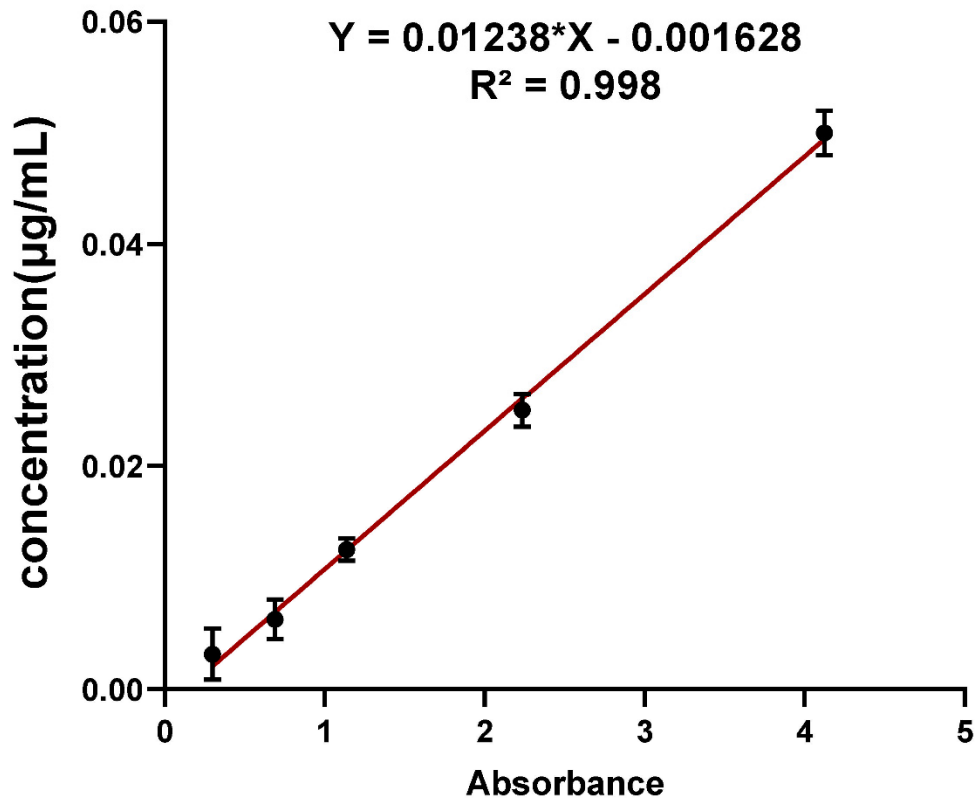
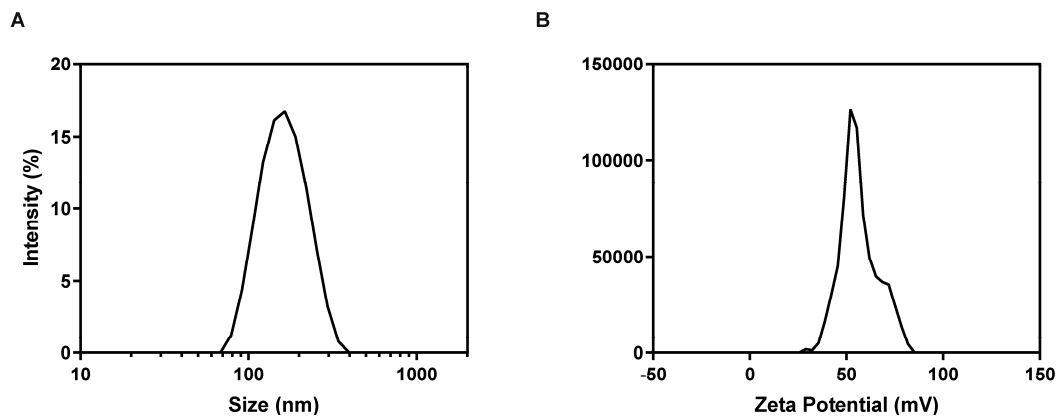


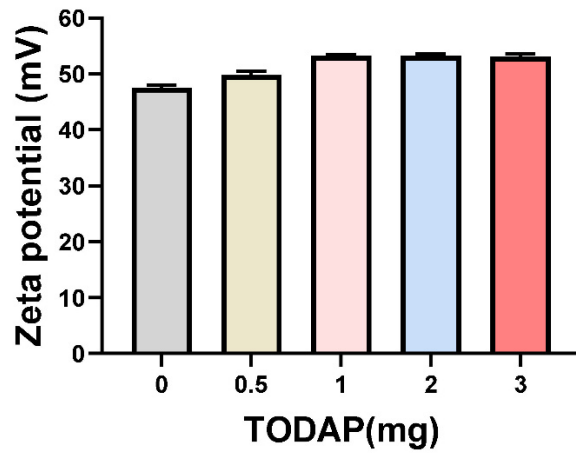
SUPPLEMENTAL INFORMATION



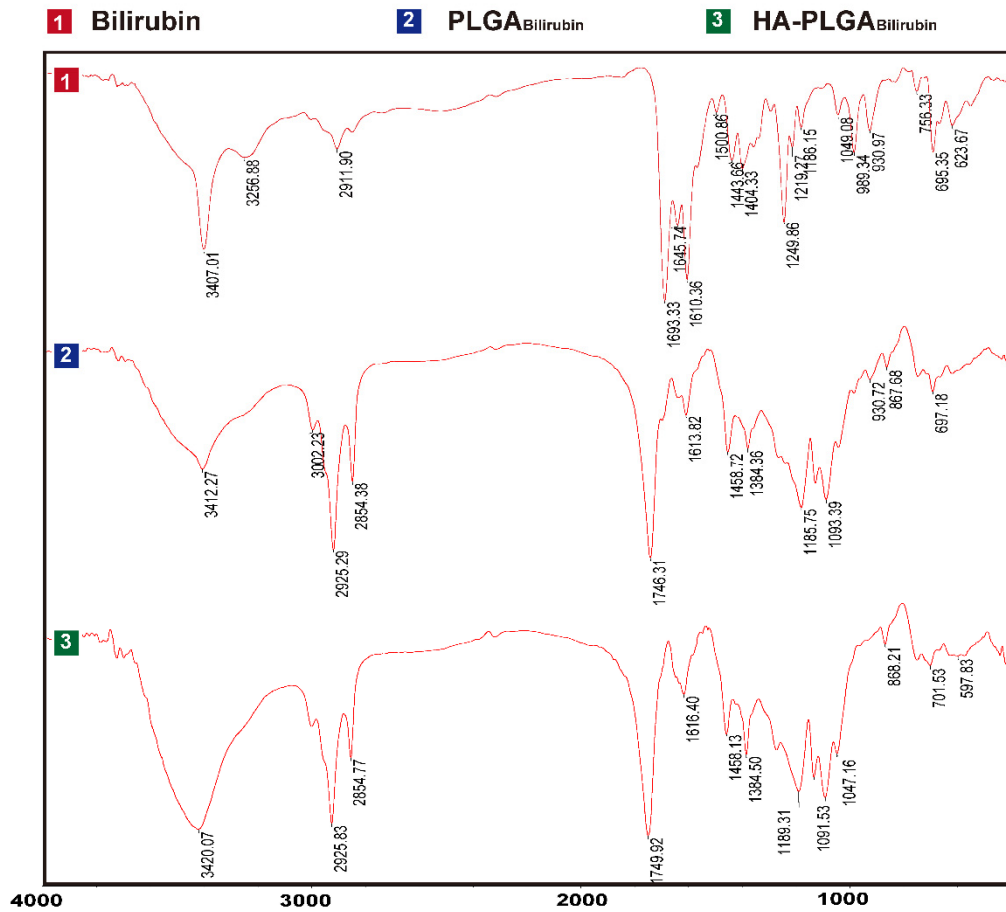
Supplementary Figure 1. The standard curve between the bilirubin concentration and absorbance.



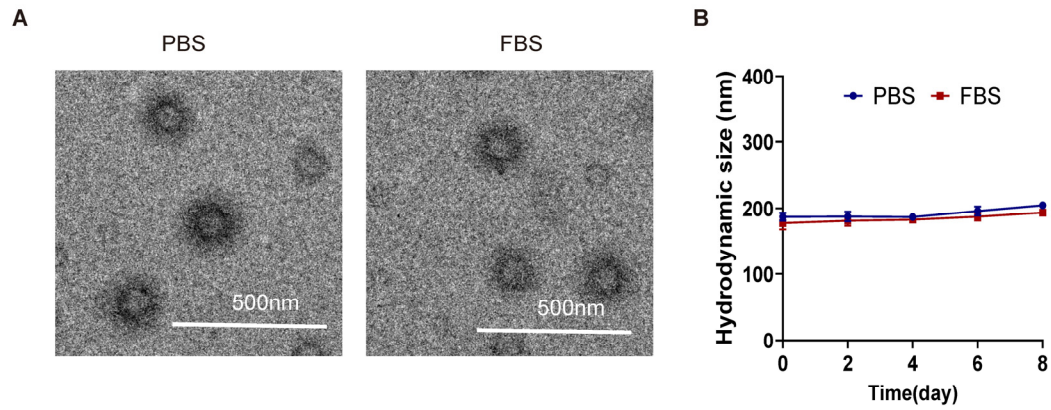
Supplementary Figure 2. Preparation of PLGA_{bilirubin} nanoparticles. (A) Size distribution of PLGA_{bilirubin}. The size of PLGA_{bilirubin} was stable at 160 nm. (B) Zeta potential of PLGA_{bilirubin}. The zeta potential of PLGA_{bilirubin} was stable at 55mV.



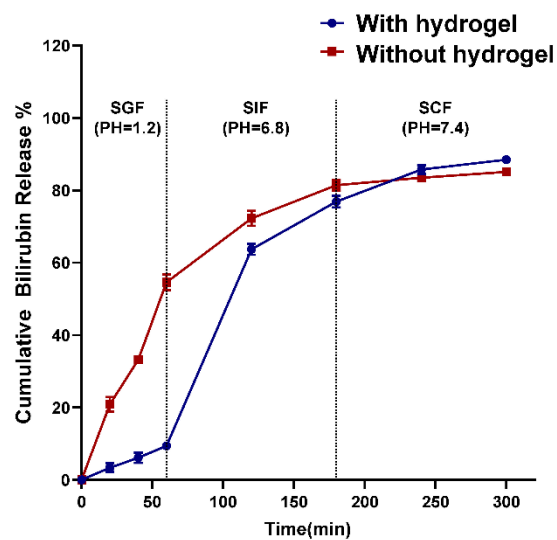
Supplementary Figure 3. The change of zeta potential with the increasing DOTAP.



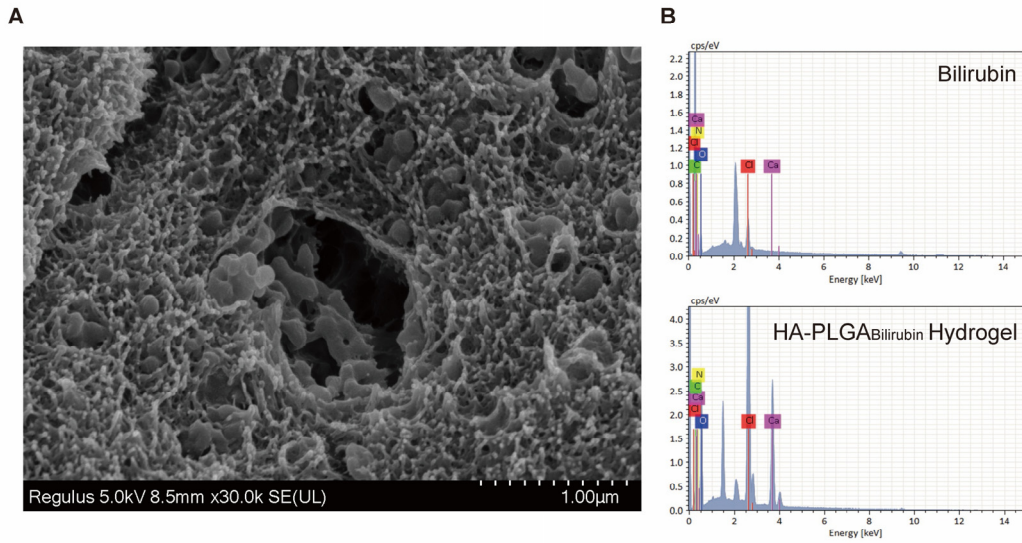
Supplementary Figure 4. The FT-IR spectra of Bilirubin, PLGA^{Bilirubin}, and HA-PLGA^{Bilirubin} revealed significant structural information.



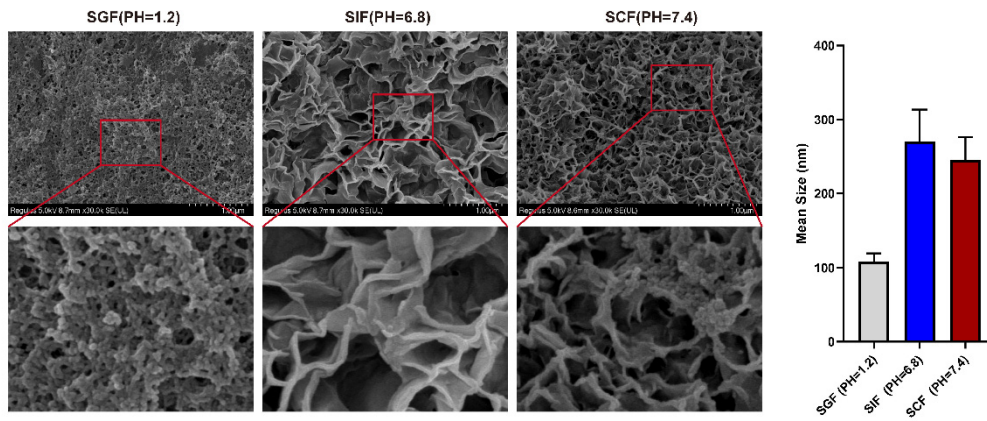
Supplementary Figure 5. Stability of HA-PLGA_{Bilirubin} nanoparticles. (A) TEM images of HA-PLGA_{Bilirubin} in PBS and FBS. (B) The hydrodynamic size of HA-PLGA_{Bilirubin} in PBS and FBS.



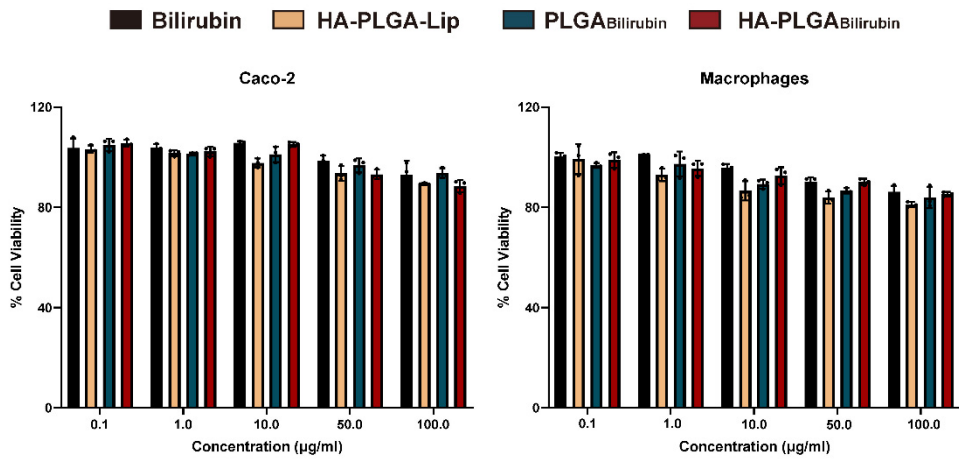
Supplementary Figure 6. Effect of the HA-PLGA_{Bilirubin} with or without hydrogel on the amount of Bilirubin release in different digestion solutions.



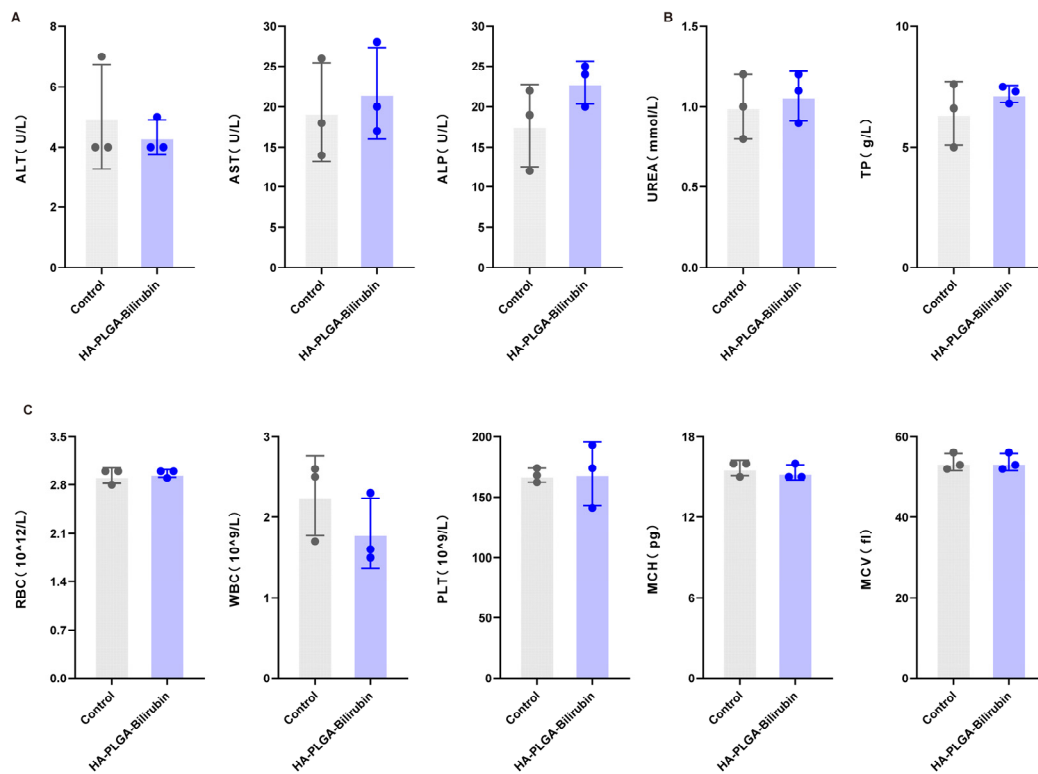
Supplementary Figure 7. SEM-EDS analysis of HA-PLGABilirubin. (A) SEM images of the HA-PLGABilirubin. (B) EDS results of bilirubin before and after Hydrogel adding.



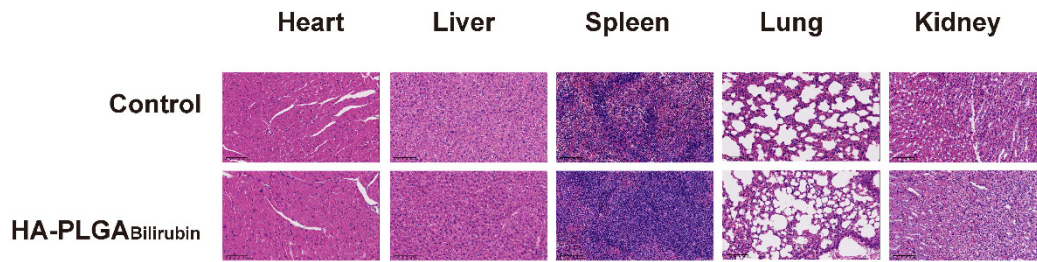
Supplementary Figure 8. The SEM photographs and mean size of HA-PLGABilirubin hydrogel at SGF (PH=1.2), SIF (pH 6.8), and SCF (pH 7.4).



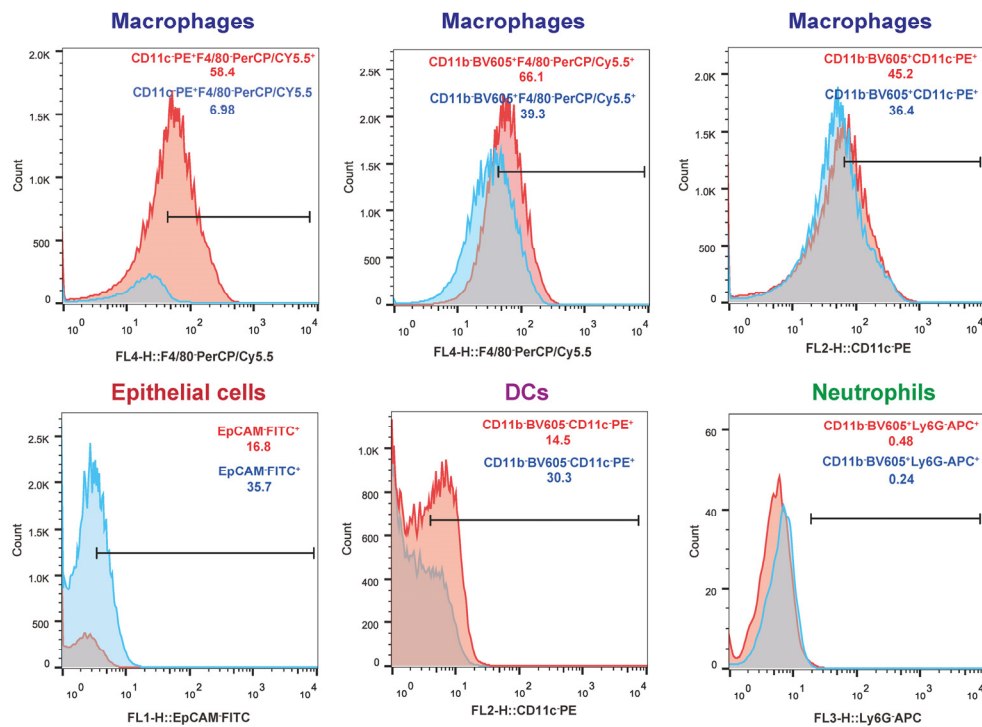
Supplementary Figure 9. Cytotoxicity studies of different nanoparticles on colon epithelial-like cells (Caco-2) and macrophages (Raw 264.7).



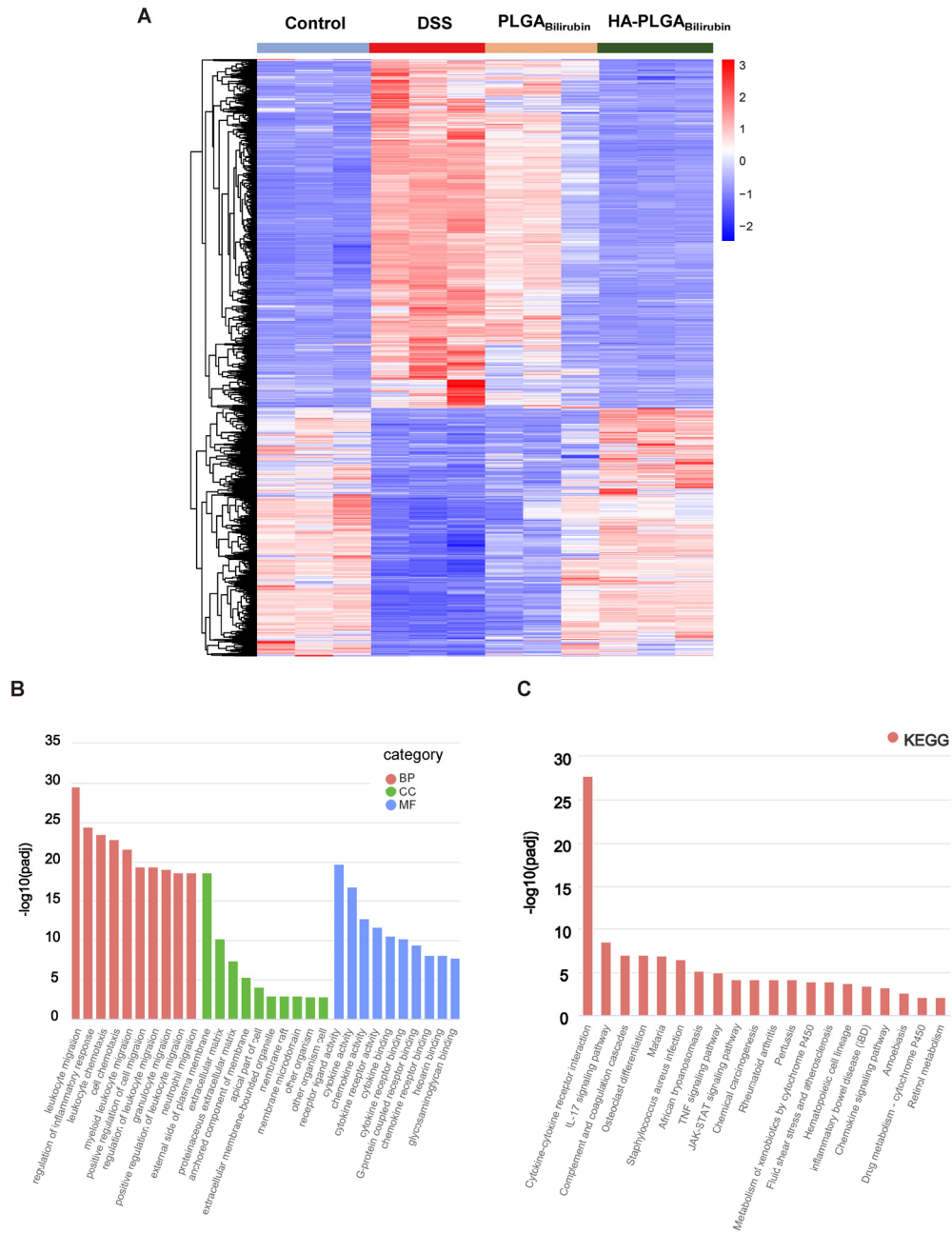
Supplementary Figure 10. Serum biochemistry and hematological indexes of HA-PLGA_{Bilirubin}. (A) Function indexes of liver (ALT, AST, ALP). (B) Function indexes of kidney (UREA, TP). (C) Hematological indexes (RBC, WBC, PLT, MCH, MCV)



Supplementary Figure 11. Representative HE-stained sections of heart, liver, spleen, lung, and kidneys of mice treated with saline (control) or HA-PLGA_{Bilirubin}.

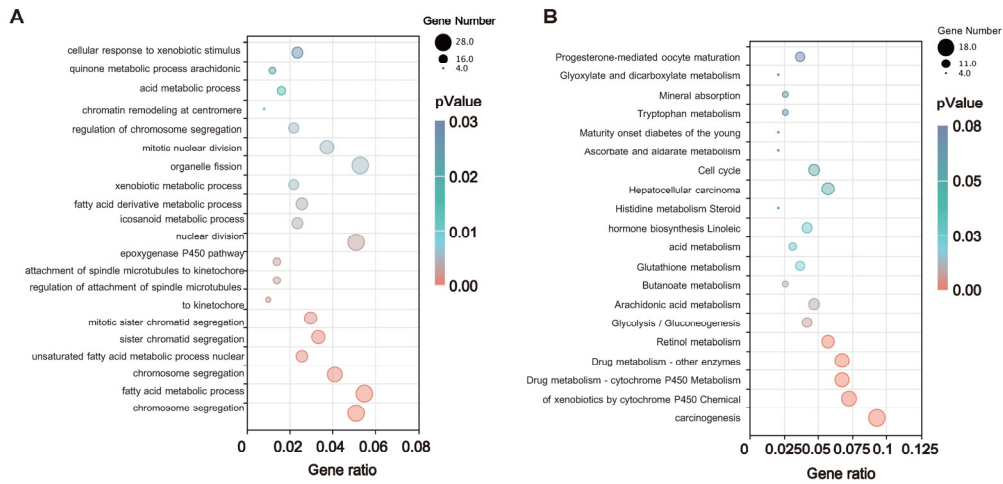


Supplementary Figure 12. Flow cytometry analysis of the percentage of Cy5.5-HA-PLGA_{Bilirubin}⁺ cells among different cell subtypes in both normal and DSS-induced colitis mice.

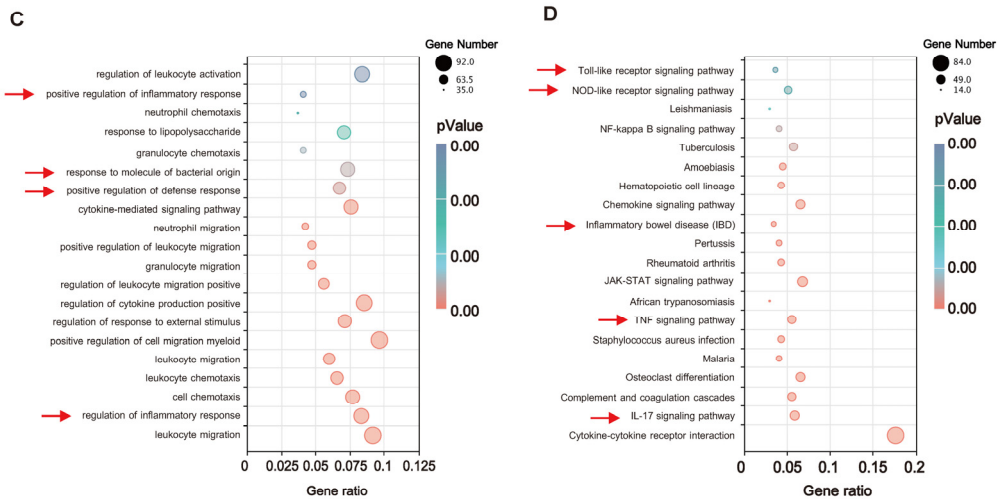


Supplementary Figure 13. (A) Differentially expressed genes of the colon tissues after treatment with PBS, DSS, DSS+PLGA_{Bilirubin}, DSS+HA-PLGA_{Bilirubin}. (B, C) GO enrichment (B) and KEGG analysis (C) of the differentially expressed genes after treatment with PBS and DSS+HA-PLGA_{Bilirubin}.

Up-regulated genes enrichment results

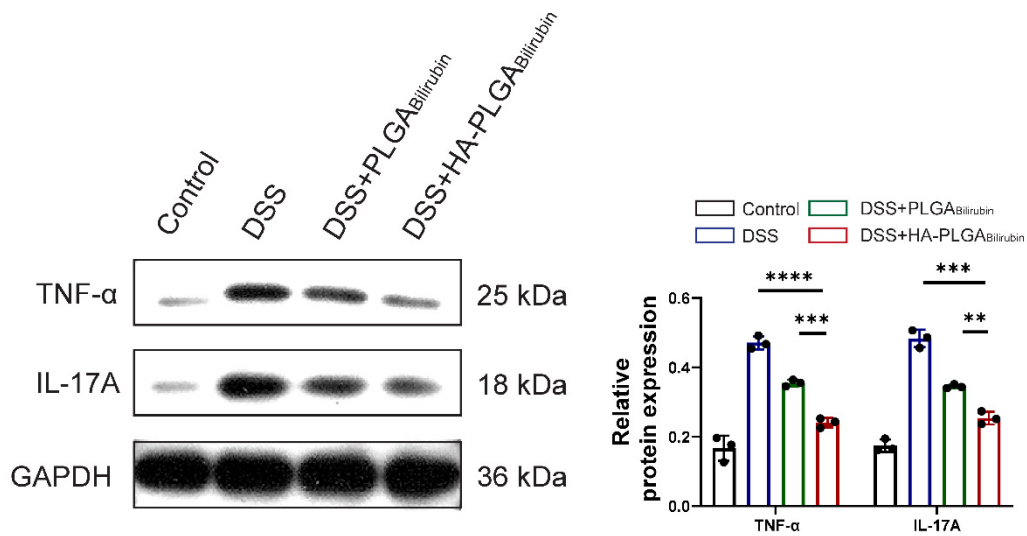


Down-regulated genes enrichment results

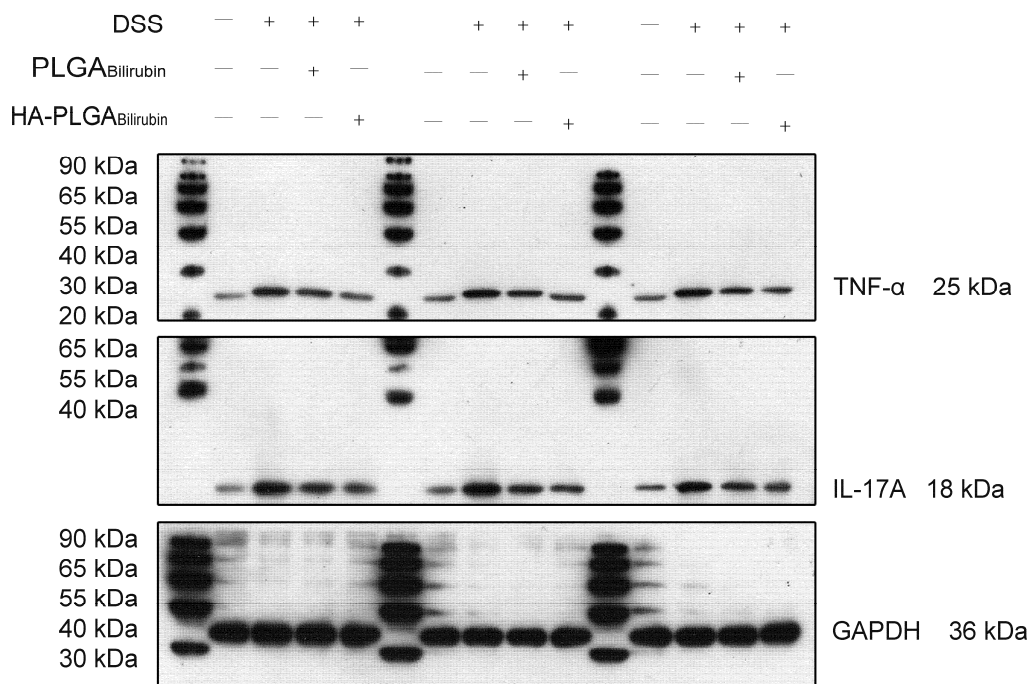


Supplementary Figure 14. GO and KEGG analysis of differential expressed genes.

(A, B) GO (A) and KEGG (B) analysis of the up-regulated genes in DSS+HA-PLGA_{bilirubin} group compared to the DSS group. (C, D) GO (C) and KEGG (D) analysis of the down-regulated genes in DSS+HA-PLGA_{bilirubin} group compared to the DSS group.



Supplementary Figure 15. Relative protein expression of TNF-α and IL-17A.



Supplementary Figure 16. Full-length Western blots.

Table S1. Physicochemical characteristics of the Bilirubin-loaded nanoparticles (mean \pm S.E.M.; n=3).

NPs	PLGA _{Bilirubin}	HA-PLGA _{Bilirubin}
Particle size (nm)	156.83 \pm 17.23	193.23 \pm 12.85 nm
PDI	0.114 \pm 0.006	0.192 \pm 0.004
Zeta potential (mV)	49.71 \pm 1.63	24.86 \pm 2.55