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REVIEW

# Chitosan-Based Nanoparticles Targeted Delivery System: In Treatment Approach for Dyslipidemia

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**Abstract:** Hyperlipidemia, characterized by abnormally high lipid levels in the bloodstream, is a significant risk factor for cardiovascular diseases. Conventional treatments have limitations in efficacy and may lead to side effects. Nanotechnology offers unique advantages in drug delivery, including improved drug stability, prolonged circulation time, and enhanced tissue targeting. Using nanoparticles as carriers, therapeutic agents can be precisely delivered to the target site, such as the liver or arterial walls, where lipid metabolism occurs. Chitosan nanoparticles represent an advanced approach engineered with precision to target atherosclerotic plaques. They have dual functionalities, serving therapeutic and diagnostic purposes in managing atherosclerosis. Targeting strategies involve coating nanoparticles with ligands or antibodies that recognize specific receptors overexpressed in hyperlipidemic conditions. This selective uptake maximizes the therapeutic effect while minimizing off-target effects, making it a promising alternative to traditional treatments. The review provides an overview of recent research developments for managing dyslipidemia based on the molecular target pathway of dyslipidemia, focusing on Chitosan-based delivery systems that allow controlled drug release, targeting, and enhancing patient compliance.

**Keywords:** hepatic drug targeting, atherosclerosis, dyslipidemia, arterial wall targeting, lifestyle modification

## Introduction

Cardiovascular disease (CVD) is a leading global cause of morbidity and mortality, with an estimated 423 million cases and responsible for 18.6 million deaths in 2019 worldwide.[1–3] It imposes a significant annual cost of 600 billion dollars. The global mortality for CVD is projected to increase to 23.6 million by 2030. Asian countries have experienced a nearly double increase in CVD deaths over the past 30 years.[4] Dyslipidemia can be classified into hypercholesterolemia, hypertriglyceridemia, or mixed hyperlipidemia. Coexisting with obesity, diabetes, and hypertension increases CVD morbidity and mortality. Understanding its underlying mechanisms is crucial for innovative CVD prevention therapies.[5–7] The coexistence of dyslipidemia and hypertension in 50–80% of patients results in a synergistic effect, raising the risk of CVDs beyond individual factors.[6] Effective management requires addressing root causes and developing targeted interventions to improve patient outcomes.

Dyslipidemia may arise from genetic predisposition or lifestyle factors, including poor dietary habits and insufficient physical activity.[8,9] Diets high in saturated fats and cholesterol and sedentary lifestyles elevate lipid levels. Obesity impacts cholesterol metabolism by influencing its absorption, synthesis, and lipoprotein handling, ultimately leading to the buildup of cholesterol in the liver. Obesity worsens dyslipidemia by disrupting lipid metabolism and promoting cholesterol and triglyceride accumulation.[10–12] Both genetic and acquired factors contribute to its development, including specific mutations causing inherited lipid disorders like familial hypercholesterolemia. Children with genetic predisposition, diabetes, renal diseases, and familial hyperlipidemia are at higher risk.[13,14] The formation of atherosclerotic plaques can begin as early as adolescence, posing a potential risk of coronary artery disease (CAD) in young adults.

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Current treatment guidelines for dyslipidemia focus on lowering low-density lipoprotein cholesterol (LDL-C) levels based on the risk of atherosclerotic cardiovascular disease (ASCVD).[15,16] High-density lipoprotein cholesterol (HDL-C) is no longer a treatment target due to insufficient evidence from clinical trials.[17,18] Triglycerides are targeted when they are markedly elevated to reduce the risk of pancreatitis.[19] Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors (such as Evolocumab and Alirocumab) are monoclonal antibodies that dramatically reduce LDL-C by preventing degradation of the LDL receptor, making them particularly effective for patients with familial hypercholesterolemia or statin resistance.[20,21] ATP Citrate Lyase inhibitors (such as Bempedoic acid) work by blocking cholesterol synthesis upstream of β-Hidroksi β-metilglutaril-CoA (HMG-CoA) reductase, making them an alternative for patients who are statin intolerant.[22,23] Antisense oligonucleotides such as Mipomersen target specific messenger RNAs, while MTP inhibitors such as Lomitapide block microsomal triglyceride transfer protein, which are particular treatments for severe familial hypercholesterolemia.[24,25] Extended research is required to evaluate the effects of lipid-lowering therapies on cardiac mortality in primary biliary cholangitis (PBC)[26] and to define treatment objectives based on ApoB-100 levels or LDL measurements obtained through Nuclear Magnetic Resonance (NMR).[27] Newer approaches under development include siRNA therapy targeting PCSK9, dual PCSK9/ANGPTL3 inhibitors, and gene therapy approaches.[28,29]

Our growing comprehension of dyslipidemia, combined with advancements in pharmaceutical technology, has paved the way for innovative therapies aimed at preventing CVD. Some recently approved drugs significantly reduce LDL cholesterol levels through unique mechanisms, while others targeting different causes of high cholesterol are in various stages of research. Thorough clinical assessment is crucial to identify the safest, most effective, and most cost-efficient agents for enhancing cardiovascular outcomes and alleviating the impact of atherosclerotic CVD. Innovative strategies, like nanoparticulate carrier systems, deliver drugs within nanoscale particles, optimizing treatment efficacy.[30] The field is moving towards personalized nanomedicine with gene-editing platforms and self-regulating systems integrated with digital health monitoring for optimal treatment outcomes. Precision medicine customizes treatments for patients by considering their genetic makeup and lifestyle, thereby improving personalization and therapeutic efficacy.

Chitosan (CS) derivatives offer advantages in drug delivery systems due to their biocompatibility, controlled release properties, ease of preparation, and high affordability.[31–33] These derivatives protect drugs from degradation and enable targeted delivery. CS is a natural polymer that is biodegradable, biocompatible, mucoadhesive, and polycationic, enhancing drug permeation.[34,35] It also improves the solubility of poorly soluble drugs, benefiting controlled drug release, especially for 80% of drugs with low solubility.[36–38] CS's main reactive sites are its amino (-$NH_2$) and hydroxyl (-OH) groups, enabling interactions with acids, bases, and crosslinking agents.[31] Functionalized CS (eg, carboxylated, PEGylated, acylated) can modify drug metabolism, prolonging delivery time or adjusting the release rate and duration. The beneficial properties of CS are valuable for therapies and diagnostics of hyperlipidemia, particularly in drug targeting. Ligand modification of CS, by attaching specific molecules known as ligands, further enhances its targeting capabilities, making it even more effective in drug delivery applications.[32,34,39,40]

A key gap in current hyperlipidemia treatment lies in the need for more targeted and individualized approaches, particularly for patients with familial hypercholesterolemia, mixed dyslipidemia, or statin intolerance. Emerging therapies, such as proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors and bempedoic acid, offer alternative options but are expensive and require careful patient selection and monitoring. CSNPs-based drug delivery systems have the potential to address these challenges by enhancing drug stability, promoting controlled release, and enabling targeted lipid-lowering effects. However, further clinical validation, long-term safety assessments, and cost-effectiveness evaluations are needed before widespread implementation in clinical practice. This review highlights using CSNPs carriers to treat hyperlipidemia based on the molecular target pathway of dyslipidemia. These advancements improve treatment effectiveness, reduce side effects, and offer patients more effective and efficient options. Targeting root causes and individualizing interventions can revolutionize hyperlipidemia management and enhance CVD outcomes.

## Overview of Dyslipidemia

Hyperlipidemia is a critical health problem that necessitates the development of improved therapeutic strategies. Addressing this need demands a thorough understanding of the pathophysiology of hyperlipidemia and the contemporary

methodologies employed in its treatment. This comprehensive approach encompasses the intricate mechanisms underlying lipid metabolism, the genetic and environmental factors contributing to dyslipidemia, and the resulting cardiovascular complications.

## Pathophysiology of Dyslipidemia

Elevated total cholesterol or triglycerides, low HDL levels, or a combination of these abnormalities characterize dyslipidemia. The most common form of dyslipidemia is hypercholesterolemia, often associated with low HDL-C (66.2%), high LDL-C (62.1%), and elevated triglyceride levels (58.2%).[41,42] LDL, the predominant ApoB-containing lipoprotein in plasma, is the primary cholesterol transporter to the arterial walls. Higher levels of LDL cholesterol, a characteristic of dyslipidemia, have a robust association with a higher risk of cardiovascular disorders, especially ASCVD. Numerous studies show that LDL-C and oxidized LDL are directly responsible for atherosclerosis progression.[43]

Atherosclerotic lesions arise from LDL transport and retention within the artery wall. Oxidized LDL recruits monocytes that transform into macrophages, promoting LDL oxidation. Oxidative stress, caused by reactive oxygen species (ROS), plays a central role in atherosclerosis and endothelial dysfunction.[44,45] Hypercholesterolemia leads to the infiltration of cholesterol into granulocytic cells, where it becomes oxidized, thereby intensifying the expression of adhesion molecules like Intercellular Adhesion Molecule 1 (ICAM-1) and E-selectin in monocytes. This leads to monocyte recruitment, cytokine production, and differentiation into macrophages that produce Monocyte chemoattractant protein-1 (MCP-1) to attract more monocytes. Macrophages use oxidized cholesterol to create foam cells to initiate plaque formation and atherosclerosis.[46,47] Atherosclerosis is an inflammatory disorder involving cytokines such as TNF-α, IL-1, and IL-6, which play a crucial role in the disease's pathogenesis by promoting adhesion molecules, migration, and mitogenesis of vascular cells on the arterial wall.[48,49]

## Management Treatment of Dyslipidemia

### Pharmacological Therapy

The primary approach to treating dyslipidemia involves lowering LDL-C and increasing HDL-C levels.[16,32,50] Statins inhibit HMG-CoA reductase, reducing cholesterol production and increasing LDL receptor expression, which lowers plasma cholesterol.[51,52] Some patients may not achieve LDL-C targets with high-dose statins and may experience intolerance (eg, myalgia, weakness). Primary prevention aims for a 30–50% LDL-C reduction with moderate-intensity statins and >50% with high-intensity statins (eg, atorvastatin, rosuvastatin). Secondary prevention in coronary disease patients targets LDL-C <70 mg/dL with high-intensity statins; if unmet, combination therapy is used. High-risk patients (eg, recent ACS, diabetes) aim for LDL <50 mg/dL, often requiring additional agents. Cholesterol levels, particularly LDL-C and triglycerides, can typically be reduced through weight loss (diet and exercise) and medication.[16]

Persistent CV events despite maximal therapy prompt research into alternative approaches to lower LDL-C. Familial Hypercholesterolemia (FH) is a genetic disorder causing dangerously high cholesterol levels, with the homozygous form (HoFH) being the most severe and challenging to treat. Recent advances in pharmacological strategies have shown promising results for HoFH management, offering new hope for patients.[53,54] Research demonstrates that reducing LDL-C is crucial in ASCVD treatment, with every 1 mmol/L reduction in LDL-C resulting in a 20–25% decrease in cardiovascular event risk over five years.[55,56] The study demonstrates rosuvastatin's dual benefit of reducing both LDL-C (50% reduction) and inflammation (37% hs-CRP reduction), resulting in a significant decrease in major adverse cardiac events (44% reduction, HR 0.56).[57] Adding ezetimibe to statin therapy consistently lowers cardiovascular event risk in post-ACS patients, regardless of baseline LDL-C levels.[58]

Other lipid-lowering agents include bile acid sequestrants, fibrates, and niacin, which may not have proven cardiovascular benefits but can be considered in specific cases. Combining therapies to achieve optimal results while minimizing side effects is a challenge, and the decision to use lipid-lowering therapy should be based on individual patient risk factors, even if their lipid levels are within normal ranges.[59]

Pharmacological therapy for hyperlipidemia is highly effective in preventing atherosclerosis, cardiovascular diseases, and stroke. However, treatment must be individualized based on lipid profile, risk factors, tolerability, and cost

considerations. Despite the availability of effective medications, adherence to therapy remains a challenge. Lifestyle modifications, including a heart-healthy diet, regular exercise, and weight management, should accompany pharmacological treatment to achieve optimal lipid control and long-term cardiovascular benefits.

## Adopting Lifestyle Changes

The management of dyslipidemia at its outset centers on adopting lifestyle modifications. This is typically achieved through lifestyle modifications, including diet, weight loss, and exercise. However, these interventions may vary among individuals based on several factors.[16] Diets deficient in fruits, vegetables, whole grains, and low-fat dairy while rich in added sugars, refined grains, fried potatoes, and processed meats are associated with increased fat mass and higher BMI during adolescence.[60] Saturated fatty acids (SFA) found in foods like milk, butter, cheese, meats, palm oil, and coconut oil raise LDL-C and HDL-C levels.[61] This comprehensive approach underscores the significance of a balanced diet, the integration of regular physical activity, and a conscious effort to minimize exposure to tobacco smoke. Early-stage smoking elevates lipid peroxidation products by increasing oxidative stress, disrupting oral cavity lipid balance through cell membrane damage.[62,63] Smoking also alters systemic lipid profiles, raising TG, TC, and LDL levels while reducing HDL levels.[63,64] The establishment of adequate sleep patterns also constitutes a crucial aspect. Sleep quality and duration showed no correlation with serum lipid profiles, including TG, TC, LDL, and HDL.[65,66] Innovative food processing techniques can support obesity prevention by enhancing dietary quality, nutrient delivery, and the palatability of healthy foods.[67]

Exercise training has emerged as a powerful intervention for improving cardiovascular health and managing lipid profiles.[68,69] Research demonstrates that consistent physical activity can significantly reduce triglyceride concentration, lower total cholesterol, decrease low-density lipoprotein (LDL) cholesterol, and increase HDL cholesterol levels. Different exercise modalities show varying impacts on these markers, with swimming proving most effective for total cholesterol, triglycerides, and LDL, while dancing exhibits superior benefits for HDL cholesterol. Experts recommend engaging in moderate to vigorous aerobic physical activity, targeting sessions of at least 40 minutes, particularly for middle-aged and elderly populations.[70]

Regular exercise offers broader health benefits beyond lipid management, including reduced mortality, improved quality of life, reduced frailty, and enhanced cardiovascular fitness. Peak oxygen uptake (VO2) is a key measure of these benefits and an independent predictor of hospitalizations and mortality in CVD patients.[71] Combined exercise approaches yield the most comprehensive health outcomes, particularly high-intensity interval training (HIIT) and moderate-intensity continuous training (MICT). To maximize these benefits, health professionals emphasize the importance of a holistic approach, including refraining from smoking, maintaining moderate alcohol consumption, and adhering to a balanced diet.[72] The synergy of these lifestyle factors and a consistent and varied exercise regimen offer a powerful strategy for improving overall cardiovascular health and metabolic function.[73,74]

A therapeutic lifestyle change (TLC) diet helps manage dyslipidemia, but compliance with the diet is complex, and certain patients may prefer medication over changes in eating habits. Education is a way to work with and includes face-to-face training, written material, and check-ins, which can foster self-management techniques. Additional TLC adherence is obtained from diet, exercise, and symptom follow-up post-discharge programs.[75] Others are preventive care, healthy practices, and advice on medications as well. TLC diet-based medical nutrition therapy (MNT) efficiency has been determined to increase the people living with HIV blood lipid profile, mainly amongst those with dyslipidemia.[76]

Lifestyle modifications should be the first-line approach for managing dyslipidemia, especially in cases where lipid levels are only mildly elevated. This strategy aligns with current clinical guidelines (eg, AHA, ACC, ESC) that emphasize non-pharmacological interventions before initiating drug therapy unless the patient is at high cardiovascular risk (eg, familial hypercholesterolemia, diabetes, previous cardiovascular event). However, for high-risk patients, early pharmacological intervention alongside lifestyle modification is necessary for optimal outcomes.

## Challenge in Dyslipidemia Management in Exceptional Cases

Managing dyslipidemia requires a personalized approach due to its complexity and varied presentation. Distinguishing between primary (genetic) and secondary (lifestyle or condition-induced) hyperlipidemia is crucial for treatment selection. In familial cases, primary care physicians (PCPs) must consider genetic factors alongside secondary causes like

obesity, thyroid dysfunction, alcoholism, medication effects (eg, β-blockers), and chronic renal failure. Tailoring treatment to each patient's underlying causes and risk factors improves disease management and prognosis, avoiding a one-size-fits-all approach.[76,77]

Statins are used to reduce cardiovascular risk in young women with conditions such as PCOS, obesity, or pregnancy complications. Statins are generally contraindicated during pregnancy, except in cases of familial hypercholesterolemia or established ASCVD, where women may continue statin therapy until pregnancy is confirmed. Bile acid sequestrants are considered safe alternatives once pregnant for lipid-lowering treatment.[78]

Comorbidities, polypharmacy, and frailty can confound statin use in older adults above 75. In several observational studies, statin discontinuation was linked with an elevated risk of cardiovascular events. Statins seem beneficial in preventing CVD in the older population.[79]

In type 2 diabetes (T2D) and obesity, increased triglyceride, diminished lipoprotein size, and impaired HDL function dyslipidemia. T2D is a chronic metabolic disorder caused by insulin resistance and deficiency, followed by high blood glucose and disrupted lipid metabolism.[80] Increased fatty acid delivery to and enhanced fatty acid synthesis in the liver, combined with increased hepatic fatty acid absorption, result in higher liver triglyceride and VLDL production, and this condition is closely linked to obesity and metabolic syndrome. Furthermore, T2D, obesity, and inflammation cause further impairment of lipid metabolism characterized by elevated Apo C—III levels, insulin resistance, and inflammation. Apo C-III was found to play a role in preventing the clearance of triglyceride from circulation and thus increases the risk of diabetes complications.[81]

Managing hyperlipidemia in chronic kidney disease (CKD) is essential due to the heightened cardiovascular risk that accompanies declining kidney function. Statin therapy, with or without ezetimibe, is advised for patients with an eGFR <60 mL/min or an elevated urinary albumin-to-creatinine ratio (3 mg/mmol) for at least 3 months.[82] For dialysis patients, statin therapy is continued but not initiated. Clinical guidelines recommend statins as the first-line treatment for dyslipidemia, even in non-dialysis CKD patients.[83] While LDL-C and total cholesterol levels are usually within normal ranges in chronic kidney disease (CKD), patients often exhibit a higher prevalence of atherogenic small dense LDL particles, which contribute to arterial plaque formation. HDL-mediated reverse cholesterol transport is compromised in CKD due to reduced Apo AI synthesis, diminished LCAT activity, and increased CETP activity. Plasma lipoprotein(a) (Lp(a)) levels, a decisive genetic risk factor for CVD, rise as kidney function declines. Effective lipid management can improve outcomes, particularly in diabetic kidney disease (DKD).[84]

## Preparation and Functionalization of Chitosan Nanoparticles

Conventional pharmacological interventions have managed hyperlipidemia by effectively lowering lipid levels and reducing cardiovascular risk. However, their limitations, such as adverse side effects, drug-drug interactions, and suboptimal patient compliance, underscore the need for innovative drug delivery systems. The search for new drugs is constantly evolving, but the total cost incurred will be very high. In this context, CSNPs have attracted attention as a cutting-edge alternative, offering superior therapeutic potential through controlled drug release and targeted delivery mechanisms, potentially overcoming the limitations of conventional treatments and improving patient outcomes.

### Overview of Chitosan Nanoparticles in Drug Delivery

Nanotechnology draws from chemistry, engineering, physics, and biosciences to design, use, and manufacture nanoparticles (NPs). New approaches to nanoparticle fabrication make it possible to fine-tune the properties of the particles that build applications across many areas like medicine, energy, and the environment. They have also made possible advancements like incorporating drug delivery systems, efficient provision of energy, treatment of the environment, and several others in many fields.[85,86]

CS, which is chitin, is a biopolymer that is degradable, non-toxic, and non-immunogenic; however, its solubility is only in acidic environments.[87,88] Its solubility and functionality have interested researchers because to modify it for better solubility, the amino and hydroxyl groups were altered.[89] It has properties like degree of deacetylation (DD) and molecular weight that determine such vital characteristics of its physical and chemical nature.[90] Ongoing investigations have established the enhanced use of CSNPs in domains including targeted liver delivery, enhanced bioavailability,

antimicrobial wound healing, and cancer treatments.[91,92] They also show that CS is increasingly used in nanotechnology technologies for biomedical and environmental uses.

## Production and Characterization of Chitosan Nanoparticles

Nanotechnology is a rapidly evolving field of interest in the synthesis of NPs, mainly targeted synthesis methods that are safe, economical, and eco-friendly. Several techniques to synthesize CSNPs and nanocapsules include ionic gelation, emulsification, crosslinking, interaction with polyelectrolytes, self-assembly, and spray drying. They entail manipulating working parameters, developing fresh crosslinking agents, and enhancing preparative methods to enhance manufacturing.[93,94] Among the utilized methods, ionic gelation and self-assembly are the most popular due to their orientation towards human benefits and environmentally friendly principles.[32,36]

Characterization and evaluation of CSNPs are vital for understanding their physicochemical properties, safety, and efficacy. Comprehensive analysis of size, surface charge, morphology, drug release profiles, and stability is crucial to fine-tuning their design for specific biomedical and pharmaceutical applications.[92,94,95] This knowledge aids in the rational development and optimization of CSNPs-based drug delivery systems, ensuring their effectiveness and safety in clinical settings.

## Functionalized Chitosan Nanoparticles for Drug Delivery

Functionalized CS derivatives are modified forms of CS where specific functional groups are introduced to enhance their properties and broaden their potential applications. The primary goal of functionalization is to improve CS's solubility, bioactivity, and targeting capabilities.[94,96,97] By attaching various groups—such as amino, thiol, or polyethylene glycol (PEG)—to the CS structure, researchers can optimize its characteristics for particular uses, such as drug delivery, wound healing, and tissue engineering.[91,97] These modifications allow for enhanced drug encapsulation, controlled release, and the ability to target specific cells or tissues, making functionalized CS a versatile and effective material in biomedical applications. CS's limited water solubility restricts its biological applications. However, its solubility can be improved by introducing functional groups into the polymer structure. One approach is the N-methylation of N,N-dimethyl chitosan to produce N,N,N-trimethyl chitosan (TMC), which increases its quaternization and enhances solubility. Another method involves introducing carboxyl groups and creating carboxymethyl (CMChi). Carboxyl groups have a pKa of approximately 4.5, meaning they deprotonate at pH $\geq$ 7, resulting in CMChi's water solubility in neutral and alkaline conditions.[94,98] These modifications improve solubility and enable CS to be used in a broader range of biomedical and industrial applications, such as drug delivery and tissue engineering.

Hydrophobization of CS is typically achieved by introducing alkyl substituents of varying lengths into its structure. This is done through reactions between CS's amino groups and fatty acids or their anhydrides, resulting in acylated derivatives. Alternatively, CS can react with aldehydes, followed by a reduction of azomethine bonds to form secondary amines, creating alkylated derivatives. These hydrophobically modified CSs can self-assemble into nanoparticles, encapsulating hydrophobic drugs within their core, enhancing drug delivery and stability in various biomedical applications.[94,99,100]

Amphiphilic-modified CS is created by attaching both hydrophilic (eg, N,N,N-trimethyl, carboxymethyl, hydroxybutyl) and hydrophobic (eg, cholesterol, deoxycholic acid) groups to the CS structure. For instance, cholesterol-modified CS is synthesized by linking cholesterol 3-hemisuccinate to the amino group of CS using EDC (1-ethyl-3-(3-dimethylaminopropyl) carbodiimide).[94,98] These amphiphilic molecules can encapsulate small molecules, DNA, and proteins, forming nanoparticles via self-assembly.

Ligand modification of CS involves attaching specific molecules, known as ligands, to the CS structure. These ligands are selected for their ability to bind to target molecules or receptors, enabling CS to interact with specific cells, proteins, or compounds.[32,90,94] For example, ligand-modified CS can direct the CS-based carrier to a particular site in the body, improving the precision and efficiency of therapeutic interventions. This approach holds significant potential for advancing the effectiveness of treatments by ensuring drugs are delivered to the intended location. A scheme depicting the preparation process, functionalization, and expected improvements is shown in Figure 1.

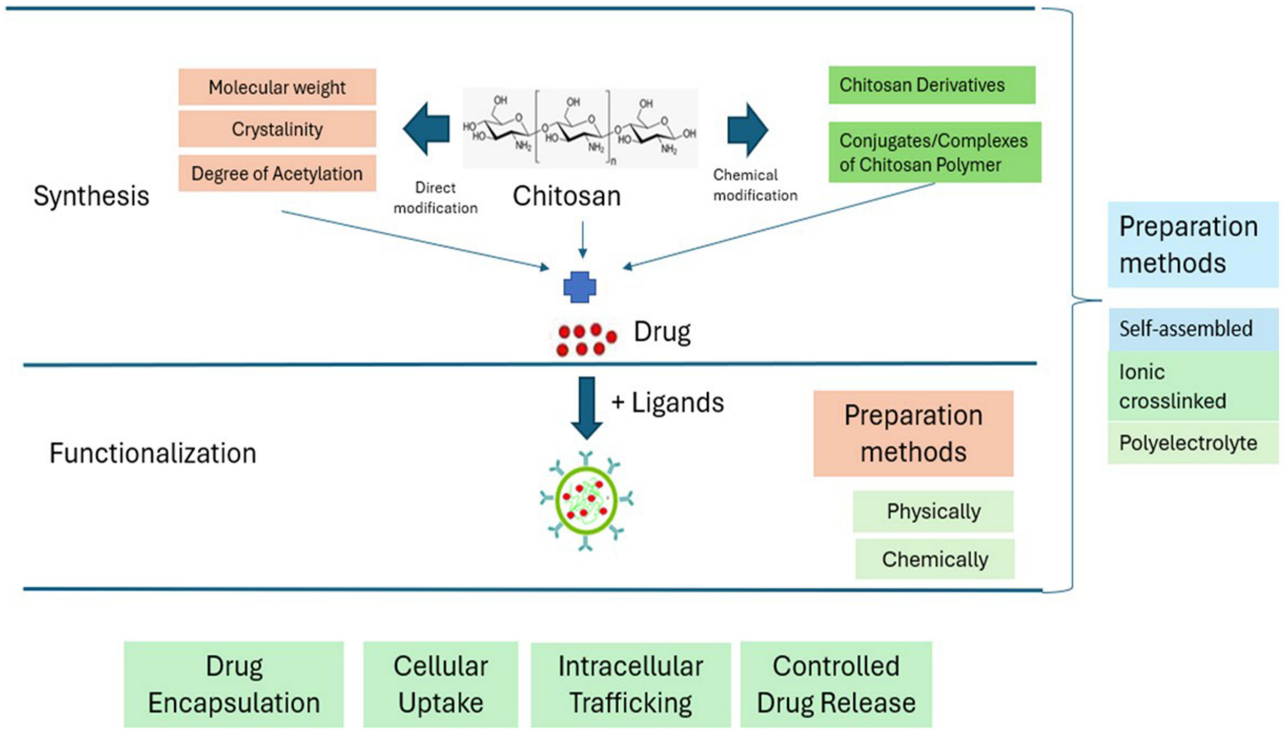


**Figure 1** The preparation process, functionalization, and action mechanism of chitosan nanoparticles.

## Molecular Target Pathways of Dyslipidemia

Functionalization strategies, like surface modification with targeting ligands or encapsulating bioactive molecules, enhance their stability, biocompatibility, and specificity. Understanding interactions between NPs-biological environments provides insights into their effectiveness in delivering therapeutic agents and improving hyperlipidemia treatment outcomes. Selecting ligands with high specificity and strong affinity ensures effective targeting and uptake of the NPs, optimizing therapeutic delivery to the desired cells.[101] Several innovative treatments for hyperlipidemia have shown promise in recent years (Figure 2).

### Lowering LDL Pathway

#### HMG-CoA Reductase Inhibitors

The enzyme acyl-CoA synthetase 1 (ACSVL1) is predominantly derived from the liver, catalyzing BA's conversion to its active metabolite ETC-1002-CoA. This active metabolite reduces cholesterol synthesis by inhibiting ATP citrate lyase, decreasing acetyl-CoA concentrations in the cholesterol synthesis pathway compared to statins that target the end of the synthetic pathway designated by HMG-CoA reductase. This, in turn, reduces cholesterol production, increases LDL receptors, and lowers the LDL-C. Activation of AMP-activated protein kinase (AMPK) inhibits HMG-CoA reductase and acetyl-CoA carboxylase, promoting improved glucose homeostasis and reducing the production of pro-inflammatory cytokines in macrophages. Skeletal muscle does not contain ACSVL1 and hence cannot activate the prodrug, which leads to fewer muscular side effects associated with statins.[103] Statin therapy is the cornerstone of dyslipidemia treatment and is the first-line pharmacological approach for reducing cardiovascular risk.[84,104,105]

Statins promote endothelial function by increasing the NO/ROS balance, eNOS expression, and stabilizing tetrahydrobiopterin. But simultaneously, they decrease coenzyme Q10 (CoQ10), which reduces cellular energy and antioxidant potential by 40% during long-term therapy. This depletion may counteract some of the beneficial effects of statins on endothelial function, highlighting the complexities of statin therapy and suggesting the potential advantage of CoQ10 supplementation during long-term statin use.[106,107]

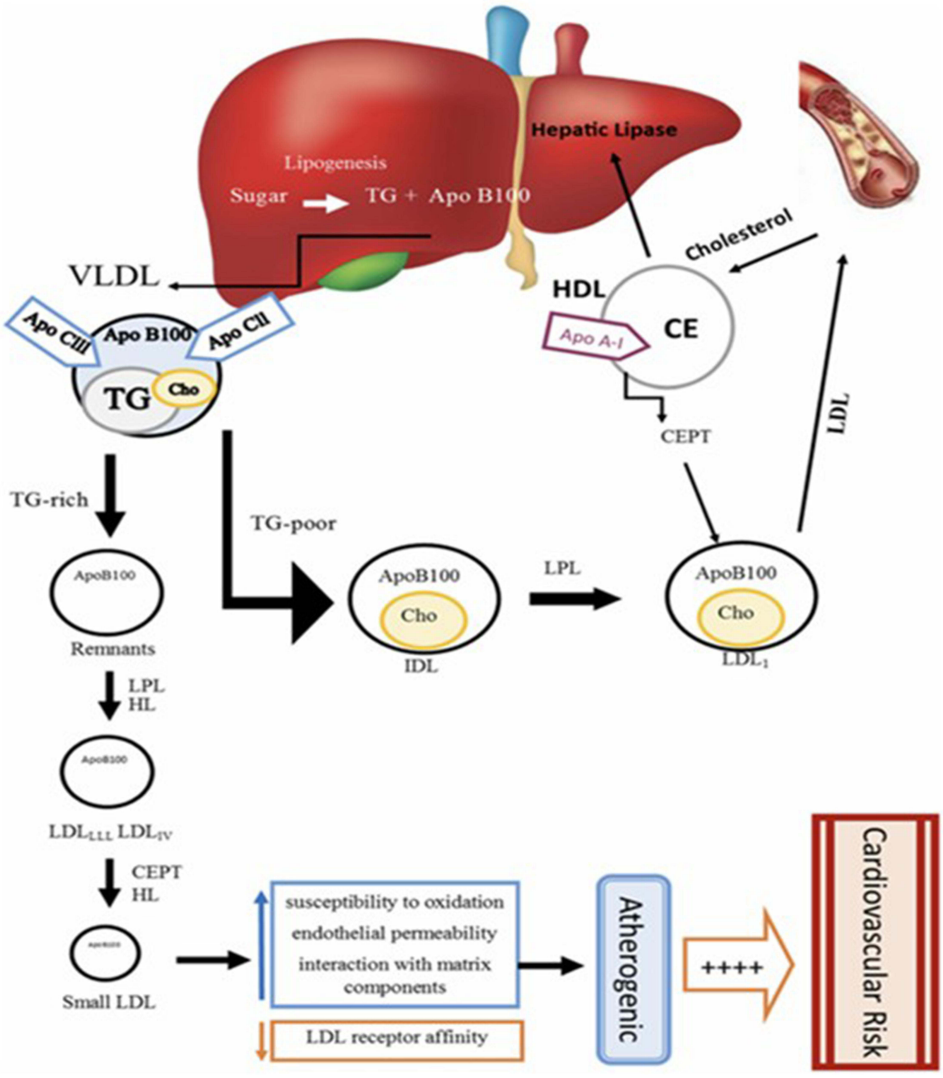


**Figure 2** Schematic summary of pathways of endogenous lipid metabolism and pathways of atherogenic and anti-atherogenic lipoproteins. Reproduced from Talebi, S.; Bagherniya, M.; Atkin, S.L.; Askari, G.; Orafai, H.M.; Sahebkar, A. The Beneficial Effects of Nutraceuticals and Natural Products on Small Dense LDL Levels, LDL Particle Number and LDL Particle Size: A Clinical Review. Lipids Health Dis. 2020, 19, 1–21. Creative Commons Attribution 4.0 International License.[102]
**Abbreviations**: sdLDL, small dense low-density lipoprotein; Apo, apolipoprotein; VLDL, very-low-density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; LDL-R, low-density lipoprotein receptor; HDL, high-density lipoprotein; TG, triglycerides; CE, cholesteryl esters; +, increased risk.

## Blocking Adenosine Triphosphate-Citrate Lyase, a Cytosolic Enzyme Upstream

Bempedoic acid effectively reduces LDL cholesterol levels by targeting adenosine triphosphate-citrate lyase. This enzyme acts earlier in the cholesterol synthesis pathway than HMG-CoA reductase, the primary target of statins. Clinical studies have demonstrated that bempedoic acid, whether used as monotherapy or in combination with statins and/or ezetimibe, significantly lowers LDL-C, apolipoprotein B, and high-sensitivity C-reactive protein levels in individuals with ASCVD or heterozygous familial hypercholesterolemia. Activated in the liver by long-chain acyl-CoA synthetase-1, its metabolite inhibits cholesterol biosynthesis.[108,109]

ATP-citrate lyase (ACLY) is a key enzyme that converts citrate to acetyl CoA, a molecule central to fatty acid, cholesterol biosynthesis, and protein acetylation. Inhibitor of ACLY, Bempedoic acid may reduce LDL cholesterol levels. It reduced LDL-C by 18–27% in hypercholesterolemic patients and 43% in type 2 diabetic patients in clinical trials and markedly reduced the level of the hs-CRP. It is combined with statins and has a half-life of 15–24 hours, given once daily.[108,110]

## PCSK9 Inhibitors (Mediating Hepatic LDL Receptor Degradation)

The serine protease PCSK9, predominantly produced in the liver, plays a crucial role in regulating plasma levels of low-density lipoprotein cholesterol (LDL-C), lipoprotein(a), and triglyceride-rich lipoproteins by targeting the low-density

lipoprotein receptor (LDLR) for degradation. This mechanism contributes to elevated CVD risk.[105,111] It degrades LDLR in lysosomes, thereby decreasing receptor recycling and increasing LDLC in blood.[112] Treatment with monoclonal anti-PCSK9 antibody is the only effective treatment to lower plasma LDL-C and suppress tumor growth.[111] However, PCSK9 production can also be stimulated by statin therapy, which lowers cholesterol in the ER by activating SREBP2, resulting in poor response to statins in some patients with ASCVD.[105]

Approval of PCSK9 inhibitors (PCSK9-iTs), monoclonal antibodies (Evolocumab, Alirocumab, Tafolecimab), and the siRNA Inclisiran are significant achievements for cardiovascular medicine. They effectively lower hypercholesterolemia and cardiovascular risk, promising possible therapeutic options for personalized care in cardiovascular disorders.[103,105] Even though PCSK9 promotes lysosomal degradation of its substrates, the underlying molecular mechanism is still elusive, limiting the development of alternative, more cost-effective PCSK9 inhibition.[111]

### ANGPTL3 Inhibitors (Promising Results in Lowering LDL Cholesterol and Triglyceride Levels)

Angiopoietin-like protein 3 (ANGPTL3) is exclusively secreted from the liver and inhibits lipoprotein lipase (LPL) and endothelial lipase (EL), thus serving a central role in vascular lipid metabolism. ANGPTL3 LOF carriers have decreased TGs, LDL-C, and HDL-C, reducing CAD risk.[113] Some treatments, such as monoclonal antibodies targeting ANGPTL3 (like evinacumab), effectively reduce LDL-C and triglycerides, especially in people with HoFH, who do not respond well to other treatments. Inhibition of ANGPTL3 can disrupt VLDL catabolism and increase the accumulation of atypical remnants and thus may be a new therapeutic option for hypercholesterolemia, particularly in subjects with inoperable LDL receptors.[103,113]

Mipomersen and volanesorsen are antisense oligonucleotide therapies targeting key apolipoproteins to manage dyslipidemia. Mipomersen binds to ApoB-100 mRNA in the liver, reducing the production of LDL, VLDL, and Lp(a). It is FDA-approved as an adjunct therapy for familial hypercholesterolemia (FH) in patients who do not achieve LDL-C targets with conventional treatments. Volanesorsen targets hepatic ApoC-III mRNA, effectively lowering triglycerides and increasing HDL-C levels. Phase 2 trials demonstrated significant reductions in triglyceride without safety concerns, highlighting its potential for management of hypertriglyceridemia. Elevated triglyceride-rich lipoproteins (TRLs), such as VLDL and IDL, are key cardiovascular risk factors due to their role in promoting atherosclerosis. Impaired lipoprotein lipase (LPL) function contributes to high triglyceride levels, regulated by proteins like ApoC-III and ANGPTL3. Emerging therapies include volanesorsen, which reduces triglycerides by 70% by targeting ApoC-III, and ANGPTL3 inhibitors like evinacumab and vupanorsen, which lower triglycerides, LDL-C, and TRLs. These novel approaches provide promising advancements for lipid management, particularly in high-risk patients.[43,103]

### Gene Therapy

Gene therapy approaches aim to modify genes involved in lipid metabolism to reduce cholesterol levels. Based on the mechanism of action, a wide range of gene therapies can be categorized into the following four main strategies: Gene replacement therapy, Gene addition, Gene knockdown by RNA interference (RNAi), or regulating messenger RNA (mRNA) splicing by ASO or small molecules, and Gene correction or editing.[114] CRISPR-Cas9-based nano-delivery systems are considered a breakthrough in gene therapy due to their ability to precisely target and modify specific genes within the genome, opening up new possibilities for treating a wide range of diseases by correcting genetic mutations at the source, making it a promising approach for personalized medicine.[115] These systems utilize nanoparticles (non-viral vector-based CRISPR/Cas9 systems for treating genetic diseases) —such as lipid nanoparticles (LNPs), polymeric nanoparticles, gold nanoparticles, and extracellular vesicles—to enhance the stability, targeting, and cellular uptake of CRISPR-Cas9 components. By addressing challenges like enzymatic degradation and immune responses, nanotechnology improves the efficiency and safety of gene editing.[116–118]

CRISPR-Cas gene editing and RNA-Seq have enabled gene modulation and biomarker identification in precision medicine.[119] Despite its potential, CRISPR-Cas9 nano-delivery faces challenges such as off-target effects, immune activation, and scalability issues in clinical translation.[119–121] Chitosan-based nanoparticles and exosome-mediated delivery systems are emerging as innovative approaches for transformative potential for treating complex diseases and advancing regenerative medicine and plant genome engineering.[122] Developing biocompatible and non-immunogenic

carriers reduces adverse effects and improves long-term stability. Manufacturing cost-effective nano-delivery systems at a large scale remains a challenge for widespread clinical use.[123,124]

CRISPR-Cas9 is a gene-editing tool that can fix disease-causing genetic mutations. It works by precisely cutting DNA at specific locations and can also influence gene expression through epigenetic changes. While promising for personalized medicine and treating genetic diseases, its use, especially in germline editing (affecting future generations), requires careful ethical oversight and safety validation.[125]

As advancements continue, CRISPR-Cas9-based nano-delivery systems are expected to revolutionize precision medicine, offering new avenues for treating genetic disorders, cancers, and other complex diseases.

Lomitapide is a microsomal triglyceride transfer protein (MTP) inhibitor indicated in treating HoFH. It independently inhibits lipoprotein synthesis and reduces ApoB-containing lipoproteins (VLDL, chylomicrons). In addition to a low-fat diet and other lipid-lowering medications, it helps manage HoFH by lowering plasma lipids, including LDL-C levels. Lomitapide can lower LDL-C by more than 50% in more than half of patients with HoFH and is also helpful for patients with non-HoFH hypercholesterolemia who cannot achieve target LDL-C levels on other therapies.[103]

### RNA-Based Therapies (Leading to Decreased LDL Levels)

In addition to LDL cholesterol, other ApoB-containing lipoproteins like lipoprotein(a) (Lp(a)) and triglyceride-rich lipoproteins also contribute to CVD. Lp(a), an LDL-like particle with a polymorphic apolipoprotein(a) bound to ApoB, independently increases ASCVD risk. Current treatments for elevated Lp(a) are limited; conventional lipid-lowering drugs have little effect, and PCSK9 inhibitors like evolocumab reduce Lp(a) by only 20–30%. Olpasiran, a small interfering RNA targeting hepatic Lp(a) synthesis, has shown potential in phase 2 trials, reducing Lp(a) levels by over 90%. Future studies will determine its impact on cardiovascular outcomes.[43]

RNA-based therapies significantly advance LDL reduction, providing long-lasting effects with less frequent dosing than statins. These therapies address unmet needs in patients with HoFH or statin intolerance, offering an alternative when traditional treatments fail. Beyond lipid-lowering, RNA-based approaches may also reduce inflammation, further decreasing the risk of cardiovascular disease (CVD) by targeting key lipid-related pathways. This combination of efficacy, convenience, and broader cardiovascular protection makes RNA-based therapies a promising addition to hyperlipidemia management.

## Reducing Triglyceride Levels Pathways

PPARs, a group of nuclear hormone receptors, include three isotypes: α, β/δ, and γ. Fibrates belong to an essential class of lipid-lowering drugs useful for managing dyslipidemia. By acting on the peroxisome proliferator-activated receptor (PPAR)-α, these drugs lower serum triglyceride levels and raise high-density lipoprotein cholesterol.[126] Thiazolidinediones are potent PPARγ agonists used for diabetes treatment. PPARβ/δ agonists are under investigation in clinical trials, showing promising results. Synthetic agonists like GW0742 and GW501516 have been studied for their potential therapeutic effects. PPAR-β/δ is widely expressed in various tissues, in insulin sensitivity, lipid metabolism, and atherosclerosis. GW501516, a potent and selective PPAR-β/δ agonist, is particularly interesting in research.[103,127] Pemafibrate exhibited superior efficacy in improving TG levels and enhanced hepatic and renal safety compared to fenofibrate.[128]

## Inhibits Absorption of Cholesterol Pathway

The Niemann Pick C1-like 1 (NPC1L1) protein is a critical receptor in cholesterol homeostasis, whose predominant expression has been reported on the intestinal epithelial cells and hepatocytes. Cholesterol absorption in the small intestine is principally gate-kept by this receptor, which makes this receptor a credible target for lipid-lowering therapy. Ezetimibe is an exceptional model drug that explicitly inhibits this receptor, illustrating how selective inhibition can affect cholesterol metabolism.[29] Ezetimibe works by binding to NPC1L1, blocking cholesterol absorption in the intestine. This lowers hepatic cholesterol levels, triggering the body to clear more cholesterol from the blood. Beyond cholesterol reduction, ezetimibe also affects caveolin 1–annexin A2 complex and aminopeptidase N activity. At a dose of 10 mg/day, it has proven to be an effective and safe treatment, confirming NPC1L1 as a key target for lipid management. Ezetimibe could also serve as an alternative mode of treatment in cases of statin intolerance.[129]

## Regulate Lipid Homeostasis and Cholesterol Transport Pathways

The liver X receptor (LXR) is a nuclear receptor that is a prominent regulator of lipid homeostasis and inflammatory response. LXRs activate genes involved in cholesterol efflux and anti-inflammation.[130] While full LXR agonists effectively regulate cholesterol metabolism, their use is limited by unwanted lipid side effects. Emerging research on selective LXRβ agonists, such as XL-652 and IMB-808, suggests a safer alternative, offering cholesterol-lowering benefits without significant adverse effects. These compounds could revolutionize cardiovascular disease (CVD) treatment by targeting lipid metabolism more precisely. Further clinical trials are needed to explore their potential as therapeutic strategies for CVD.[103,131]

## Inhibition of Formation and Progression of Atherosclerosis Pathway

The primary prevention strategy, at its core, focuses on managing dyslipidemia since elevated LDL cholesterol initiates atherosclerotic plaque formation by promoting macrophage uptake and accumulation in the sub-endothelial space. The critical mechanism by which CD163+ macrophages inhibit VC through NF-κB–induced HAS augmentation and thus promote high-risk plaque development.[132] The development of PET radiotracer binding CD163+ macrophages. The elevated expression of CD163+ resident macrophages on human plaques indicated the potential of CD163 as a biomarker for vulnerable plaques.[132] Advanced targeting methods, like anti-CD163 mAb and CD44-hyaluronic acid conjugates, improve efficiency by enhancing plaque visualization while reducing imaging agent doses by over 90%.

## Targeting Endothelial Cell Adhesion Molecules Pathway

The targeting of angiogenesis is a practical approach to improving the visibility of atherosclerotic lesions. Integrin αvβ3 and adhesion molecules such as VCAM-1, ICAM-1, and selectins, which are upregulated in plaques, provide suitable addresses for nanoprobe targeting.[133] VCAM-1-peptides such as VHPKQHRAEEAK have been applied in ApoE knockout mice, while anti-ICAM-1 mAb enhances molecule-mediated endocytosis for targeting.[134,135]

Microparticles carrying microRNAs (miR-146a/-181b) have been directed to E-selectin using thioaptamers. ICAM-1, upregulated in inflammation, is highly expressed in atherosclerotic plaques and can be targeted by nanoparticles. CLABL peptides have been used to direct nanoparticles to endothelial cells with increased ICAM-1 expression, targeting inflammatory sites. VCAM-1, upregulated in damaged vascular regions, is another target for nanoparticle delivery in atherosclerosis.[134]

## Target for Atherosclerotic Lesions Pathways

Two cross-links interconnect collagen molecules: Cross-links can arise from enzyme-driven cross-links from lysyl oxidase (LOX) or disease-related cross-links such as advanced glycation end products (AGEs). Proteoglycans assist enzymatic crosslinks to increase collagen strength, but AGE crosslinks seen in atherosclerotic plaques stiffen the collagen matrix and hamper everyday cell interactions. Inflamed, unstable plaques prone to rupture contain these AGE crosslinks.[134] Collagen IV targeting and binding peptides were used to design theranostic nanoparticles to deliver therapeutic payloads to atherosclerotic plaques. Moreover, marine collagen peptides make an effective natural remedy for atherosclerosis.[136] Modern imaging assesses collagen cap thickness and plaque features, but predicting rupture risk remains challenging. Collagen fibers are key to plaque stability, and rupture in carotid arteries is a major cause of cerebrovascular events, highlighting the need to understand tissue failure and collagen architecture for better prevention.[137,138]

Profilin-1 is one of the actin-binding proteins which is overexpressed in atherosclerosis and other cardiovascular complications. Polyethylene glycol (PEG) nanoparticles functionalized with anti-profilin-1 antibodies have recently been employed to deliver profile-1 siRNA to the plaque regions. Silencing profilin-1 decreases the growth and movement of smooth muscle cells in the aorta of mice, which could be of clinical value.[139,140]

Fibrin in thrombi accumulates in atherosclerotic lesions, promoting growth and inflammation. Immune activation in atherosclerosis leads to monocyte recruitment via CCR2, driving macrophage differentiation and tissue damage. SR-B1 glycoproteins, key in endocytosis and signaling, recognize LDL, oxidized LDL, and VLDL, influencing plaque progression.[46]

## Mechanisms of Action Chitosan-Based Nanoparticles in Hyperlipidemia

To assess the real-world applications of CSNPs as drug carriers, it's crucial to understand their molecular mechanisms. Preclinical studies demonstrate CSNPs' potential in modulating lipid metabolism and reducing lipid levels in animal models. In contrast, clinical studies show promise in lowering LDL cholesterol, raising HDL cholesterol, and improving cardiovascular outcomes in human subjects. Evaluating long-term safety and efficacy through rigorous trials is essential to integrating CSNPs into treatment regimens, enhancing patient compliance, and reducing the adverse effects of conventional medications. Researchers can optimize their effectiveness in hyperlipidemia treatment by understanding the mechanisms of action and fine-tuning the characteristics of nanoparticulate carrier targeted systems. Leveraging the EPR effect, receptor-mediated targeting strategies, and appropriate surface modifications, these systems hold great potential in combating hyperlipidemia (as shown in Table 1) and its associated complications.

CS has been shown to improve the physicochemical properties of drugs, particularly enhancing their solubility, as demonstrated by López-Manzanara Pérez et al. Their study found that CS exhibited a high ratio of protonated amino groups (NH3+) and increased intramolecular hydrogen bonding. These changes led to an expansion of the interpolymer chains and a higher dissolution rate of SIM.[141] Such improvements may contribute to advances in controlled drug release, particularly for about eighty percent of drugs that exhibit poor solubility. In this study, we demonstrate our ability to achieve the desired drug delivery rate of a water-insoluble drug through CS membranes tailored to fit the needs of medicine.[152]

The obtained and synthesized CS with a deacetylation level of 70.57% presents the prospect of the ideal anti-cholesterol agent. The efficacy data show a 29.57% decrease in cholesterol levels, comparable to the reduction of Simvastatin by 30.07% and significantly higher than other formulations, ranging between 12.01% and 18.44%. This characteristic of CS to lower cholesterol may be due to its interference with fat or bile acid absorption.[153] Given 750 mg/kg BW, total cholesterol levels in rats were significantly reduced from 127.1 to 74.2 mg/dL.[154]

CS possesses an adjustable structure and a high density of functional groups; it can be formed into various forms for use in numerous contexts. It can be observed that due to the presence of OH and NH groups in the backbone, this polymer has the potential to bypass certain limitations.[155] Cross-linking reactions can improve the mechanical and thermal properties of CS. Covalent bonding between specific functional groups of CS molecules can result in cross-linking reactions.[156–158] For example, TMC-coated gold NPs are preferred for cancer; PEGylated CS NPs conjugated with collagen are liver-directed, and TMC and bufalin-incorporated NPs are lungs tumor-directed. Functionalized CSs can modify the drug metabolism and their availability in the body and thus increase the time for drug delivery (carboxylated, quaternized, or PEGylated forms of CS) or the rate of drug delivery and their duration (acylated, succinylated, benzoylated, methacrylate, TPP-crosslinked, and CS–EDTA). These alterations increase solubility modified, carboxylated, aminated, succinylated, part and pegylated, Pylated, sulfonated, CSCD derivatives, andolic acid–CS) and stability Nphthaloyl-, PEGylated-, CS–TA, TPP-cross and cyclic structure CS derivatives) and effectiveness of bioavailability of the drug. Some CS derivatives can be used as carriers for gene delivery, the uptake dock of hydrophobic medications [benzoylated, acylated, PEGylated, cholic acid – CS derivatives].[31]

Hirpara et al formulating long-circulating PEGylated CSNPs. The result showed that pharmacokinetic studies demonstrated that optimized rosuvastatin nanoparticles (RST-NPs) provided prolonged drug release over 72 hours. In pharmacodynamics studies with a hyperlipidemic rat model, RST-NPs exhibited superior lipid-lowering effects compared to plain rosuvastatin. The nanoparticles enabled sustained delivery and enhanced therapeutic efficacy, making them a promising drug delivery option for statins.[144]

CSChSNPs localized to liver-targeted CSNPs endorse restricted liver cancer cell proliferation and enhance drug uptake. This method increased the solubility of simvastatin significantly, indicating that CSChSNPs could be a potential therapeutic strategy for liver cancer and other associated illnesses. The hepatic targeting involved the N-acetylgalactosamine (GalNAc) residues of ChS that bound at receptor ASGPR, which are known to be resident on the hepatocytes. The present study employed simvastatin as an anticancer agent against hepatocellular carcinoma cells (HCC).[159] In cancer therapy, with the challenges facing the problem of low therapeutic efficacy and systemic toxicity, it is feasible to exert significant influences on therapeutic ratios by selectively confining the therapeutic agents to the tumor site. A successful strategy contains targeted nanosystems such as glutamine-decorated tetrandrine and doxorubicin-

**Table 1** Chitosan-Based Nanoparticles in Hyperlipidemia

| No | Drug | CS/Derivates | Characterization | Target | Physicochemical Enhancement | Pharmacological Enhancement | Ref |
|---|---|---|---|---|---|---|---|
| 1 | Simvastatin (SIM) | CS/Sodium Carboxymethylcellulose Complexes (CS-CMC Complexes) | SEM revealed surface morphology changes in CS/CMC interpolymeric networks based on CS content. FTIR, DSC, and XRPD analyses confirmed high swelling in these complexes. | Various kinetic models were used to analyze the dissolution rate of simvastatin and how CS/calcium carboxymethylcellulose interactions enhance the release of poorly soluble drugs. | Polyelectrolyte complexes (PEC) of CS and carboxymethylcellulose (CMC) at various ratios enhanced SIM dissolution by 2.54-fold in a simulated intestinal medium (pH 4.5). PECs with abundant protonated amino groups (NH3+) improve dissolution profiles by reducing drug crystallinity and increasing wettability through ionic interactions with the medium. | – | [141] |
| 2 | Atorvastatin. | Glycyrrhetinic acid (GA)-CSNPs | Product structure was validated with IR and NMR, and formulation properties were assessed using DSC, particle size analysis, and cellular uptake investigations. | GA, a key component of liquorice and a glycyrrhizin hydrolysis product, binds specifically to high-affinity sites on rat liver cell membranes. | Release profiles, pharmacokinetics, and organ distribution studies revealed enhanced liver uptake of the developed formulation. | The improved formulation increased plasma levels compared to CTS nanoparticles and the drug alone, showing liver accumulation about 2.59 times higher than CTS nanoparticles. | [142] |
| 3 | Atorvastatin | Galactose- trimethyl CS NPs (GTANPs) | – | Baf60a siRNA and anti-miR-33 pDNA were successfully encapsulated by targeting both hepatocytes and lesional macrophages, enabling the combined delivery of statins and nucleic acids. | – | In vitro, GTANPs/siBaf60a and GTANPs/pAnti-miR-33 showed anti-inflammatory and lipid-regulating effects. In ApoE-knockout mice, GTANPs/siBaf60a IV reduced cholesterol and plaque area, while GTANPs/pAnti-miR-33 orally boosted HDL-C and anti-inflammatory cytokines, improving anti-atherosclerotic outcomes. | [143] |

(*Continued*)

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**Table 1** (Continued).

| No | Drug | CS/Derivates | Characterization | Target | Physicochemical Enhancement | Pharmacological Enhancement | Ref |
|---|---|---|---|---|---|---|---|
| 4 | Rosuvastatin calcium | TPP-PEGylated CS was reacted with a PEG carboxylic acid derivative using carbodiimide. | The particle size is <200 nm, with a spherical entrapment efficiency of approximately 14%. | Conduct a long-term, repeated dosing study to assess NP efficacy and toxicity. | In phosphate buffer at pH 7.4, in vitro tests revealed a gradual release of rosuvastatin, with cumulative releases at 14.07 ±0.57 and 22.02±0.81% over 120 hours. | Rosuvastatin nanoparticles (RST-NPs) showed prolonged release and enhanced lipid-lowering effects, outperforming plain rosuvastatin in a hyperlipidemic rat model. | [144] |
| 5 | A single-chain fragment variable (scFv) targeting LDL(-). | CS-coated lecithin-lipid-core nanocapsules were modified with scFv-anti-LDL(-) by creating an organometallic complex using $Zn^{2+}$. | Lecithin-lipid-core nanocapsules (LNCs) appeared and turbid with a slightly acidic pH. The optimized LNC9, with 9 mg/mL lecithin, measured 117±4 nm with a low polydispersity (PDI 0.1) and a zeta potential of −20.0mV. | Pure, surface-modified nanocapsules with scFv targeting LDL(-) were tested for their impact on LDL(-) uptake by primary macrophages and the advancement of atherosclerotic lesions in Ldlr −/− mice. | The refined scFv-anti-LDL(-)-MCMN-Zn nanoformulation is taken up by human and mousephages through different endocytosis pathways. | The scFv-anti-LDL(-)-MCMN-Zn nanoformulation decreased LDL(-) absorption and IL1B/MCP1 levels in macrophages. In Ldlr−/− mice, it halted atherosclerosis advancement without impacting vascular permeability or interactions between leukocytes and endothelial cells. | [145] |
| 6 | Superparamagnetic iron oxide nanoparticles (SPIONs)- CCh-anti-VCAM-1 maghemite nanoparticles | Iron oxide nanoparticles were coated with cationic CS and functionalized with monoclonal antibodies targeting VCAM-1 and P-selectin. | The high zeta potential of the nanoparticles ensures stable dispersions in aqueous media, and antibody attachment to SPION-CCh particles does not significantly affect their magnetic properties. | Superparamagnetic iron oxide nanoparticles (SPIONs) were designed to target vascular endothelium altered during early inflammation, a precursor to many CVDs. | In vitro studies confirmed that SPIONs with anti-VCAM-1 antibody specifically interact with inflamed aortic endothelial cells from diabetic db/db mice. | SPION-CCh-anti-VCAM-1 nanoparticles were detected via MRI in atherosclerotic mice, showing promise as sensitive, site-specific contrast agents for endothelial inflammation in diseases like atherosclerosis, diabetes, and cancer. | [146] |
| 7 | CD47 antibody | The nanoparticles were created through charge neutralization using CS and hyaluronic acid (HA). | Nonstoichiometric CS-HA /CD47 polyelectrolyte complexes demonstrated 1-month stability in water/PBS, with 375–620 nm nanoparticles and positive zeta potential. | Blocking CD47 with an anti-CD47 antibody significantly decreased arterial plaque accumulation. | The anti-CD47-loaded CS-HA nanoparticles displayed quick kinetics and high loading capacity in both water PBS. | CS-HA/CD47 nanocarriers effectively targeted VECs and atheromatous plaques, showing potential for drug delivery in atherosclerosis. | [147] |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 8 | miRNAs-33 | CS-TPP carriers were created via the ionic gelation technique. | NPs sizes ranging from 150–200 nm | miRNAs with a negative charge were enclosed within CS/TPP nanoparticles through ionic interactions with the polymer components. | Macrophages treated with miR-33-loaded chNPs showed reduced efflux, confirming effective miRNA delivery and its role in regulating cholesterol levels. | miR-33 CSNPs reduced cholesterol transport, while efflux-promoting miRNAs enhanced RCT, showing potential for atherosclerosis targeting. | [148] |
| 9 | Cinnamomum casia Extract | CS-TPP (the ionic gelation method). | Nanoparticles showed 84.93% encapsulation efficiency and a zeta potential of 193.3 mV, confirming CS's suitability for drug delivery. CSNPs have a size of 64.9 nm. | – | CS-Na-TPP interaction stretches CS chains, protonating amine groups (-NH3+), which bind cinnamomum. Encapsulation efficiency reflects cinnamomum coating in nanoparticles. | CSNPs encapsulating Cinnamomum cassia extract (150 ppm) reduced cholesterol by 49.66%, showing its cholesterol-lowering potential. | [149] |
| 10 | Epigallocatechin gallate (EGCG) | CS -polyaspartic acid | Protect from the harsh environment of the gastrointestinal tract. | Nanoparticles (93 nm) are made from PAA (30–50 kDa) and CS (3–5 kDa) at a 1:1 ratio. EGCG-loaded nanoparticles (102 nm) were pH-responsive with diverse release profiles in gut media. | Oral EGCG-CS-PAA nanoparticle intake in rabbits resulted in a lipid deposition ratio of 16.9 ± 5.8%, similar to oral simvastatin at 15.6 ± 4.1%. EGCG alone showed a 42.1 ± 4.0% lipid deposition ratio, while blank nanoparticles had a 65.3 ± 10.8% ratio. | Incorporating EGCG into the nanoformulation significantly enhanced its effectiveness against rabbit atherosclerosis. | [150] |
| 11 | Pandanus tectorius fruit extract | CS-TPP (ionic gelation method). | – | Scavenger Receptor Class B type 1 (SR-B1) pathway. | Enhancing the extract's solubility may be achievable by synthesizing CS-P. tectorius fruit extract nanoparticles. | In vivo, nanoparticle therapy lowered TC (197%), LDL (360%), and TG (109%) levels while elevating HDL cholesterol by 150% compared to the untreated high-cholesterol diet group. These nanoparticles are safe and efficient in managing hypercholesterolemia via the SR-B1 pathway. | [151] |

loaded nanoparticles (GDTNPs). This strategy, which operates at the tissue level directly on the neoplasm, is effective in cancer therapy and other diseases.[160] Despite limited clinical research, CSNPs have shown anti-hepatotoxicity on free radicals and decreased lipid peroxidation, opening a window to future HCC treatment. To achieve more excellent delivery of drugs to HCCs, galactosylated CS has been used to create nanoparticles, which selectively adhere to asialoglycoprotein receptors (ASGPR) predominantly located on hepatocyte membranes rather than on extrahepatic tissues.[161] Lin et al were pioneering researchers who utilized glycyrrhizin derivatives of CS to create nanoparticles with active hepatic targeting. Many glycyrrhetinic acid receptors exist on the surface of hepatocytes, which can bind specifically to glycyrrhizic acid and glycyrrhetinic acid. Their work involved preparing CSNPs modified with glycyrrhizin, demonstrating that these nanoparticles tended to accumulate specifically in hepatocytes.[162]

To improve the therapeutic index of doxorubicin and tetrandrine in tumor therapy, thereby minimizing their systemic toxicity, glutamine-functionalized doxorubicin-tetrandrine loaded nanoparticles (GDTNPs) for liver targeting were developed.[160] Covalently-conjugated galactose, recognized by asialoglycoprotein receptors exclusively expressed in hepatocytes, targeted the liver.[163] The asialoglycoprotein receptors in the hepatocytes and CS-lactose conjugation through the Maillard reaction enhanced liver-specific drug delivery in the case of TLM-LCH nanoparticles. They proved superior liver targeting for HCC therapy.[164]

Most drugs are concentrated in the liver, and diverse hepatic status requires targeted delivery within the liver cell to therapy and diagnoses. This has underlined the significance of accurate, safe, and inexpensive techniques for liver-targeted drug delivery with even higher selectivity. These platforms allow drugs to target the liver passively or actively, thereby reducing systemic circulation and increasing the "effective dose" in the liver.[165]

PEC nanoparticles of positively charged HA and CS were synthesized while remaining stable in a physiological solution for 30 days.[147] Target binding at the particle interface can be effectively attained without compromising the designed antibody's stability. While Stabilin-2 is less abundant in standard vessel walls than in atherosclerotic plaques, it is expressed by macrophages and endothelial and smooth muscle cells within the plaques.[166] Lee et al identified S2P, a peptide targeting stabilin-2, which efficiently localized to plaques when conjugated to HGC NPs. S2P also accumulated in lymph nodes, spleen, and liver, likely due to hepatic uptake of hydrophobic compounds.[167]

Jiang et al demonstrated that co-delivering statins and nucleic acids effectively regulate cholesterol metabolism and reduce inflammation, offering a novel approach to atherosclerosis treatment. This study developed galactose-modified trimethyl CSNPs (GTANPs) for dual targeting of hepatocytes and macrophages, encapsulating siBaf60a and pAnti-miR-33. In ApoE-knockout mice, intravenous GTANPs/siBaf60a lowered plasma cholesterol and plaque areas, while oral GTANPs/pAnti-miR-33 increased HDL-C and anti-inflammatory cytokines, yielding significant antiatherosclerotic effects. These findings underscore the therapeutic potential of this dual-targeting system.[143]

The natural products that are used in this study include Sweet star fruit (*Averrhoa carambola L*), Tamarind (*Tindus indica L*), Kemuning (*Murraya paniculata L jack*), Mahkota Dewa (*Phaleria. Macrocarpa (Scheff)*). These substances include phenols, flavonoids, tannins, and alkaloids, which have antioxidant effects that reduce cholesterol.[151] The mentioned botanicals combined with nutraceuticals and omega-3 fatty acids may benefit dyslipidemia, improve cardio-metabolic, and possibly decrease the risk of CVD. For example, monacolin K, along with L-arginine, coenzyme Q10, and ascorbic acid, not only brings about a significant reduction in LDL cholesterol but also decreases the triglycerides level without affecting the level of HDL cholesterol level.[102,168] In this way, such an approach provides an opportunity to reduce Apo B levels, possibly prevent and treat CVDs without expensive treatments, and gradually improve people's quality of life.[169]

Probiotics, pectin, Ginkgo biloba, flaxseed, red wine, resveratrol, curcuminoids, and new soy products rich in isoflavones have shown potential in lowering cholesterol levels.[170] Soy products are rich in isoflavones, fiber, and phospholipids and can reduce LDL cholesterol.[171] When used appropriately, sterols, coenzyme Q10, and probiotics like Lactobacillus fermentum ME-3 are highlighted for their cholesterol-lowering effects. Soy proteins and omega-3 fatty acids offer health benefits when replacing animal products in the diet.[172] Natural compounds like vitamin E, resveratrol, and quercetin demonstrate promise in inhibiting LDL oxidation and preventing atherosclerosis, but standardized studies are needed for optimal dosages and efficacy.[173] CS shows promise in delivering natural products effectively. This will also highlight the importance of integrating materials that provide better therapeutic benefits and the least effects on the

natural environment. As industries shift focus to sustainability, CS is one of the most promising players as it drives the environmentally and ethically more conscious search for innovative solutions.[174]

Potentialities of CS-based self-assembling injectable hydrogels as multi-functional and highly permeable moistened micro-environments for various tasks, such as loading live cells, drugs, growth factors, and miRNA for enhanced cell viability and cell adhesion. Due to this, they can be explicitly administered, which reduces the unnecessary side effects of the drug. These hydrogels have applications in tissue engineering, drug delivery, wound healing, and cancer therapy. Conjugated controlled release studies supported by in vitro and in vivo dissolution tests on rodents prove their drug release effectiveness.[175]

The clinical efficacy of alirocumab and evolocumab, FDA/EMA-approved monoclonal antibodies targeting PCSK9, underscores its significance in treating hypercholesterolemia and associated CVDs. However, challenges like high costs, subcutaneous administration, and potential immunogenicity hinder widespread use. The lack of affordable oral PCSK9 inhibitors limits their benefits. The discovery of natural PCSK9 inhibitors offers promise for developing oral, small molecules for combined therapy with statins. These inhibitors act at transcriptional levels, showing effective anti-PCSK9 activity, though fewer target the autocatalytic secretion step or PCSK9 interaction with the LDL receptor.[176]

Finally, the biology of bioavailability proved marginal when given as AT suspension compared to normal AT, but when combined with CH-AT conjugate, the effect was significantly reduced. These results indicate that CS-conjugated nano-prodrugs will likely become useful sustained-release polymeric prodrugs for enhancing bioavailability.[177]

Unlike LDL or triglyceride-rich lipoproteins, HDL cholesterol, enriched with apolipoprotein AI, is inversely associated with ASCVD risk. HDL's potential antiatherogenic effects include anti-inflammatory, anti-thrombotic, and antioxidant actions and cholesterol efflux from macrophages. While raising HDL levels was once seen as a promising ASCVD therapy, clinical data reveal limited cardiovascular benefits and possible non-cardiovascular risks. Current evidence emphasizes improving HDL quality over merely increasing its levels.[43]

Simvastatin's therapeutic applications extend beyond its conventional use. CS channels loaded with simvastatin/Pluronic F-127 hydrogels enhanced peripheral nerve regeneration and functional recovery in mice by promoting neurotrophic factor expression.[178] This study also marks the first incorporation of simvastatin and citicoline into CS, aiming to maximize statin benefits while mitigating adverse effects in Alzheimer's disease (AD).[179] Additionally, simvastatin-loaded cubosomes demonstrated wound-healing potential in vivo.[180] Cone beam computed tomography, bone density measurements, and histopathology further confirmed the efficacy of SIM CS-TPP nanoparticles in promoting bone regeneration compared to untreated controls after six weeks of implantation.[180,181]

By conjugating nanoparticles on their surface, therapy can be administered directly to affected receptors regarded as overexpressed in atherosclerosis: the targeted therapy has minimal off-target effects. CS-NPs offer numerous advantages for drug delivery, including biocompatibility and mucoadhesiveness. Still, their limitations must be carefully considered, particularly in biodegradability, drug release rate control, and stability in physiological environments.[36,96] CS's biodegradation in the environment is influenced by several factors, including molecular weight, degree of deacetylation, environmental conditions (such as pH, temperature, and presence of enzymes), and microbial activity. While chitosan degrades enzymatically via lysozyme, the degradation rate varies significantly depending on tissue conditions.[182] In highly acidic or enzymatically rich environments, excessive degradation can lead to premature drug release, reducing therapeutic efficacy. Conversely, degradation may be too slow in neutral or alkaline environments, potentially causing nanoparticle accumulation and delayed drug clearance, which could raise safety concerns.[36] The controlled release of drugs from CS-NPs is another critical challenge, as drug release profiles can be highly variable depending on the physicochemical properties of the drug and the nanoparticle formulation.[183] Chitosan's pH-responsive nature makes it an attractive carrier for site-specific drug delivery, particularly in gastrointestinal or tumor-targeted applications.

Despite promising in vitro performance, addressing these stability challenges in vivo remains crucial for successfully translating CS-NPs into clinical applications, necessitating further research and optimization of nanoparticle formulations.[184,185] The stability of CS-based NPs in physiological conditions is often improved by covering them with synthetic (eg, polyethylene glycol) or natural (eg, alginate) polymers. Such nanocarriers are usually sensitive to pH and capable of drug release in mildly acidic conditions, characteristic of tumor tissues.[186] Encapsulation of FX in ALG/CS-NPs improved its GI stability and bioaccessibility.

## Perspective

Despite several promising results from preclinical studies, significant challenges remain in translating CSNPs-based therapies into clinical practice. Current research endeavors aim to address gaps, enhance nanoparticle technology, and explore future directions for advancing hyperlipidemia treatment. This ongoing research underscores the potential of CSNPs-based therapies to revolutionize the management of hyperlipidemia and other lipid-related disorders. Pharmaceutical nanotechnology is advancing from addressing drug delivery and nutraceutical challenges, which include complications of metabolic syndrome like type 2 diabetes, hypertension, and obesity, to supporting genetic and epigenetic solutions. This technology utilizes lipid particles, non-lipid, and bacterial/viral platforms for liver diseases such as HCC, hepatitis, and fibrosis. And can be used in hepatic drug delivery systems. CS can be described as a natural nanocarrier material that allows enhancements through vitamin incorporation or interaction with other polymers for higher efficiency in drug application.[151]

Many natural products and drugs are limited by poor solubility, low bioavailability, and limited liver distribution, reducing their clinical applications. These problems could be solved by liver-targeted drug delivery systems (HTDDS), which enhance the effectiveness of treatment for NAFLD and lessen side effects.[187] An effective drug delivery system requires a homing device to target the drug to specific cells, targeting particular receptors in the liver, such as asialoglycoprotein receptor (ASGP-R), glycyrrhizinic acid (GA-R), glycyrrhizin (GL-R), and hyaluronan (HA-R) for the treatment of hepatic diseases.[162]

Nearly all drugs achieve very high concentration in the liver, but many liver pathologies need a high accumulation of drugs in some types of hepatocytes. This emphasizes developing efficient, safe, cost-efficient, and highly targeted drug delivery systems for the liver.[188] The liver architecture is composed of various cells, including Kupffer cells (KCs), hepatic stellate cells (HSCs), sinusoidal endothelial cells (SECs), hepatocytes, biliary cells, and stem cells. Passive and active targeting to specific liver cells, mainly mediated by receptors, commonly targeted receptors on HCC cells include asialoglycoprotein receptor (ASGPR), glycyrrhizinic acid receptor (GAR), CD44, folate receptor (FR), and transferrin receptor (TfR).[177]

Prodrugs such as bempedoic acid are well suited for drug delivery systems due to their specific activation mechanism. With limited activity in target organs such as the liver and minimal impact on peripheral tissues, these prodrugs reduce the risk of side effects and increase therapeutic efficacy, making them a superior choice in modern medicine.[189]

Treatment of obesity is tailored to the severity and chronicity of the condition, with a healthy lifestyle as the basis of therapy due to its low cost and minimal risk.[190] The Brazilian CVD care model focuses on patient education, awareness campaigns, mandatory blood pressure and cholesterol screening, and training of non-physician workers for screening. Point-of-care testing and handheld echocardiography can improve disease management.[104]

Many people choose herbal medicine because of its affordability, availability, and compatibility with personal beliefs. Approximately 25% of new drugs approved by the FDA in 2020 were derived from plants. While herbal medicine is effective for chronic diseases and cases where conventional medicine is inadequate, its safety is still not fully understood. Nanotherapy utilizing natural products is an alternative for treating obesity, with nanocarriers improving plant extracts' bioavailability, stability, and targeting.[191,192] Despite significant progress, more research is needed to understand the mechanisms of herbal medicine and monotherapy to enhance efficacy and reduce toxicity in treating obesity and other health conditions.

Improving the stability of rupture-prone atherosclerotic plaques is a priority for atheroprotective nanoparticles. Research focuses on inflammation contributing to plaque instability, with detection and development of imaging probes critical for treatment.[193,194] Future advancements involve theranostic nanoparticles integrating treatment and monitoring progress.[195,196] While the murine model encompasses various stages of atherosclerotic lesion advancement, it cannot replicate the plaque rupture observed in humans, highlighting a key limitation in translating findings to human CVD.[197]

Optimizing circulation time, minimizing liver uptake, and targeting unstable plaques will yield more effective nanomedicine candidates. Targeting inflammatory atherosclerotic plaques and designing multitasking nanocarriers are essential for selective delivery and release of payloads. HDL-mimetic nanoparticles face challenges of liver affinity and high cost, while other nanocarriers containing anti-inflammatory or anti-proliferative molecules, such as statins, have shown therapeutic potential.[198]

PCSK9's possible significance as a crucial marker in cancer outlook and its promising as an innovative focus for cancer therapy[105] Fang et al developed a PCSK9 nanoparticle vaccine by fusing the PCSK9 catalytic domain to a 24-mer

ferritin NP. This vaccine induces anti-PCSK9 antibodies and reduces serum lipid levels, aortic plaque lesions, and macrophage infiltration in atherosclerosis, with efficacy dependent on T follicular helper cells and LDL receptors, making it potential for treating hypercholesterolemia and atherosclerosis.[199]

The increasing use of nanoparticles has raised concerns about their potential toxicity and adverse effects on human health and the environment.[200] While NPs show potential in drug delivery systems (DDSs), their application in the clinic is hindered by various drawbacks, such as toxicity, high material costs, and time-consuming and challenging preparation procedures.[201] The key barriers to large-scale production include variability in chitosan source and molecular weight (Román-Doval et al; Wang and Roman). The clinical translation of chitosan nanoparticles (CS-NPs) faces significant challenges, particularly in mass production, stability, biocompatibility, immunogenicity, and lack of translation to clinical trials.[39,202] Additionally, existing synthesis methods, such as ionic gelation and emulsion crosslinking, often struggle with reproducibility and scalability. To overcome these limitations, advancements in microfluidic technology and continuous flow synthesis are being explored to ensure batch-to-batch consistency.[203,204]

Another major challenge is the physicochemical and biological stability of CS-NPs.[205] Their tendency to aggregate due to electrostatic interactions and pH fluctuations affects drug encapsulation efficiency and controlled release. Since chitosan is pH-sensitive, ensuring sustained drug release in physiological conditions remains difficult.[206,207] Strategies such as surface modifications (eg, PEGylation or polyelectrolyte coatings) and lyophilization with cryoprotectants have been investigated to improve nanoparticle stability. Additionally, biocompatibility concerns arise as the cationic nature of chitosan can lead to cytotoxicity at high concentrations. Although its degradation products, such as N-acetylglucosamine, are biocompatible, their long-term safety in human tissues requires further study.[208,209] Furthermore, immune responses triggered by chitosan nanoparticles, such as macrophage activation and cytokine release, pose potential risks, necessitating modifications like PEGylation or incorporating biocompatible polymers to reduce immunogenicity.

Despite these challenges, clinical studies have demonstrated promising applications for CS-NPs in drug delivery, vaccine adjuvants, and cancer therapy. In particular, chitosan-based carriers have been explored for oral insulin delivery, intranasal vaccines, and targeted chemotherapy, with early-phase trials showing improved drug stability and bioavailability.[32] However, limitations remain, including variable patient responses, a lack of long-term toxicity data, and the need for regulatory approval tailored to nanomedicine. The regulatory landscape surrounding nanotoxicology is explored, emphasizing the need for standardized testing protocols and risk assessment frameworks. Furthermore, the article highlights the importance of a multidisciplinary approach, integrating expertise from material science, toxicology, and pharmacology to address the complexities of nanotoxicity assessment.[200] In shrimp aquaculture, viral-based delivery methods for dsRNA are limited due to challenges in large-scale production and administration routes. To address these challenges, biopolymeric nanoparticles have been employed for dsRNA delivery.[210] In targeted delivery and vaccine efficacy, challenges remain in scalability, regulatory approval, and transitioning from preclinical studies to clinical applications.

## Conclusion

It's important to note that these innovative treatments may have specific indications and considerations. Still, it is crucial to determine the most appropriate treatment approach based on individual patient characteristics and needs. Characteristics of CS enable enhanced drug permeation and protection, especially for poorly soluble drugs, facilitating controlled and targeted drug release. Functionalized CS further improves drug metabolism and delivery rates through PEGylation or ligand attachment modifications. It is an effective tool in therapeutic and diagnostic applications, particularly in treating conditions like hyperlipidemia.

Recent research has focused on nanotechnology-based therapies, aiming to improve treatment delivery, safety, efficacy, and bioavailability. Managing dyslipidemia is vital in preventing cardiovascular events, and adhering to standard guidelines can enhance clinical practice. Chitosan nanoparticles sangat prospek menghantarkan obat dengan berbagai mekanisme molecular. Clinical trials are ongoing to assess their effectiveness for improving patient care, and the integration of nanoparticulate carrier targeted systems holds the potential to optimize hyperlipidemia treatment through enhanced drug delivery and reduced side effects. Collaboration among stakeholders is crucial to successful adoption in clinical practice and personalized medicine.

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## Disclosure

The author(s) report no conflicts of interest in this work.

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