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A supramolecular nanoprodrug for prevention of gallstone formation

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ABSTRACT

Cholelithiasis affects approximately 10%-20% of the adult population globally. And cholesterol accumulation and nucleation of cholesterol crystals are commonly recognized as the primary process in the initiation and progression of gallstones. Hydroxypropyl-β-cyclodextrin (HPCD) is a supramolecular host compound that can solubilize cholesterol, potentially serving as a preventative or therapeutic agent for cholelithiasis. However, we found that the administration of HPCD treatment did not impede the formation of gallstones in mice, mainly attributed to the pre-complexation of its cavity during the transition process. Here we synthesized a prodrug of HPCD and prepared a HPCD nanoparticle (HPCD-NP), which can be transported efficiently to the gallbladder through the hepatobiliary system following an intravenous injection. In the bile, the HPCD-NP degraded into free HPCD, bound to cholesterol crystals and gallstones within the gallbladder and effectively increased cholesterol solubilization, leading to gallstones regression. Given the established safety of both HPCD and cyclodextrin-based nanoparticles in numerous animal and human studies, HPCD-NP shows considerable promise for the prevention and treatment of human cholelithiasis.

Gallstones, also known as cholelithiasis, are crystal formations in the biliary tract or gallbladder. They prevail in adults globally at a rate of 10%−20%, leading to the greatest socioeconomic cost among all digestive disorders [1–3]. Apart from the blockage of the bile duct and pancreatic duct, gallstone disease also contributes to other medical complications such as cholecystitis, pancreatitis, gallbladder and gastrointestinal (GI) cancers [2,4,5].

Cholecystectomy has long been the preferred method for treating symptomatic gallstones. However, this invasive procedure carries potential side effects, such as bile duct injury, intolerance to fat, metabolic irregularities, and post-cholecystectomy syndrome [2-4,6,7]. Older patients are often deemed unsuitable candidates for cholecystectomy. Furthermore, the operation may lead to issues such as residual stones and stone recurrence in the bile duct [8,9]. Oral administration of bile acids, such as ursodeoxycholic acid (UDCA), has been used for clinical treatment gallstones by lowering hepatic cholesterol secretion [10]. Nonetheless, this approach necessitates high doses of UDCA (approximately 1000 mg daily) for prolonged periods (ranging from 6 months to several years) and limited efficacy with low cure rates and high relapse rates [11,12]. More recently, UDCA was found to have no beneficial effects in treating symptomatic gallstones [13–15]. Consequently, there is an urgent need to develop new medications for the effective management of gallstones.

Cholesterol plays a pivotal role in the pathogenesis of gallstone formation. The predominant type of gallstones, namely cholesterol gallstones, consists mainly of cholesterol. Moreover, the initial stage of gallstone formation is characterized by the crystallization of cholesterol [16]. Consequently, strategies aimed at improving the solubility of cholesterol may effectively slow down the process of cholesterol gallstone formation.

As a supramolecular host compound, 2-hydroxypropyl-β-cyclodextrin (HPCD) is widely used as a pharmaceutical excipient to improve the solubility and stability of drug molecules due to its ability to form molecular complexes [17]. Additionally, HPCD demonstrates a high affinity for cholesterol, effectively increasing its solubility [18,19]. Recent studies have reported that HPCD exhibits antiatherogenic effects and is effective in treating Niemann-

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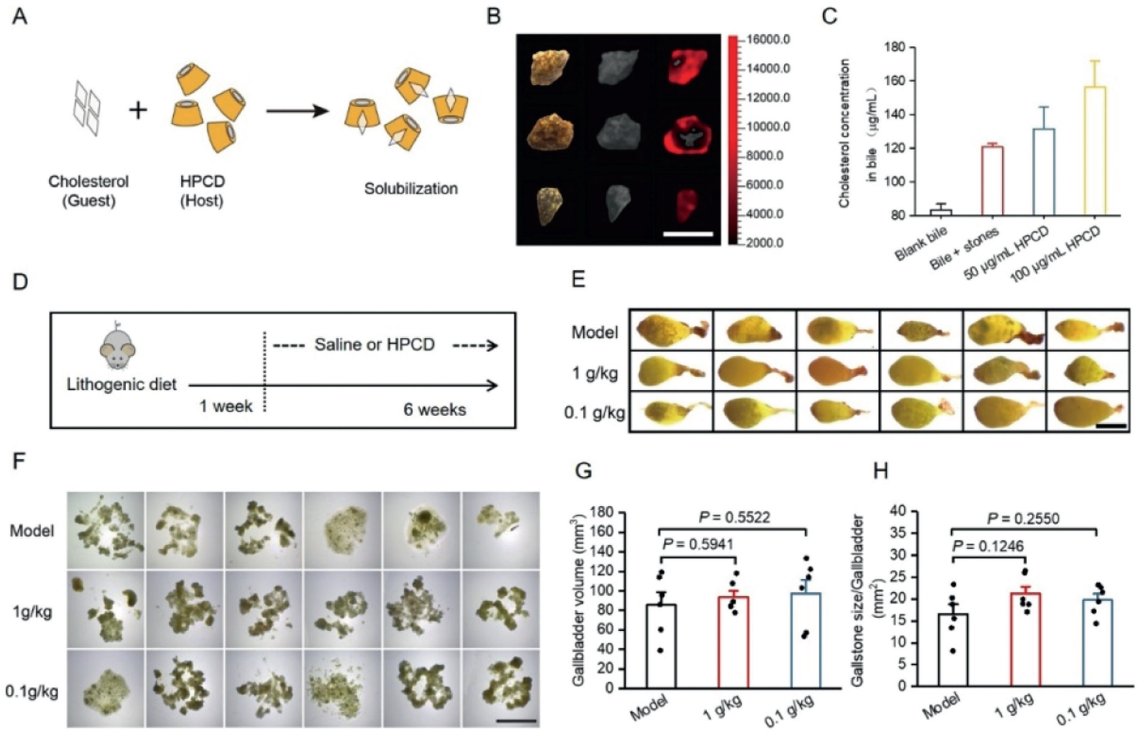

Fig. 1. Evaluation of HPCD for prevention of gallstone formation. (A) Schematic illustration of how host-guest interactions enhance the solubilization of cholesterol. (B) Fluorescence images of human gallstones, previously immersed in an aqueous solution of HPCD-Cy5. Scale bar = 1 cm. (C) Cholesterol levels in bile samples that were suspended with gallstones and varying concentrations of HPCD. (Data = mean ± SE, $n = 3$). (D) Schematic illustration of the therapeutic regimen. C57BL/6 mice were initially fed a lithogenic diet for one week, followed by six more weeks of the same diet with daily treatment of either saline or HPCD (at a dosage of 1 g/kg or 0.1 g/kg). (E, F) Digital photos of gallbladders and gallstones collected from gallbladders, scale bar = 0.5 cm. (G) Gallbladder sizes in various groups. (H) Cumulative size of gallstones per mouse.

Pick type C1 disease through cholesterol sequestration in animal models [20,21]. Based on this, we hypothesize that HPCD may regress gallstone formation and growth by solubilizing cholesterol and alleviating cholesterol's supra-saturation in bile.

Herein, we discovered that HPCD enhanced the solubilization of gallstones in bile. Nonetheless, the subcutaneous injection of HPCD did not prevent gallstone formation in a mouse model. This lack of preventive effect may be attributed to the pre-complexation with other competing guest molecules, such as lipids and amino acids, during the transition process [22–24]. Previously, researchers have developed supramolecular prodrugs that utilize host-guest interactions to release active drugs in response to specific stimuli, such as pH, biomarkers, and redox [25,26]. Herein, we synthesized a ROS-responsive prodrug of HPCD and developed a nanoparticle (HPCD-NP) capable of preventing occupation of the cavity until its degradation into free HPCD. We found that HPCD-NP, administered intravenously, could be translocated to the gallbladder through the hepatobiliary transition, degrade into the free HPCD in bile, and ultimately impede gallstone formation and progression in a mouse model.

HPCD exhibits a high affinity for cholesterol through host-guest interactions, which in turn enhances its solubility in aqueous solutions (Fig. 1A) [18]. As gallstones consist mainly of cholesterol, we conducted an initial assessment of the potential of HPCD to interact with and dissolve gallstones in bile. As shown in Fig. 1B, a robust fluorescence was detected on the surface of human gallstones post a 4-h incubation with the HPCD-Cy5 solution in bile, which suggests a strong interaction between HPCD and gallstone. Human gallstones were then immersed in bile with or without HPCD for 4 h, and the concentration of cholesterol was determined to verify HPCD's ability to dissolve gallstones. The results depicted in Fig. 1C indicates that HPCD could increase the solubilization of gallstone in bile in a dose-dependent manner. Therefore, HPCD could interact with gallstone and promote its solubilization in bile.

Based on these findings, we subsequently investigated whether HPCD could induce regression of gallstone formation in a mouse model. Mice were initially fed a lithogenic diet for 1 week, then continued on this diet for 6 consecutive weeks while receiving daily subcutaneous injections of either saline or HPCD at doses of 1 g/kg and 0.1 g/kg, respectively (Fig. 1D). Mice were then sacrificed, gallbladders and gallstones were collected to determine the treatment efficacy of HPCD. The gallbladder and the gallstones images were shown in Figs. 1E and F. There was no significant difference in the volume of the gallbladder and the cumulative size of gallstones between the model group and the groups undergoing HPCD treatment (Figs. 1G and H). Therefore, subcutaneous injection of HPCD could not impede the development and enlargement of gallstones.

There are several potential explanations for the ineffectiveness of HPCD treatment in regressing gallstone formation and growth. The prerequisite for regressing gallstone development of the supramolecular therapy would be the effective distribution of HPCD in gallbladder and its ability to solubilize cholesterol in bile. We initially assessed the absorption and biodistribution of HPCD following subcutaneous injection. The fluorescence of HPCD-Cy5 is detectable in blood at 5 min post-administration, indicating the rapid absorption into the bloodstream (Fig. S1 in Supporting information). Accordingly, HPCD-Cy5 fluorescence can be detected in the gallbladder within 5 min to 8 h after administration, indicating rapid and continuous transport of HPCD *via* the hepatobiliary route (Fig. S1). However, competing guest molecules such as amino acids and lipids, can occupy the HPCD cavity during blood circulation and hepatobiliary transport [22–24]. As a result, HPCD that is dispersed in the bile has a limited capacity to dissolve gallstones. Therefore, preventing pre-complexation within the cavity during

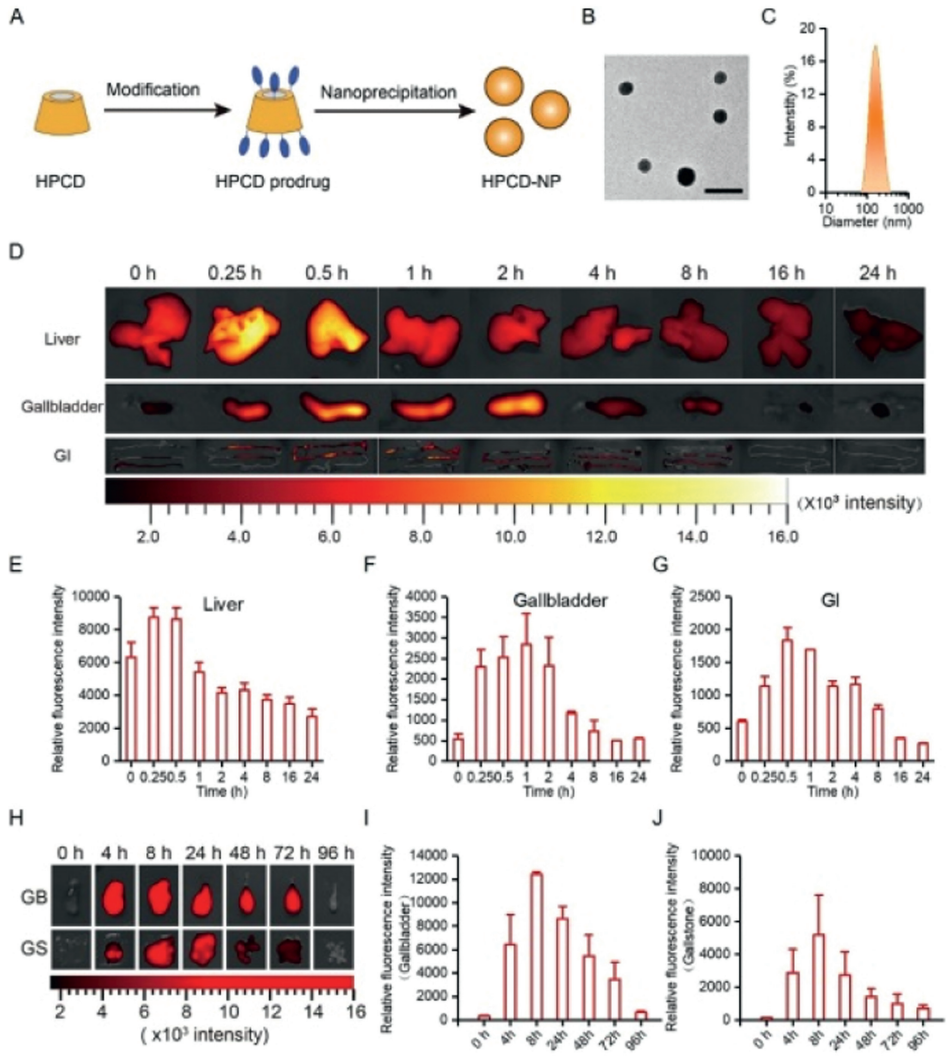

Fig. 2. Preparation and *in vivo* fate of HPCD-NP. (A) A sketch illustration of HPCD-NP engineering. TEM micrograph (B) and size distribution (C) of HPCD-NP, scale bar = 200 nm. *Ex-vivo* fluorescence (D) and quantitative analysis of HPCD-Cy5-NP distribution in the liver (E), gallbladder (F) and gastrointestinal tract (G) of healthy mice after intravenous injection. Data = mean ± SE, $n = 3$. *Ex vivo* fluorescence images and quantitative analysis showing the distribution of HPCD-Cy5-NP in the gallbladder (H, I) and localization of HPCD-Cy5 in gallstones (H, J) upon administration in mice with gallstones. Data = mean ± SE, $n = 3$.

the transition process may facilitate its anti-cholelithiasis properties.

It is commonly understood that most nanoparticles will accumulate in liver upon intravenous injection. And nanoparticles can be gradually transported into the bile ducts *via* the hepato-biliary transport system, with the potential for very high transportation efficiencies (up to 100% in certain cases) [27,28]. In the microenvironment of gallstone disease, reactive oxygen species (ROS) generated by granulocytes in the inflammatory gallbladder mucosa would be secreted into the bile [29]. Based on the information presented, we developed a ROS-responsive HPCD nanoparticle (HPCD-NP) with a previously described method [30,31]. We speculate that HPCD-NP would be transported into the gallbladder *via* the hepato-biliary transport system upon an intravenous injection, and the product of the HPCD-NP in the bile would solubilize the gallstone, thereby reducing gallstone formation and growth (Fig. S2 in Supporting information). The ROS-responsive HPCD prodrug was first synthesized by chemically conjugating phenylboronic acid pinacol ester (PBAP) onto HPCD (HPCD-PBAP, Fig. 2A, Figs. S3 and S4 in Supporting information) with the method that previously reported [32,33]. About 4 PBAP were successfully conjugated onto HPCD according to the ^{1}H NMR result. And HPCD-PBAP was then assembled into HPCD-NP using a nanoprecipitation method (Fig. 2A). The morphology of HPCD-NP was characterized using a transmission electron microscopy (TEM) analysis and exhibited a uniform spherical shape (Fig. 2B). The dynamic light scattering (DLS) analysis revealed a Z-average diameter of 157.6 ± 2.17 nm with a PDI of 0.104 ± 0.027 for HPCD-NP (Fig. 2C). The zeta potential was found to be −14.5 ± 0.321 mV. Since the size of HPCD-NP is smaller than 200 nm, it would pass through sinusoidal fenestrations of the liver during the blood circulation and interact directly with hepatocytes upon intravenous injection, and be further translocated into the bile [27,28]. Under the ROS-enriched environment, HPCD-PBAP would degrade into HMP and free HPCD following a mechanism seem to that previously described in the literature (Fig. S5 in Supporting information) [32,33]. Therefore, HPCD-NP may degrade into free HPCD, in conditions of inflammatory gallbladder bile with a high level of ROS.

Proper distribution of HPCD throughout the bile is essential for the dissolution of gallstones. After intravenous injection, the majority of the nanoparticles may accumulate in the liver and then pass through the hepatobiliary process to the gallbladder [27,28]. In this study, we evaluated the biodistribution of HPCD-NP in both normal mice and mice with gallstones. The imaging data showed that

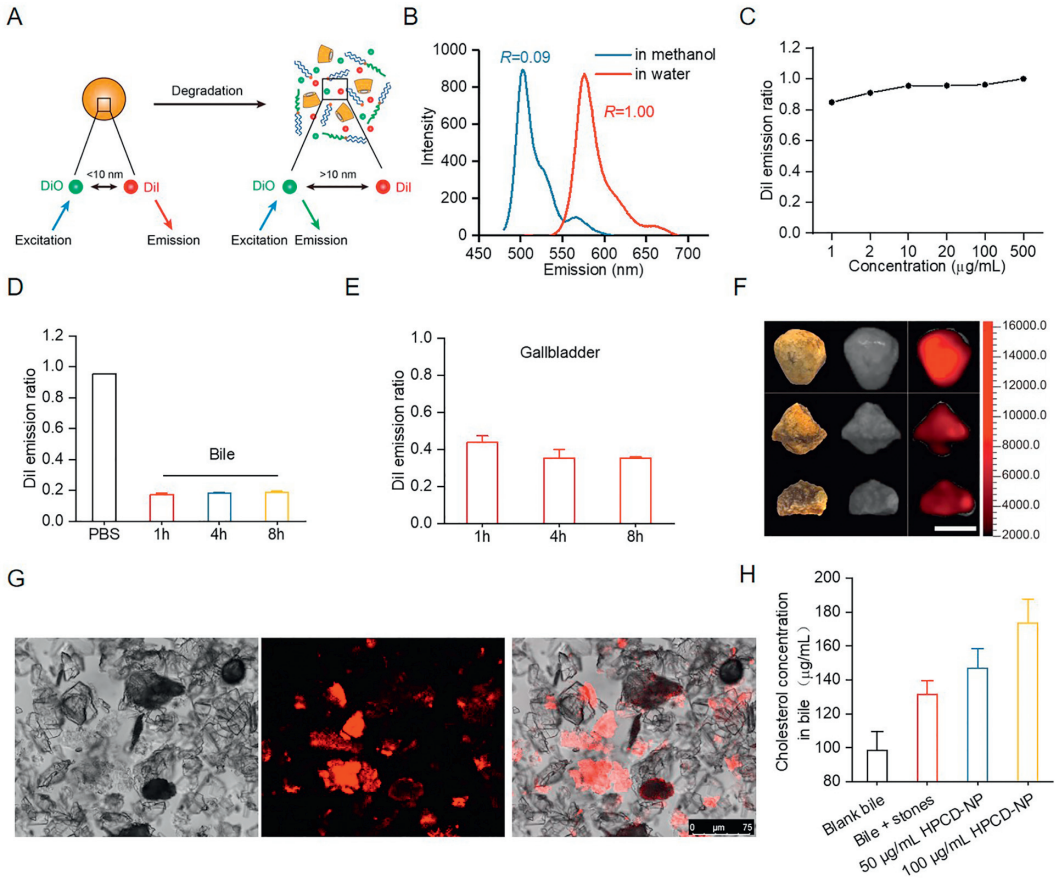

Fig. 3. HPCD-NP degrade into free HPCD and dissolve gallstones in bile. (A) The working principle of the fluorescent dequenching technique for characterizing HPCD-NP in their intact or dissociated states. (B) Fluorescence spectra and DiI emission ratio of HPCD-NP in methanol (blue) and water (red) at a concentration of 500 μg/mL. (C) Study of the dilution effect on the dissociation of HPCD-NP. (D) Investigation into the disintegration of HPCD-NP through DiI emission ratio alterations in bile at 37 °C for 1, 4 and 8 h. The PBS solution was set as the control group. Data = mean ± SE, $n = 3$. (E) Study of the HPCD-NP disintegration in the gallbladder by monitoring DiI emission ratio changes at 1, 4 and 8 h post intravenous injection. Data = mean ± SE, $n = 3$. (F) Fluorescent images of human gallstones, previously immersed in bile containing 50 μg/mL of HPCD-Cy5-NP. Scale bar = 1 cm. (G) Representative confocal images of gallstones and cholesterol crystals. Mice with gallstones (fed a lithogenic diet for 8 weeks) were intravenously injected with HPCD-Cy5-NP, and the gallstones and cholesterol crystals were collected at 8 h post injection. (H) Cholesterol levels in bile suspended with gallstone and different concentrations of HPCD-NP, Data = mean ± SE, $n = 3$.

HPCD-Cy5-NP accumulated promptly in the liver of normal mice after intravenous injection and reached the highest concentration at 0.25 h before declining by 0.5 h (Figs. 2D and E, Fig. S6A in Supporting information). Correspondingly, the fluorescent intensity of gallbladder increased gradually within 1 h (Fig. 2F and Fig. S6B in Supporting information), indicating that HPCD-Cy5-NP was transited from blood into the bile *via* the hepatobiliary transport system. We can also observe that HPCD-Cy5-NP was further excreted from gallbladder into the intestine as displayed in Figs. 2D and G, and Fig. S6C (Supporting information), and only little HPCD-Cy5-NP was reserved in gallbladder at 8 h (Figs. 2D and F, and Fig. S6B). We further determined the distribution of HPCD-Cy5-NP in gallbladders of mice with gallstones (GS mice). Surprisingly, HPCD-Cy5-NP retained in gallbladder for as long as 72 h in mice with gallstones as indicated by Figs. 2H and I. The fluorescence was also detected in the gallstones, with intensity of gallstones rising within 24 h and subsequently declining until 96 h post NP treatment (Figs. 2H and J). The prolonged presence of HPCD-Cy5-NP in the gallbladder of mice with gallstones compared to normal mice can possibly be credited to the interplay between HPCD-Cy5 and the gallstones/cholesterol crystals. These findings indicate that intravenously administered HPCD-NP could enter the gallbladder through the hepatobiliary transit process and potentially interact with the pre-existing gallstones/cholesterol crystals.

To dissolve pre-existing cholesterol crystals or gallstones, the HPCD-NP distributed in the bile must degrade into free HPCD. It has been reported that ROS including H_2O_2 and free radicals are present in bile in both normal and gallstone conditions [34,35]. We further performed experiments to study the fate of HPCD-NP in bile *in vitro* and *in vivo* upon intravenously injection. A fluorescent dequenching technique was applied to study the disintegration of HPCD-NP in bile (Fig. 3A) [36]. Briefly, the emission of DiO fluorescence would further excite DiI when DiO and DiI were co-encapsulated into the HPCD-NP, and the DiI emission ratio [$I_{DiI}/(I_{DiI} + I_{DiO})$] could represent the integration of HPCD-NP. For instance, HPCD-PBAP is hydrophobic and insoluble in water, the HPCD-NP loaded with DiO/DiI displayed a 100% DiI emission ratio in aqueous solution, suggesting the HPCD-NP is in an intact state (Fig. 3B). On the other hand, when HPCD-NP was disintegrated and dissolved in methanol, the DiI emission ratio decreased to 0.09. And dilution in PBS had minimal impact on the degradation of HPCD-NP (Fig. 3C). DiO/DiI loaded HPCD-NP was subsequently incubated in fresh bile at 37 °C and shaken at 100 rpm. As depicted in Fig. 3D and Fig. S7 (Supporting information), its DiI emission ratio declined from 0.95 in PBS to less than 0.20 at 1, 4 and 8 h after HPCD-NP exposure to bile, indicating the rapid degradation of HPCD-NP in bile. To determine the disintegration of HPCD-NP in the gallbladder, mice were intravenously administered with DiO/DiI loaded HPCD-NP, and gallbladders were collected and imaged at 1, 4 and 8 h post injection. As shown in Fig. 3E and Fig. S8 (Supporting information), the DiI emission ratio was declined to about 0.4 at all 3 time points in the gallblad-

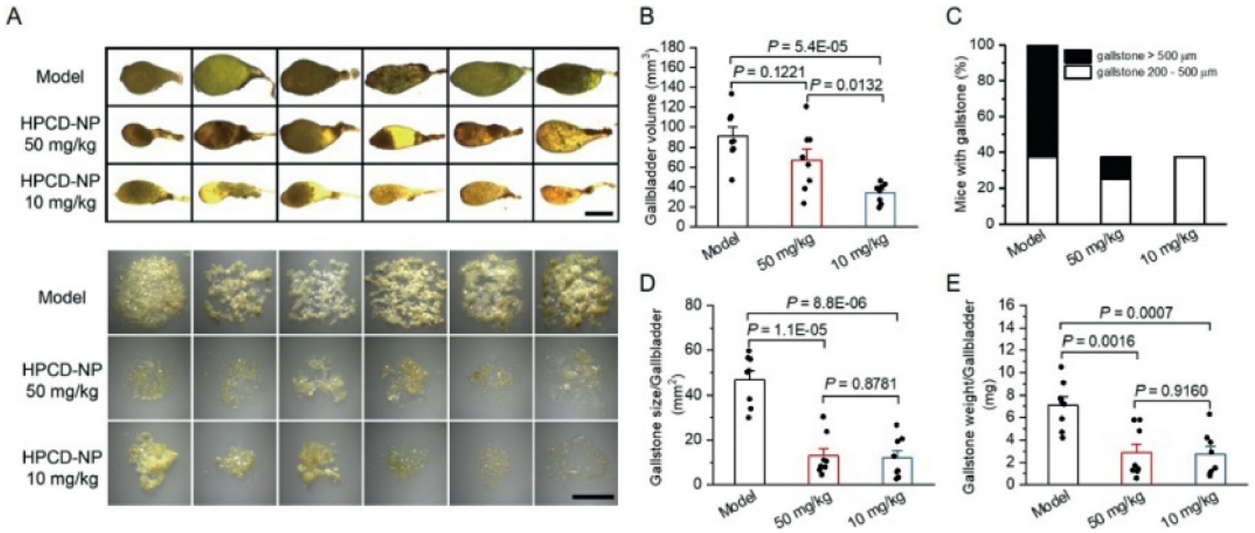

Fig. 4. Treatment with HPCD-NP facilitates regression of gallstone formation and growth in mice. Mice were initially fed a lithogenic diet for 2 weeks and subsequently injected with HPCD-NP every 4 days for 6 weeks during lithogenic diet exposure. (A) Representative digital photos of gallbladders and gallstones collected from gallbladders, scale bar = 0.5 cm. (B) Gallbladder sizes in various groups. (C) Prevalence of gallstones. (D) Cumulative size of gallstones per mouse. (E) Cumulative weight of gallstones per mouse.

der, implying the degradation of HPCD-NP within the gallbladder. Interestingly, the DiI emission ratio in bile did not decrease to the same value as that of HPCD-NP dissolved in methanol. This phenomenon may be attributed to the formation of multilamellar vesicles (40–100 nm) in bile that are able to encapsulate both free DiO and DiI [34]. We further examined the impact of HPCD-NP on gallstones present in the bile. Human gallstones were incubated in the bile with the presence of 50 μg/mL HPCD-Cy5-NP for 4 h at 37 °C, and the robust HPCD-Cy5 florescence was observed from the human gallstones (Fig. 3F), suggesting the interaction between gallstones and HPCD-Cy5, the degradation product of HPCD-Cy5-NP. To verify the interaction between HPCD-NP with gallstone *in vivo*, GS mice were intravenously injected with HPCD-Cy5-NP and gallstones/cholesterol crystals were collected at 4 h post administration. The strong fluorescence of HPCD-Cy5 were both observed from the gallstones and cholesterol crystals, as depicted in Fig. 3G and Fig. S9 (Supporting information), indicating the degradation of HPCD-NP in the gallbladder and interaction between HPCD-Cy5 and gallstones/cholesterol crystals. These findings suggest that free HPCD-Cy5, the degradation product of HPCD-Cy5-NP in bile, may further interact with gallstones and cholesterol crystals. Furthermore, we investigated the effect of HPCD-NP on the solubility of human gallstones and discovered that the addition of HPCD-NP increased the dissolution of gallstones in bile in a dose-dependent manner (Fig. 3H).

Having observed the above-mentioned results, we conducted a further analysis of the impact of HPCD-NP in preventing gallstone formation and inhibiting their growth. In our preliminary experiments, we observed that the gallbladder volume increased significantly when mice were fed a lithogenic diet for 1–8 weeks (data not shown). And cholesterol crystals and gallstones were formed when mice were fed the lithogenic diet for 2–5 weeks. In contrast, no significant differences in gallbladder volume were observed in healthy mice fed with normal diet for 0–8 weeks, with the value of about $8.5 \pm 3.8\ mm^3$ (Fig. S10 in Supporting information). In this study, mice were fed a lithogenic diet for 8 weeks and injected intravenously with HPCD-NP or saline every 4 days from week 3 to week 8. As displayed in Figs. 4A and B, the gallbladder volume increased to $90.9 \pm 9.3\ mm^3$ and a significant number of gallstones and cholesterol crystals were observed in the model group. HPCD-NP treatment at the dose of 10 mg/kg (equivalent to 5.7 mg/kg free HPCD) induced a significant decrease of gallbladder volume, comparing with those in the model mice treated with saline. Gallstones (>500 μm) were found in 60% mice in the model group, while no gallstones (>500 μm) were found in 10 mg/kg HPCD-NP (equivalent to 5.7 mg/kg free HPCD) treated mice (Fig. 4C). Accordingly, the cumulative size and weight of gallstones per mouse were significantly lower in 10 mg/kg HPCD-NP treated mice than in the control group (Figs. 4D and E). HPCD-NP treatment at the dose of 50 mg/kg (equivalent to 28.5 mg/kg free HPCD) also showed a significant decrease in gallstone prevalence, cumulative size and weight than that in the control group. And the cumulative size and weight of gallstones per mouse showed no significant differences between 10 mg/kg and 50 mg/kg HPCD-NP treated groups (Figs. 4D and E). These results indicate that treatment with HPCD-NP resulted in a deceleration of both gallstone development and growth in a mouse model. However, the treatment effects of 10 mg/kg HPCD-NP were better than those of the 50 mg/kg dose in reducing the volume of gallbladder and gallstones larger than 500 μm (Figs. 4B and C). This may be due to the increased bile secretion, which can induce more stress on the gallbladder, as bile will be secreted during the transportation of nanoparticles through the hepatobiliary system. And the optimal treatment dose of HPCD-NP will be investigated in further studies.

In summary, we present a potent supramolecular therapy designed for solubilization of cholesterol in bile, aiming to regress gallstone formation. While HPCD demonstrated the capability to solubilize cholesterol crystals, its efficacy in hindering gallstone formation or growth in a mouse model was limited. Mechanistically, the limitation might be attributed to the pre-occupation of its cavity by competitive small molecules. To address this challenge, we developed a ROS responsive HPCD prodrug nanoparticle. This formulation could efficiently translocate into the gallbladder through the hepatobiliary transition system, breaking down into free HPCD in bile. This, in turn, facilitated interaction with and solubilization of gallstones/cholesterol crystals. Consequently, the treatment with HPCD-NP demonstrated significant impairment of gallstone formation and growth. Therefore, HPCD-NP might be a potent supramolecular therapeutic for preventing the formation and advancement of gallstones *via* cholesterol sequestration.

Declaration of competing interest

X. Z and R.W. are currently applying for a patent related to the content of this work. All authors declare no other competing interests.

CRediT authorship contribution statement

Xiangjun Zhang: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Writing – original draft, Writing – review & editing. **Xiaodi Yang:** Data curation, Methodology. **Yan Wang:** Investigation, Methodology. **Zhongping Xu:** Resources. **Sisi Yi:** Methodology. **Tao Guo:** Methodology. **Yue Liao:** Methodology. **Xiyu Tang:** Methodology. **Jianxiang Zhang:** Conceptualization, Writing – review & editing. **Ruibing Wang:** Conceptualization, Funding acquisition, Supervision, Writing – review & editing.

Acknowledgments

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2024.109854.

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