Supporting Information

Materials: 2-Cl-trityl chloride resin (1.2 mmol/g) was obtain from Nankai University resin Co., Ltd. Fmoc-amino acids and o-benzotriazol-1-yl-N,N,N',N'-tetramehtyluronium hexafluorophosphate (HBTU) were bought from GL Biochem. (Shanghai). Ketoprofen and fenofibrate were obtained from Baomanbio (Shanghai). Chemical regents and solvents were used as received from commercial sources. Hematoxylin and eosin (H&E) reagent was obtained from Solarbio. Oil red O staining kit was purchased from Sciencell (USA).

General methods: ^{1}H NMR (Bruker ARS 400) and HR-MS (Agilent 6520 Q-TOF LC/MS) was used to character the compounds. TEM (JEM100CXII) was performed at the Tecnai G2 F20 system, operating at 100 kV. Rheology (TA instrument) test was done on an AR 2000ex system, 40 mm parallel plates was used during the experiment at the gap of 500 μm. Circular dichroism (CD) spectrum was obtained by a BioLogic (MOS-450) system. Fluorescence spectrum was measured by a fluorospectro photometer (F-280).

Preparation of peptide: The peptide was prepared by standard solid phase peptide synthesis (SPPS) by using 2-chlorotrityl chloride resin and the corresponding N-Fmoc protected amino acids with side chains properly protected. Firstly, the C-terminal of the first amino acid was conjugated on the resin. Anhydrous N,N'-dimethyl formamide (DMF) containing 20% piperidine was used to remove Fmoc protected group. To couple the next amino acid to the free amino group, O-Benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate (HBTU) was used as coupling reagent. Peptide chain was entended according the standard SPPS protocol. After ketoprofen coupling the last amino acid, 5 times DMF wash and following 5 times DCM wash were used to remove excessive reagents. Lastly, 95% trifluoroacetic acid (TFA) containing 2.5% H_2O and 2.5% TIS (trimethylsilane) was used to cleave peptide from resin. After removing DCM by rotary evaporation, ice diethylether was added for precipitating the peptide solid. After removing the supernatant, the solid was dried by vacuum pump to gain resulting compound. The pure peptide were obtained by HPLC and lyophilization.

Characterization of the compounds:

Compound Kep-G^{D}F^{D}F^{D}Y:

^{1}H NMR (400 MHz, DMSO) δ 8.23 – 8.14 (m, 2H), 7.97 (m, 1H), 7.72 (t, *J* = 4.1 Hz, 3H), 7.68 – 7.64 (m, 1H), 7.63 – 7.51 (m, 3H), 7.50 – 7.44 (m, 1H), 7.22 (d, *J* = 4.3 Hz, 2H), 7.20 – 7.08 (m, 7H), 7.02 (dd, *J* = 8.5, 2.8 Hz, 2H), 6.65 (dd, *J* = 8.5, 2.9 Hz, 2H), 4.57 – 4.50 (m, 1H), 4.48 – 4.42 (m, 1H), 4.36 (m, 1H), 3.82 – 3.73 (m, 2H), 3.70 (d, *J* = 6.5 Hz, 1H), 3.00 – 2.88 (m, 3H), 2.78 (m, 11.1, 3.6 Hz, 2H), 2.67 – 2.59 (m, 1H), 1.32 (d, *J* = 7.0 Hz, 3H).

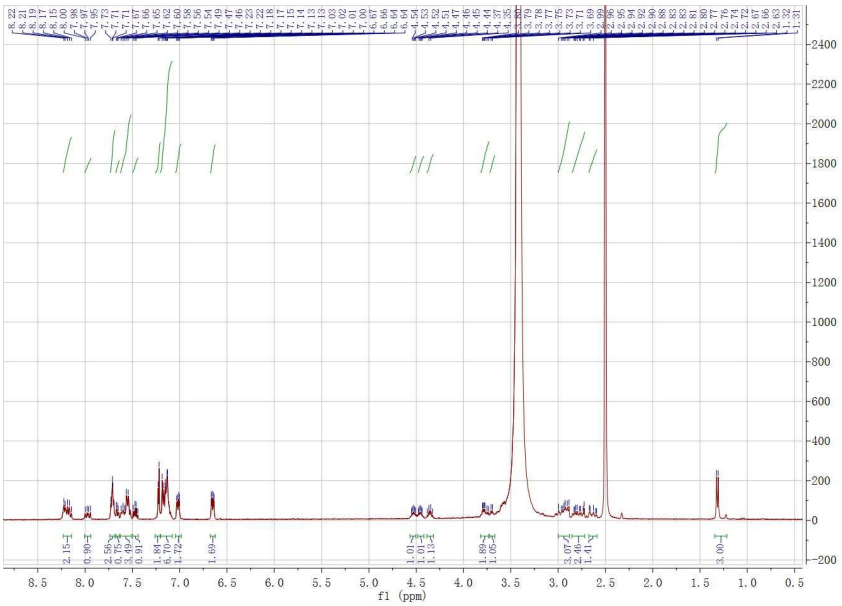

Fig. S1 ^{1}H-NMR of Kep-G^{D}F^{D}F^{D}Y

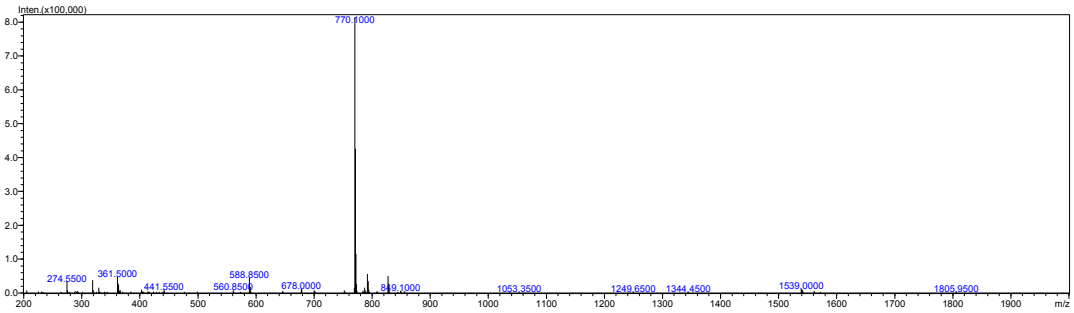

Fig. S2 The mass spectrum of Kep-G^{D}F^{D}F^{D}Y

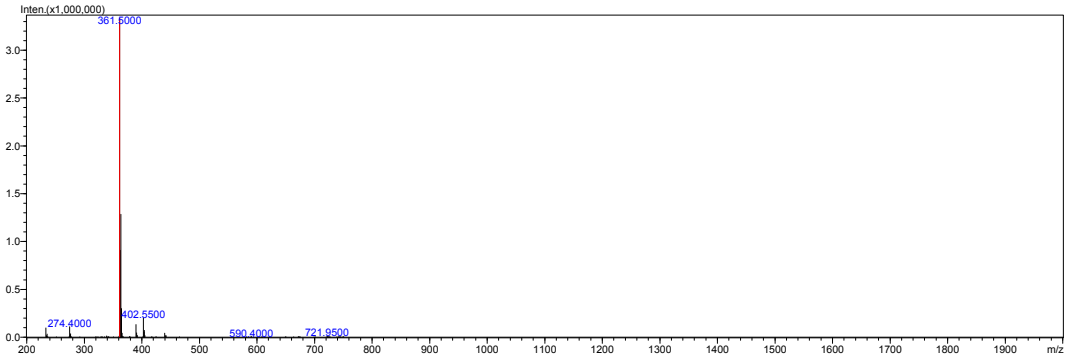

Fig. S3 The mass spectrum of fenofibrate

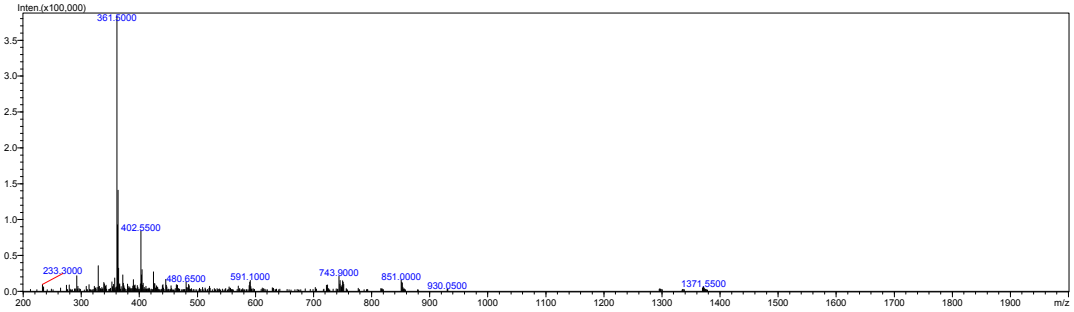

Fig. S4 The mass spectrum of fenofibrate after heating

Transmission electron microscopy

Negative staining technique was used to observe the nanostructures in hydrogels. 10 μL hydrogels were firstly loaded on the carbon-coated copper grids, dd-water was then used to rinse grid. Subsequently the samples were stained with 2 % uranyl acetate. Finally the grids were placed in a desiccator overnight before observation.

Coassembly analysis

The hydrogel was centrifuged to separate nanofibers and solvent (15000 rpm, 15 minutes). The settlings at the bottom was then dissolved with DMSO and analyzed by a liquid chromatography analyzer.

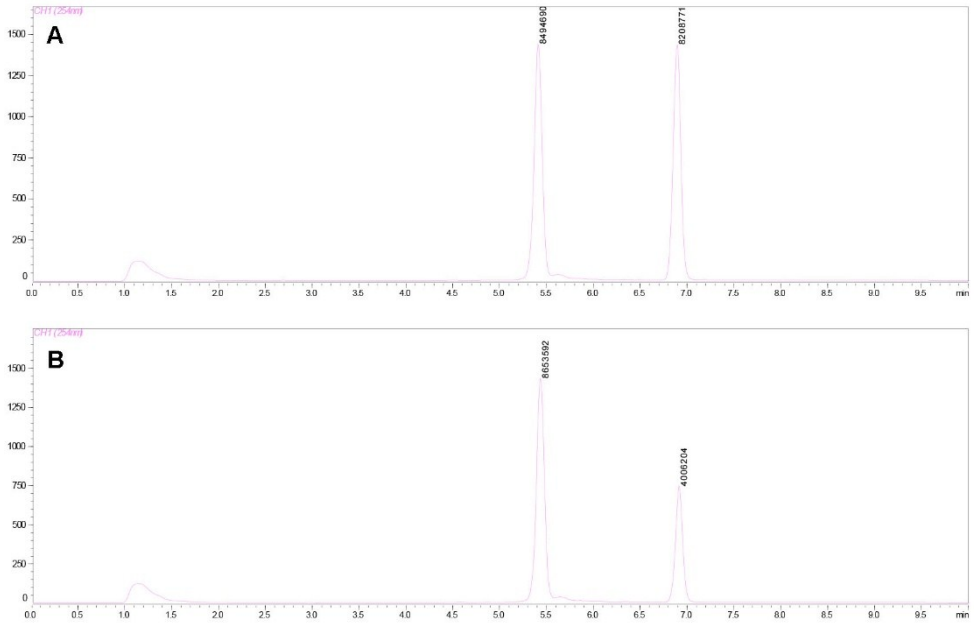

Fig. S5 The liquid chromatogram of (A) ***1*** and Fnb in gel-2 and (B) sediment from centrifuged gel-2

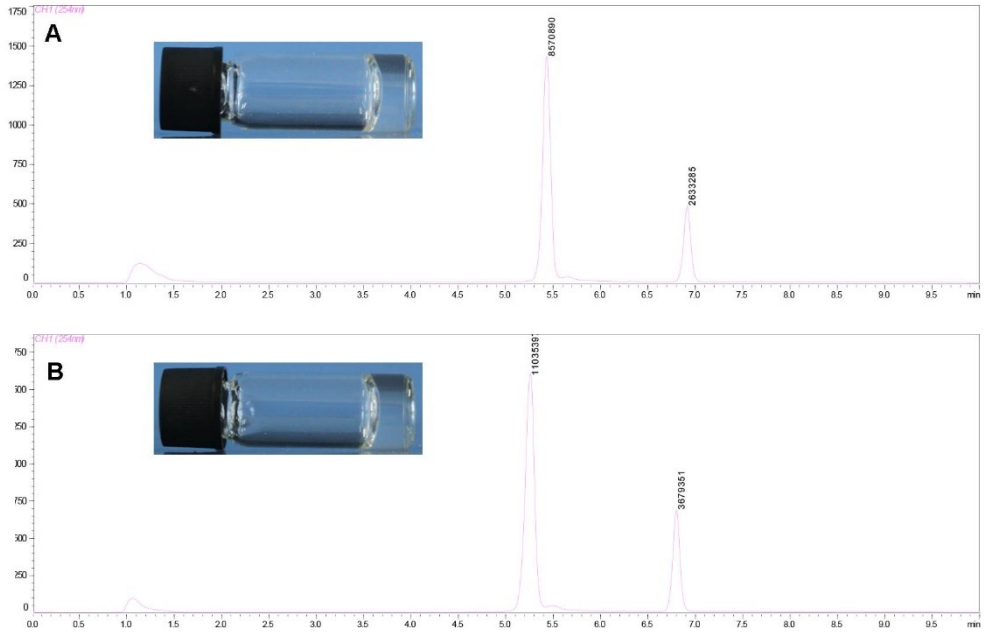

Fig. S6 The gel images and liquid chromatogram of ***1*** and Fnb with molar ratio of (A) 1:0.5 and (B) 1:2 (The concentration of ***1*** was 5 mg/mL)

Fig. S7 The optical images of ***1*** and Fnb with molar ratio of 1:18 and 1:20 (The concentration of ***1*** was 5 mg/mL)

Fig. S8 The chemical structure of Npx-G^{D}F^{D}F^{D}Y (compound ***2***) and Oxp-G^{D}F^{D}F^{D}Y (compound ***3***) and optical images of Gel-3 and Gel-4

Tab. S1 The molar absorption coefficients of Fnb, ***Comp. 1***, ***Comp. 2*** and ***Comp. 3***.

Compound	Fnb	***Comp. 1***	***Comp. 2***	***Comp. 3***
Absorption coefficient (L/mol/cm)	1.456	1.427	1.362	1.375

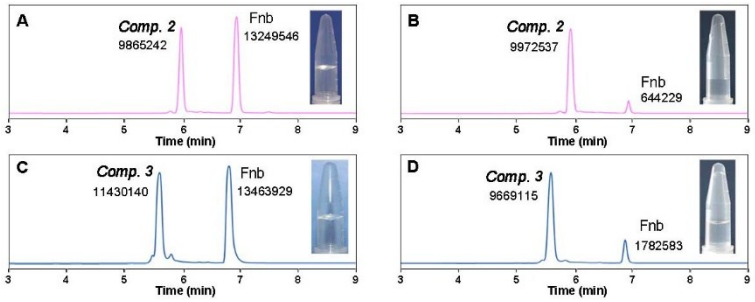

Fig. S9 (A) The liquid chromatogram of ***2*** and Fnb in Gel-3 with molar ratio of 1:1. (B) The liquid chromatogram of ***2*** and Fnb in sediment from centrifuged Gel-3 at 15000 rpm for 15 min. (C) The liquid chromatogram of ***3*** and Fnb in Gel-4 with molar ratio of 1:1. (D) The liquid chromatogram of ***3*** and Fnb in sediment from centrifuged Gel-4 at 15000 rpm for 15 min.

Circular dichroism (CD) spectrum

CD spectrum were measured by a BioLogic (MOS-450) system. All gels were placed in 0.1 cm quartz spectrophotometer cell (20-C/Q/0.1). The wavelength range was from 190 to 300 nm. The acquisition period was 0.5 s and the step was 0.5 nm. The resultant CD spectra was acquired after subtracting the solvent background.

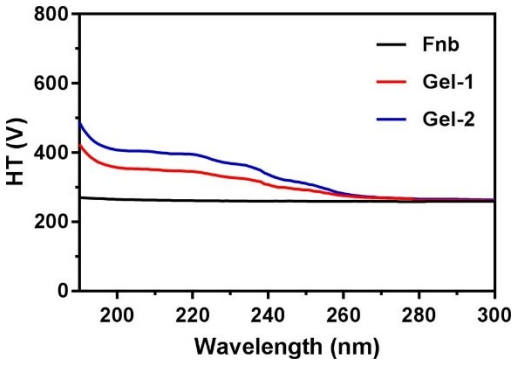

Fig. S10 The HT spectrum of Fnb, gel-1 and gel-2 at the concentration of 0.5wt%

Rheology

Rheology test was carried out on an AR 1500ex (TA instrument) system, 25 mm parallel plates was used during the experiment at the gap of 500 μm. For the dynamic strain sweep, the gels were directly transferred to the rheometer and it was conducted at the frequency of 1 rad/s and the strain of 1% immediately. The gels were also characterized by the mode of dynamic frequency sweep in the region of 0.1-100 rad/s at the strain of 1%.

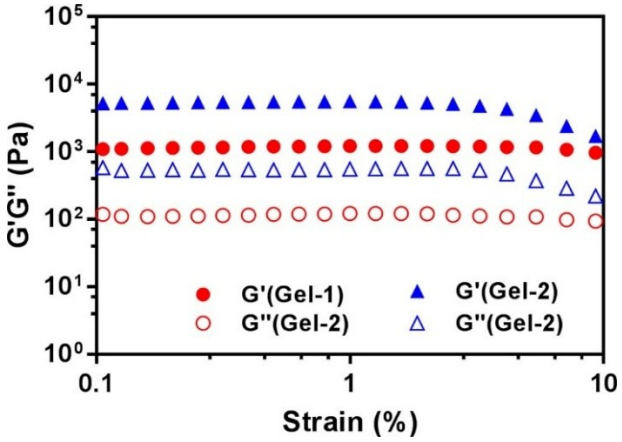

Fig. S11 The dynamic strain sweep of Gel-1 and Gel-2

Release profile

One hour after gelation, 0.4 mL of Gel-2 was treated with 0.4 mL of dissolution media (DM, PBS buffer containing 0.5% of (sodium dodecyl sulfate) SDS) at 37°C. 0.3 mL of the upper buffer solution was taken out and used to test by LC-MS (Shimadzu) at the wavelength of 254 nm at designated time intervals. A fresh 0.3 mL of DM was then added back to the gel. The experiment was conducted in three parallel samples.

Cell culture

All cell lines were purchased from ATCC (Manassas, VA). HepG2 cells were

cultured in complete DMEM medium containing 10% FBS, 50 μg/mL penicillin/streptomycin and 2 mM glutamine. HepG2 cells (~85% confluence) received different treatment (10 μg/mL of Fnb in DMSO, 7 μg/mL of Kep in DMSO, 21.4 μg/mL of Gel-1 and 31.4 μg/mL of Gel-2, respectively) in serum-free medium. The treatment was based on the mounts of Fnb and the molar ratio of Fnb and ***1*** was 1:1.

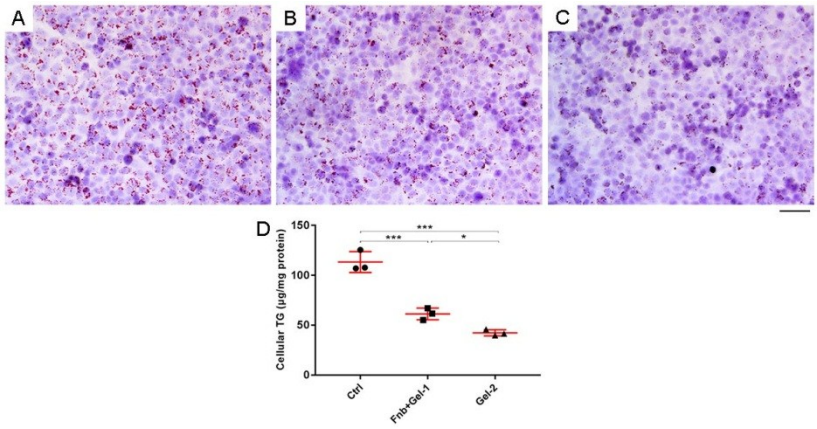

Fig. S12 (A-C) Representative images of ORO staining on HepG2 cells after treatment with PBS, Fnb+Gel-1, and Gel-2, respectively. (F) Quantitative analysis of cellular triglyceride in HepG2 cells. Scale bar = 50 μm. *p<0.05, ***p<0.001.

Plasma concentration of Fnb

The mice were randomly divided into three groups and treated with the Fnb, Fnb+Gel-1, and Gel-2, respectively. After 12 hours, the mice plasma were extracted. Then acetonitrile/1 M HCl (95:5, v/v) was added to precipitate protein. After centrifugation at 15000 rpm for 20 miniutes, the supernatant was analyzed by HPLC. In plasma, FNB is rapidly hydrolyzed by plasma esterase to the fenofibrate acid (FNB acid). The concentration of fenofibrate in plasma was determined according to the concentration of fenofibrate acid because the fenofibrate is rapidly hydrolyzed to the fenofibrate acid in plasma.

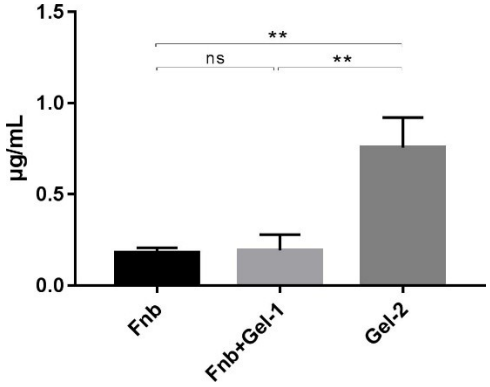

Fig. S13 The plasma concentrations of fenofibrate acid in the mice treated with the Fnb, Fnb+Gel-1, and Gel-2, respectively. **p<0.01.

***In vivo* studies**

The protocol for *in vivo* studies was approved by the Ethics Committee of Chinese Academy of Medical Sciences and conforms to the Guide for the Care and Use of Laboratory Animals published by the NIH (NIH publication, eighth edition, updated 2011). Eight-week-old wild-type male C57BL/6J mice were purchased from Beijing Vital River Laboratory Animal Technology Co., Ltd. and were housed in SPF units of the Animal Center at Institute of Radiation Medicine of CAMS, at 23 ± 1°C, with a relative humidity of 60-70% and a 12 h light/dark cycle. Food and water were available *ad libitum*. Mice were randomly assigned into five groups of 5 animals and fed HFD (D12492, Research Diets Inc.). At the beginning of week 10, mice received subcutaneous injection with fenofibrate (Fnb) [10 mg day^{-1} kg^{-1} bodyweight (mpk)] or hydrogels for another 6 weeks, respectively. At the end of experiment, all mice were anesthetized and euthanized as we previously reported[1], and the liver, blood samples and other tissues were collected for determination of the associated metabolic parameters.

Oil red O staining and lipid content determination

Hepatic lipid contents were evaluated by oil red O staining with liver frozen sections as described[1]. The content of TG was determined by quantification kits according to the manufacturer's instructions.

Analysis of histology

To assess liver damage, tissue was briefly washed with PBS and fixed in 4% paraformaldehyde. Necrosis was determined by hematoxylin and eosin (H&E) staining as reported[2].

Determination of inflammatory factors in liver tissue fluid

The expression of IL-1β, IL-6 and TNF-α in liver tissue was determined by quantitative real-time polymerase chain reaction with total RNA extracted from liver tissue and the following primers: IL-1β 5'-GACCTTCCAGGATGAGGACA-3', 5'-AGCTCATATGGGTCCGACAG-3'; IL-6 5'-CTGCAGCCACTGGTTCTGT-3' ,5'-CCAGAGCTGTGCAGATGAGT-3'; TNFα 5'-TGGCCCAGGCAGTCAGA-3' ,5'-GGTTTGCTACAACATGGGCTACA-3'; GAPDH 5-ACCCAGAAGACTGTGGATGG-3, 5-ACACATTGGGGGTAGGAACA-3 and normalized by GAPDH mRNA in the corresponding samples.

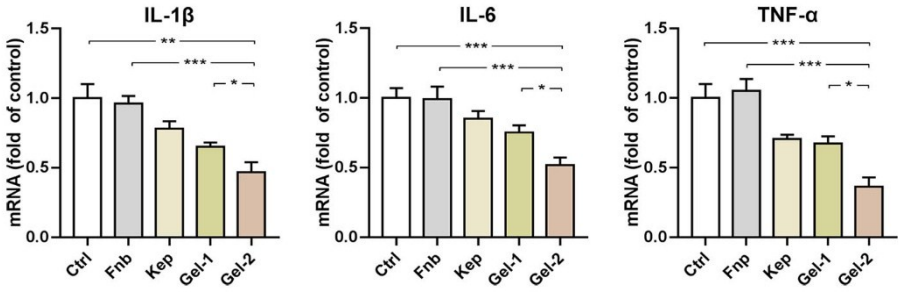

Fig. S14 The inflammatory factors in liver tissue

The cytocompatibility of coassemblied nanofibers

cytocompatibility of cassemblied nanofibers was evaluated by the MTT assay. The HepG2 cells were seeded in 96-well plates at a density of 5000 cells per well with medium volume of 100 μL. After incubated for 24 hours, 100 μL fresh medium containing a serial of concentrations of nanofibers was added. 72 hours later, 10 μL MTT (5 mg/mL) was added into cells. After 4 hours, DMSO was added to dissolve the formazan crystals. The optical densities of the solutions at 490 nm were measured by a microplate reader. Meanwhile, cells without any treatment were used as the control. The percent of cell viability was calculated according to the following formula:

The percent of cell viability (%) = $OD_{sample}/OD_{control}\times100\%$.

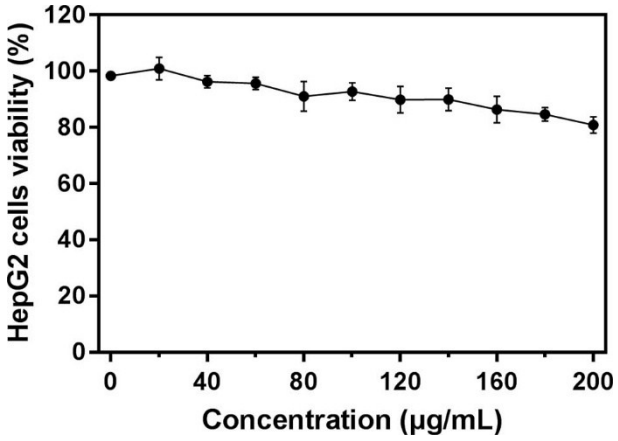

Fig. S15 The cytocompatibility curve of coassemblied nanofibers against HepG2 cells

Reference

1 C. Ma, W. Zhang, X. Yang, Y. Liu, L. Liu, K. Feng, et al. *Br. J. Pharmacol*. 2018, **175**, 1486-1503.

2 T. Zhang, J. Hu, X. Wang, X. Zhao, Z. Li, J. Niu, et al. *J. Hepatol*. 2019, **70**, 87-96.