SUPPLEMENTARY INFORMATION

- Supplementary Figure 1. A scheme for the synthesis of hyaluronic acid-bilirubin conjugate (HA-BR)
- Supplementary Figure 2. Characterization of HA-BR.
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- Supplementary Figure 4. Responsiveness of HABN to peroxy radicals.
- Supplementary Figure 5. Identification of extracellular ROS.
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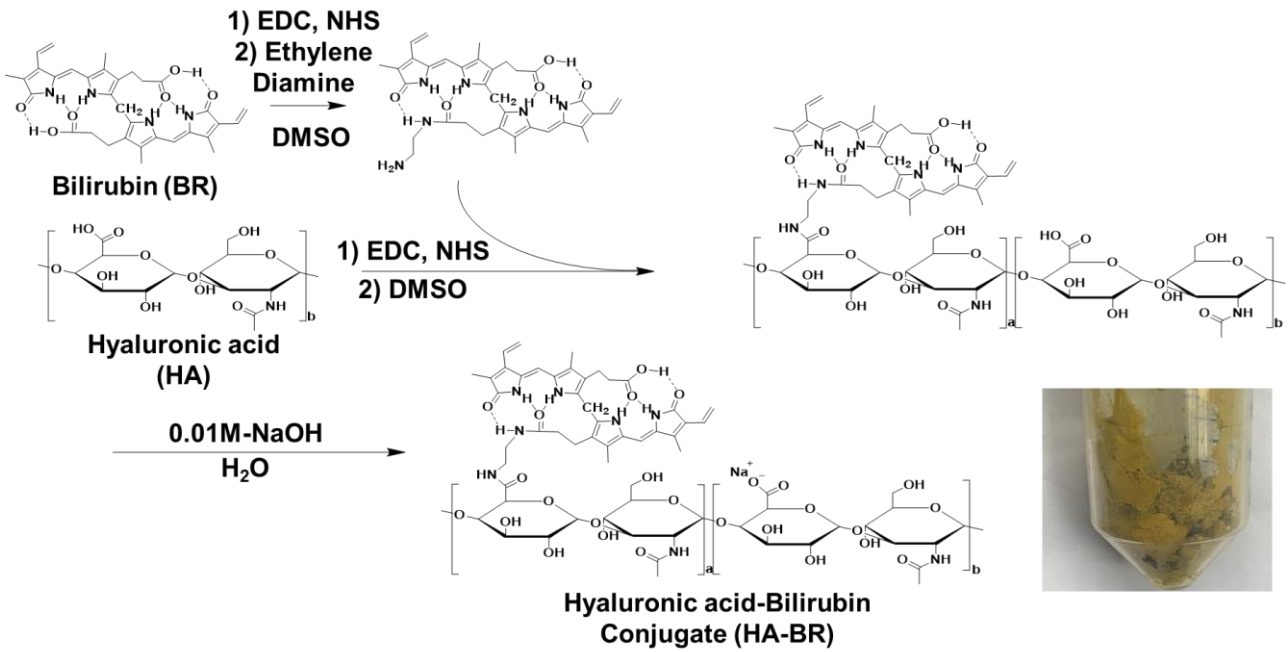
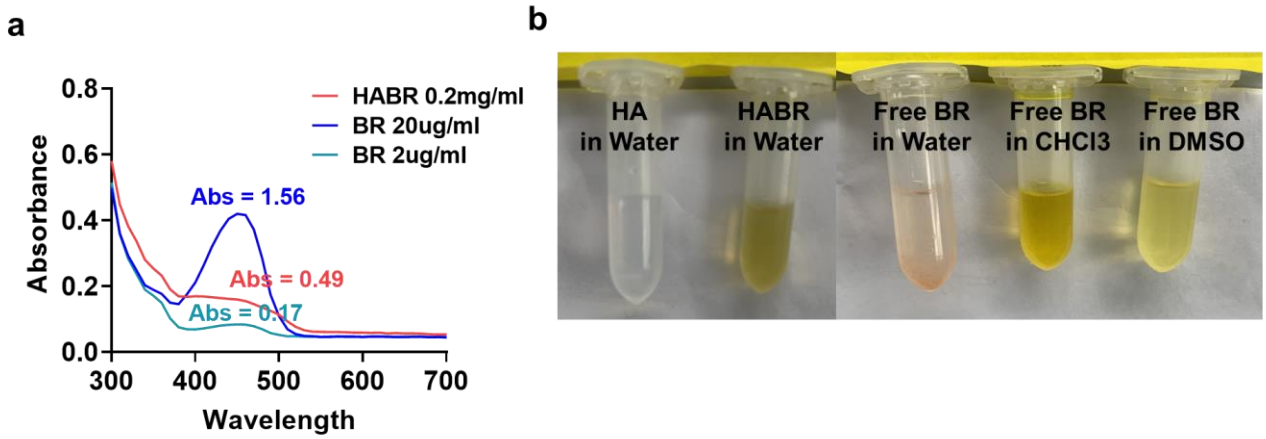
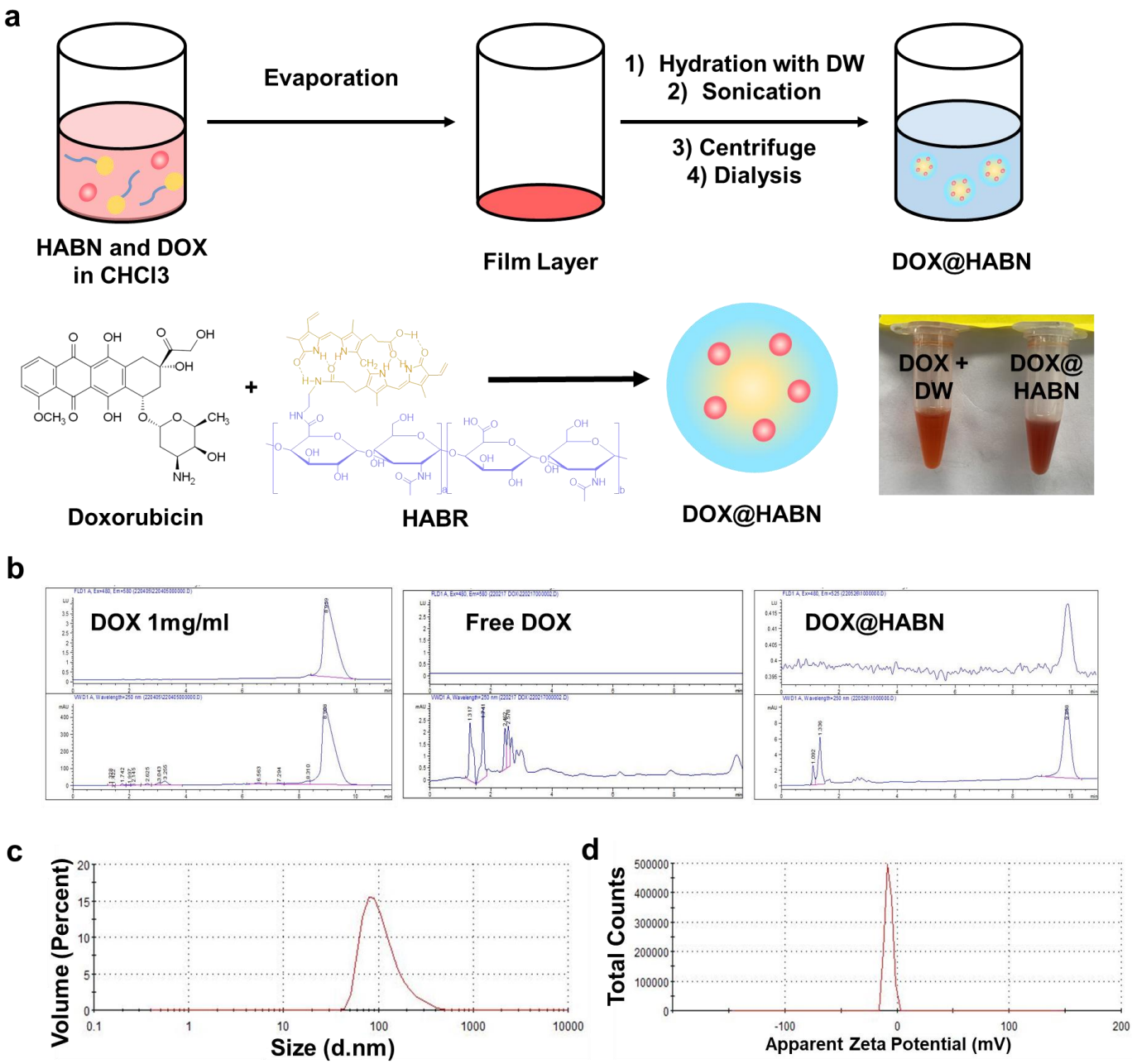


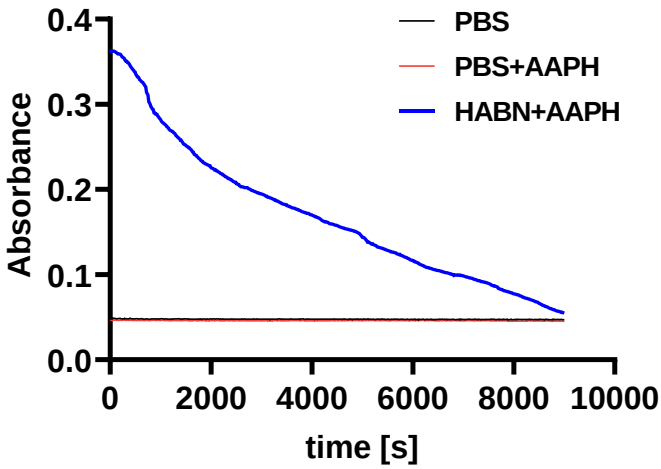
Supplementary Figure 1. A scheme for the synthesis of hyaluronic acid-bilirubin conjugate (HA-BR).



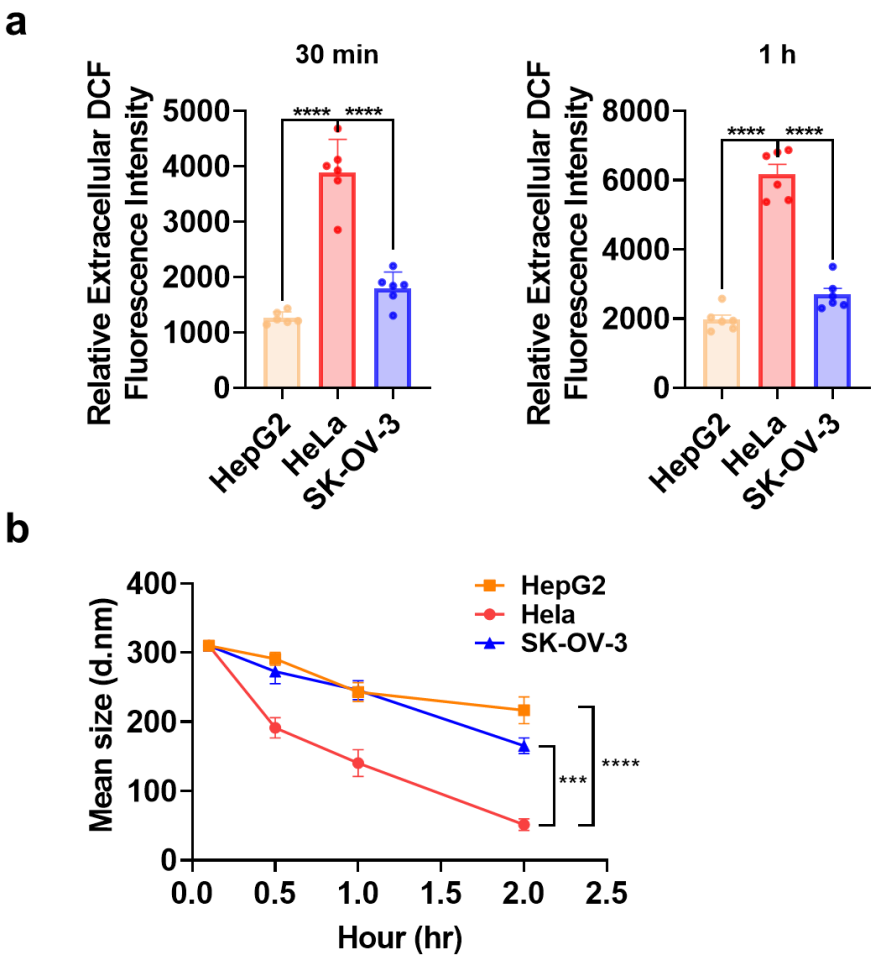
Supplementary Figure 2. Characterization of HA-BR. a, UV/Vis spectra of HA-BR (0.2 mg/ml) and Bilirubin (20 μg/ml and 2 μg/ml). **b,** Solubility or dispersibility of HA (3 mg/ml), Bilirubin (100 μg/ml), or HA-BR (3 mg/ml) in water, $CHCl_3$, or DMSO.



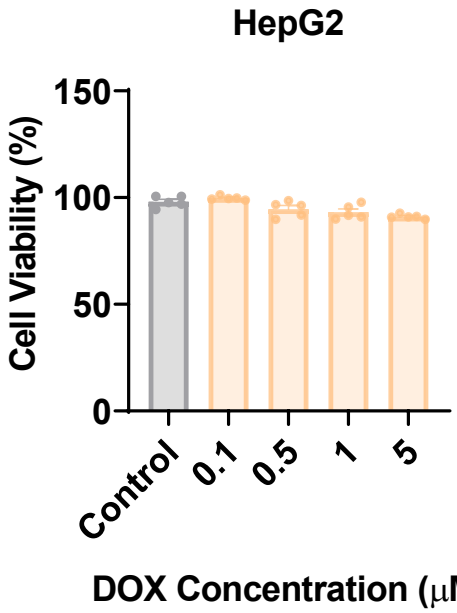
Supplementary Figure 3. **Preparation and characterization of DOX@HABN a**, Scheme for the formulation of hyaluronic acid-bilirubin nanoparticles (HABN) loaded with DOX **b,** HPLC chromatograms of DOX·HCl (1 mg/ml) in water, DOX in water, and DOX in DOX@HABN (in water). **c-d,** Hydrodynamic sizes (**c**) and zeta potential (**d**) of DOX@HABN.



Supplementary Figure 4. **Responxiveness of HABN to peroxy radicals.** Change in UV/Vis absorbance at 450 nm of HABN treated with the peroxy radical generator AAPH for 1 h.



Supplementary Figure 5. Identification of extracellular ROS. a, Comparison of the correlation of extracellular ROS levels (determined DCFDA dye) with fluorescence intensity in cell culture medium of HeLa, HepG2 and SK-OV-3 cells. **b,** Size changes of HABN (1 mg/ml) in cell culture medium of HeLa, HepG2 and SK-OV-3 cells. Data are presented as mean ± s.e.m. from a representative experiment. ***P<0.001, ****P<0.0001, analyzed by one-way ANOVA with Tukey's HSD multiple comparison post hoc test.



Supplementary Figure 6. In vitro cytotoxicity of DOX@HABN in HepG2 cells. Cell viability of HepG2 cells treated with different concentrations of DOX@HABN (10% DOX loading percentage) for 30 min, followed by further incubation for 48 h. Data are presented as mean ± s.e.m. from a representative experiment.