is the dried root of plant Salvia miltiorrhiza, which belongs to the family of Labiatae Lagurus (see Fig. 2 and 3). These plants are cold in test and mostly used to treat heart and liver and are widely used in eastern countries, especially China. In recent times these extracts have been widely used for the cure of CVD and cerebrovascular disorders (Nikitina *et al.,* 2021; Dinan *et al.,* 2021). The medicine is popular now in most parts of the globe and widely used. Moreover, the drug is also used for kidney, liver and lungs (Orgah *et al.,* 2020; Liu *et al.,* 2020; Zhang *et al.,* 2019; Wu *et al.,* 2020; Long *et al.,* 2022). The drugs showed significant results in ischemia-reperfusion injury. According to Chinese herbal medicine studies the drugs have good results in blood circulation, regulating menstruation cleaning heart fire calming nerves and many more functions. The new research on this medicine Salvia showed significant pharmaceutical properties like blood flow in coronary arteries, healthy myocardial functions, kidney functions, stomach functions anti-inflammatory, antioxidant and many more functions**.**

Salvia medicine in China has been used for thousands of years for the treatment of CVDs and other disorders (Guo *et al.,* 2020). The drugs from the last 60 years have been extensively studied and experiments were conducted in clinical sciences. In recent times, researchers have conducted research on salvia and studied their chemical as well as functional analysis in labs and clinical trials. The chemical composition of *Salvia miltiorrhiza* extract is classified into two categories, water soluble compound and lipophilic diterpenoid (LDQs and WSCs) (Zhu *et al.,* 2020). Further classification on the base of pharmacy the compound is classified into phenolic acids like protocatechuic aldehyde, caffeic acid, protocatechuic acid and 3,4-dihydroxyphenyl lactic acid and polyphenolic acids like lithospermic acid salvianolic acid and other. LDQs are Tanshinone I, Tanshinone IIA, Tanshinone IIB and other Tanshinone (Zhao *et al.,* 2020). The current research status on salvianolic acid showed that the medicine has significant effect on signal transduction pathways in vascular endothelial cells, smooth muscle cells, and cardiac muscle cells and prevents and treat CVDs (Zhao *et al.,* 2020; Yu *et al.,* 2019). The medicine salvia is currently used for the treatment of coronary heart diseases, chest tightness and angina embolism. The formulations of salvia commonly used are injections, dipping pills like Danshen injection, the salvia infusion injection Danshen dripping pill and many others. The current research on *Salvia miltiorrhiza* is extensively increased like control randomised trials and systematic reviews and it showed the significance of the medicine. Danshen medicine containing salvia is used and showed significant results than ISDN and treat angina pectoris (Yuan *et al.,* 2019).

Turmeric or curcumin extract used as medicine for CVDs

Curcuma longa is a flowering plant belonging to Zingiberaceae of the ginger plant family. The extract curcumin is widely used around the globe for multiple disorders treatment. Curcumin nicotinate also known as Curtn used to lower the blood lipid level (Fig. 4). The medicine is currently used in nanomedicine and has shown significant results (He *et al.,* 2023). The tremendous application of curcumin as antioxidant and anti-inflammatory provides him a useful medicine used in CVDs treatment hence nanoparticle containing curcumin nicotinate was designed and delivered for the treatment of atherosclerosis and cleaning of blood circulation (Li *et al.,* 2022).

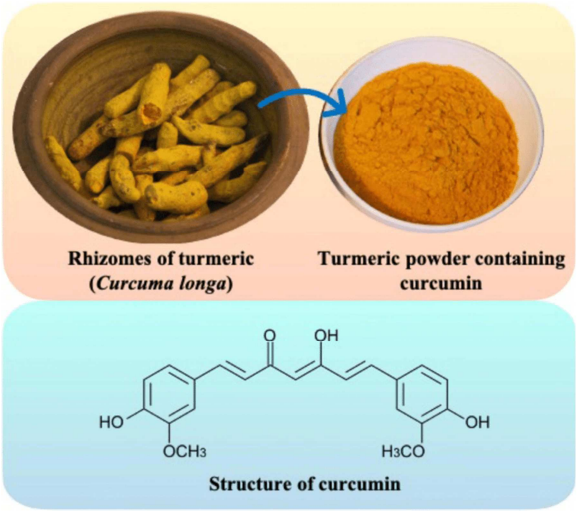

Fig. 4. Rhizomes of turmeric and turmeric powder and chemical structure of curcumin

The use of curcumin in nanoparticles showed significant outcomes with good efficiency and lower side effects (Chen *et al.,* 2020). The antioxidant and anti-inflammatory properties of these extracts give significant sight to use in CVDs (Oppedisano *et al.,* 2020). The beneficial properties of curcumin used in animal models provide an approach for scientists to use it in CVDs and other disorders (Cox *et al.,* 2022). Furthermore, the use of curcumin is healthy for elder patients and shows positive results in lowering endothelial dysfunction and arterial hemodynamics (De Oliveira and Alvares, 2022). Curcumin also activates the sirtuin 1 (SIRT1), and also induces heart rate after consuming it (Ren *et al.,* 2020). It is also involved in the inhibition P53 and P21 pathways and decreasing the expression of P53 which are involved in oxidative stress (Yang *et al.,* 2019). Curcumin also activates NRF2 which also prevents oxidative stress, the curcumin was used in insulin resistant mice where it improved glucose tolerance and decreased oxidative stress and also upregulated the NRF2 in muscles and liver (Ashrafizadeh *et al.,* 2020). The curcumin also showed good results in vitro analysis of the preadipocyte cell line where it improved the oxidation of fatty acid (Alalaiwe *et al.,* 2021; Koboziev *et al.,* 2020). In obesity, curcumin use also showed significant outcomes by reducing the deposition of fats in adipose tissue (Du *et al.,* 2024). Curcumin's atheroprotective properties showed in different animal models by using curcumin, the decrease in atherosclerotic lesions was also found in some studies by using curcumin. Collectively from these studies, we found that curcumin could be significant medicine for the treatment of cardiovascular disorders. It also activates signaling pathways which inhibit aging in cardiac muscle cells. Hence using nanomedicine coating with curcumin will be an effective medicine with significant efficiency and lower side effects.

Conclusion

The current situation of cardiovascular problems around the globe is a serious issue of concern. Further CVDs are the major cause of mortality worldwide although advancements in technology especially diagnosis and treatment have reduced the mortality. However, these available approaches have some limitations like delivery, solubility and side effects, so nanomedicine could be a significant and more precise approach for cure and treatment.

Nanoparticles have recently developed dramatically and the use of herbal medicine has also increased significantly. In this study, we have reviewed the current status of Nanoparticle and herbal medicine approaches for curing and controlling atherosclerosis and cardiovascular disorders. We concluded from the studies that in many clinical trials and lab studies the use of nanoparticles and herbal medicine shows significant outcomes like reducing the LDL, TC, TG,

and other lipids which are the leading cause of heart problems. Furthermore, the targeted drug delivery to the infected region using nanoparticles showed significant outcomes in animal models. However, very few studies were found on using nanomedicine in human beings, hence we recommend more research and study on human trials it will provide significant outcomes about the nanomedicine efficiency. Interestingly herbal medicine has been used for long time by humans for many disorders. Currently, the use of these medicines is increasing and people using these medicines worldwide. From the study about the nanoparticle's delivery, like lipid coated nanoparticles which are diffused in the plasma membrane, we did not find suitable approaches for the delivery of this nanoparticle to the targeted regions. Like using injection or oral it may be possible this particle will diffuse into blood or gut cells and we try to deliver it to the lungs. Therefore, the question is here how it will be delivered hence more studies are needed in this regard.

The study on Curcumin and Salvianolic acid showed that these compounds can reduce blood lipids level enhance blood circulation provide strength to the muscle's cells, activate signaling pathways and have anti-oxidant and anti-inflammatory properties. Hence these compounds could be significant medicines for the cure and treatment of CVDs. Therefore, using pharmaceutical approaches to design new drugs with these herbal medicines could be a breakthrough in the treatment of Cardiovascular, especially atherosclerosis.

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