

## Supplementary Materials

### Microenvironment Activatable Nanoprodrug Based on Gripper-like Cyclic Phenylboronic Acid to Precisely and Effectively Alleviate Drug-induced Hepatitis

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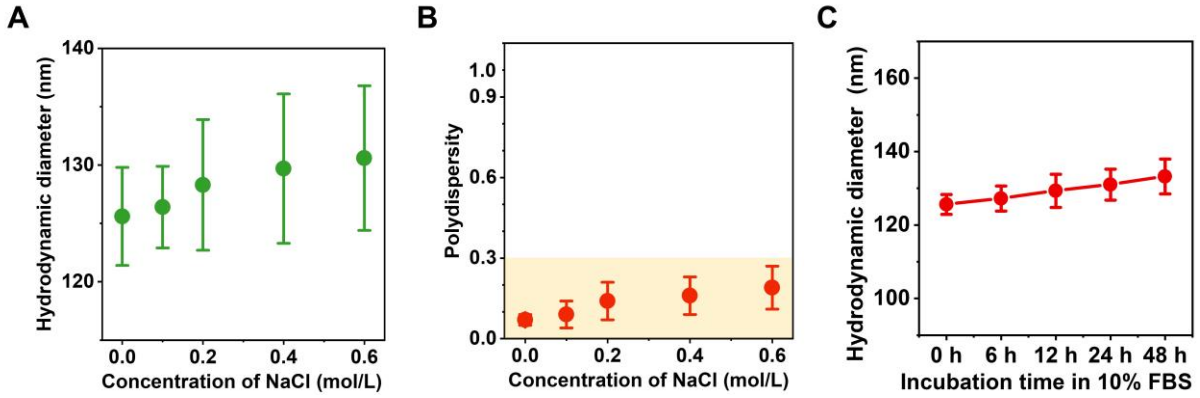
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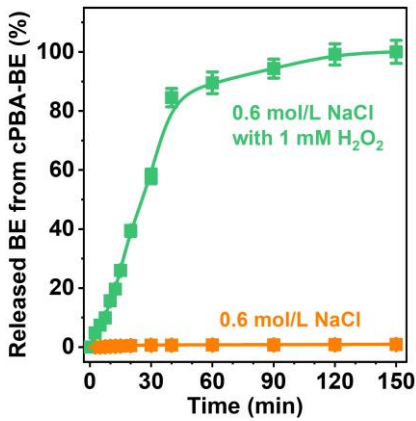
Rongsheng Tong, PhD, Prof.,

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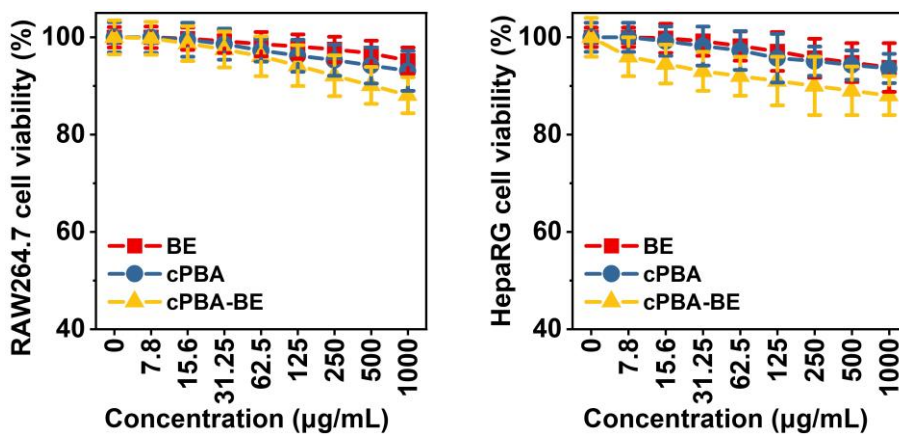
E-mail: [2207132448@qq.com](mailto:2207132448@qq.com) (Rongsheng Tong)



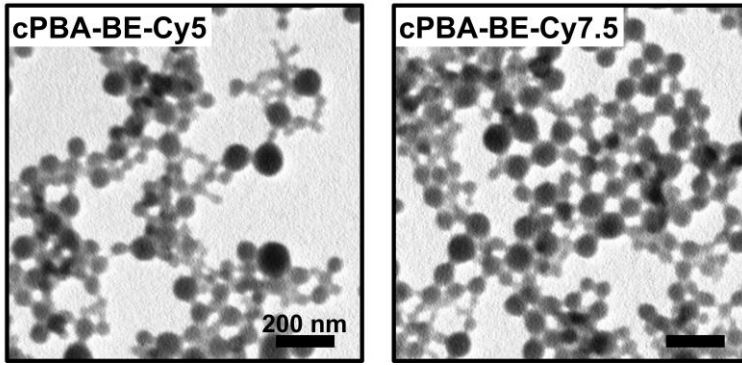
**Figure S1.** Hydrodynamic diameter (A) and polydispersity (B) of cPBA-BE at different concentrations (0–0.6 mol/L) of NaCl. Hydrodynamic diameter of cPBA-BE in the medium with 10% FBS at different incubation time points (C). All data are presented as mean  $\pm$  SD (n = 6).



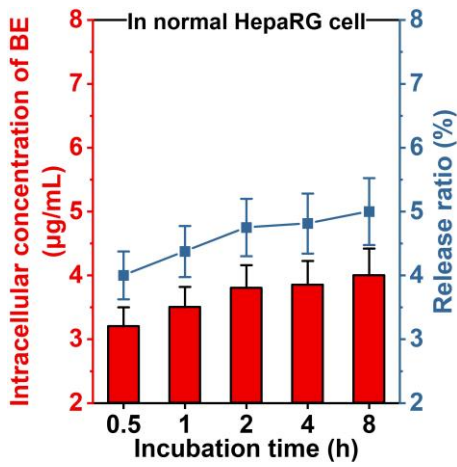
**Figure S2.** Drug release profiles of cPBA-BE at 0.6 mol/L NaCl with or without 1 mM H<sub>2</sub>O<sub>2</sub>. All data are presented as mean  $\pm$  SD (n = 6).



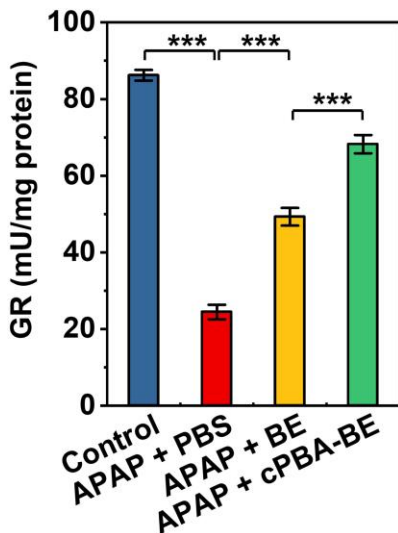
**Figure S3.** Toxicity of BE, cPBA and cPBA-BE. MTT proliferation assay in RAW264.7 cells and HepaRG cells. All data are presented as mean  $\pm$  SD (n = 6).



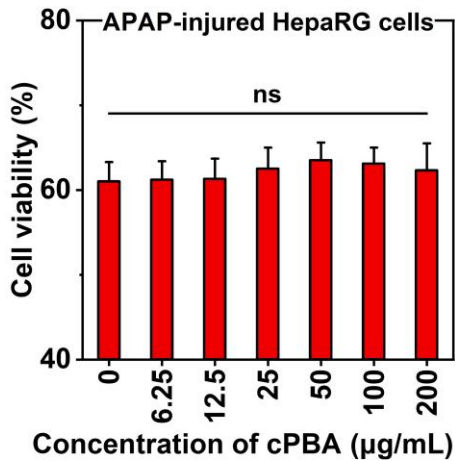
**Figure S4.** TEM images of cPBA-BE-Cy5 and cPBA-BE-Cy7.5.



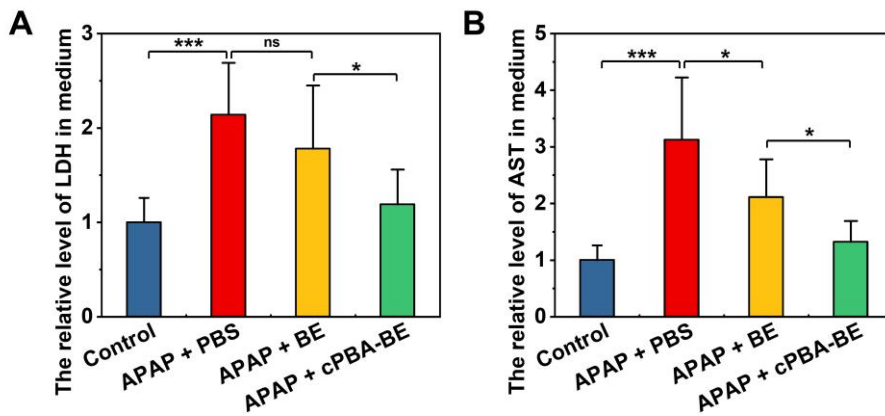
**Figure S5.** The intracellular concentration of BE and drug release ratio of 80 µg/mL cPBA-BE in normal HepaRG cells at different time. Data are presented as mean ± SD (n = 6).



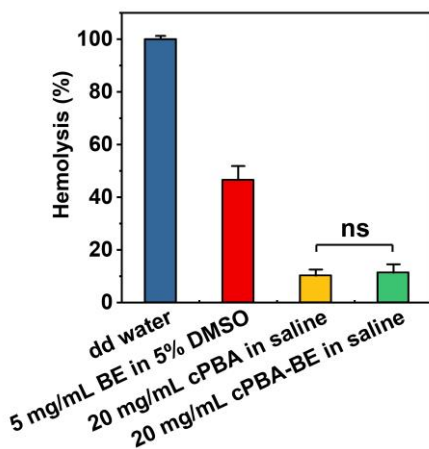
**Figure S6.** The content of glutathione reductase (GR) in APAP-injured HepaRG cells determined by kits. All data are presented as mean ± SD (n = 6). \*\*\*p < 0.001.



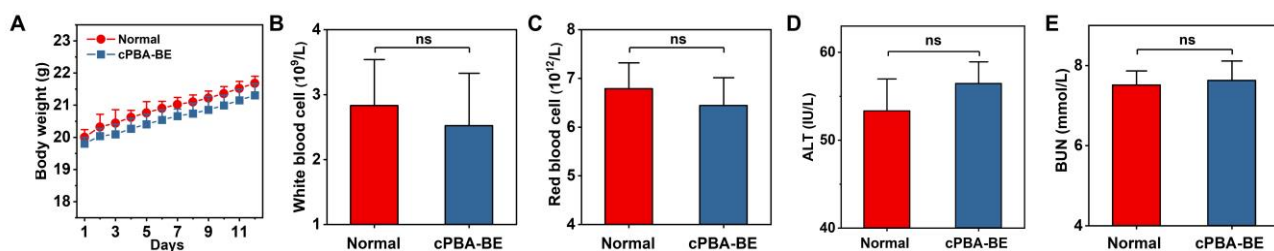
**Figure S7.** Cell viability of APAP-injured HepaRG cells after incubation with different concentrations of cPBA. All data are presented as mean  $\pm$  SD ( $n = 6$ ). ns means no significance.



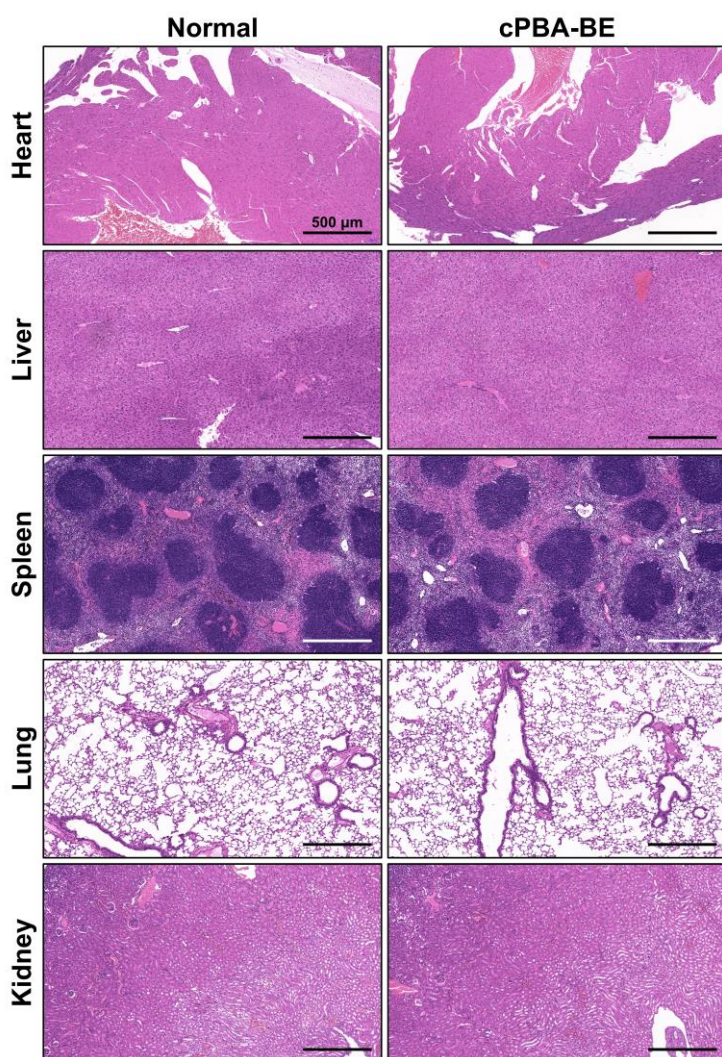
**Figure S8.** The level of biomarkers of APAP-induced injury in HepaRG cells. **A-B**, The relative level of LDH (A) and AST (B) in culture medium. All data are presented as mean  $\pm$  SD ( $n = 5$ ). \* $p < 0.05$ , \*\*\* $p < 0.001$ ; ns, no significance.



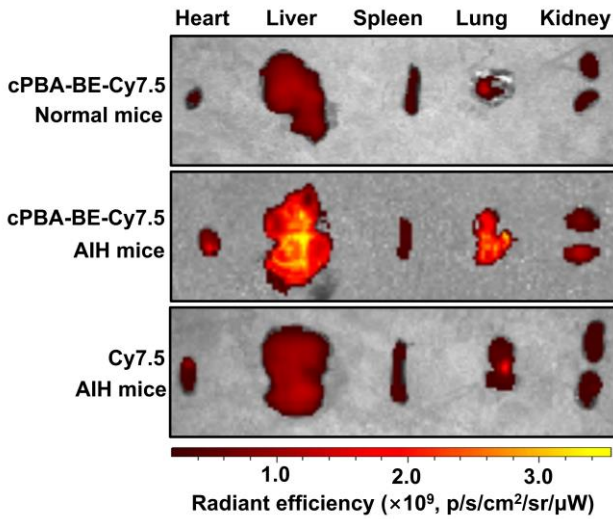
**Figure S9.** Hemolysis rates of 5 mg/mL BE in 5% DMSO, 20 mg/mL cPBA in saline and 20 mg/mL cPBA-BE in saline. All data are presented as mean  $\pm$  SD ( $n = 6$ ). ns, no significance.



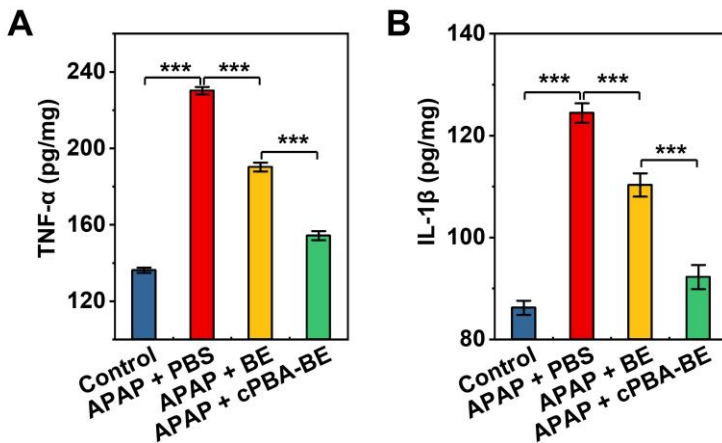
**Figure S10.** Mice were daily administrated 100  $\mu$ L 20 mg/mL cPBA-BE for 12 days by intravenous injection. **A**, Body weight changes of the mice during 12 days. **B-C**, Typical hematological parameters including white blood cell and red blood cell on day 12. **D-E**, Levels of biochemical markers relevant to liver (aspartate aminotransferase, AST) and kidney (blood urea nitrogen, BUN) functions on day 12. All data are presented as mean  $\pm$  SD ( $n = 5$ ). ns, no significance.



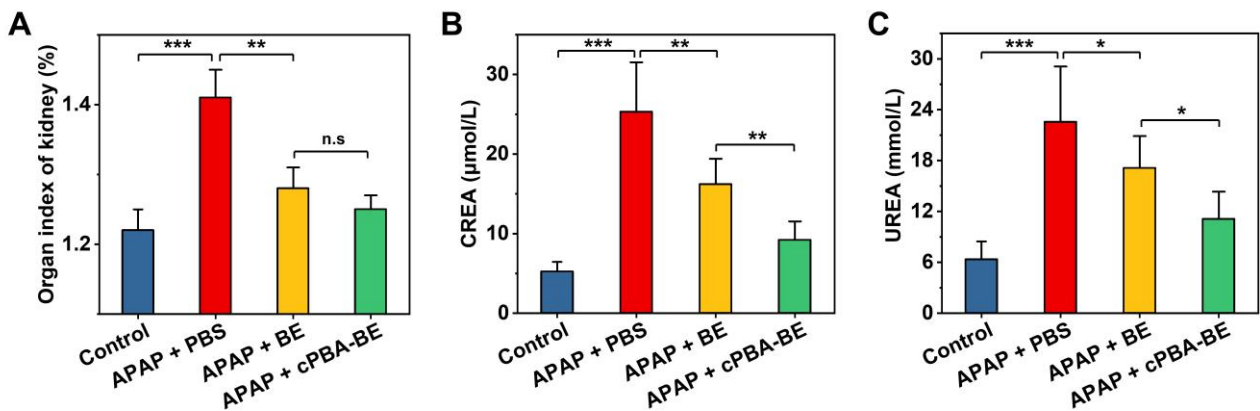
**Figure S11.** H&E-stained sections of major tissues. Major organs were resected from mice after intravenous administration of 100  $\mu$ L of cPBA-BE (20 mg/mL) for 12 days. All scale bar represent 500  $\mu$ m.



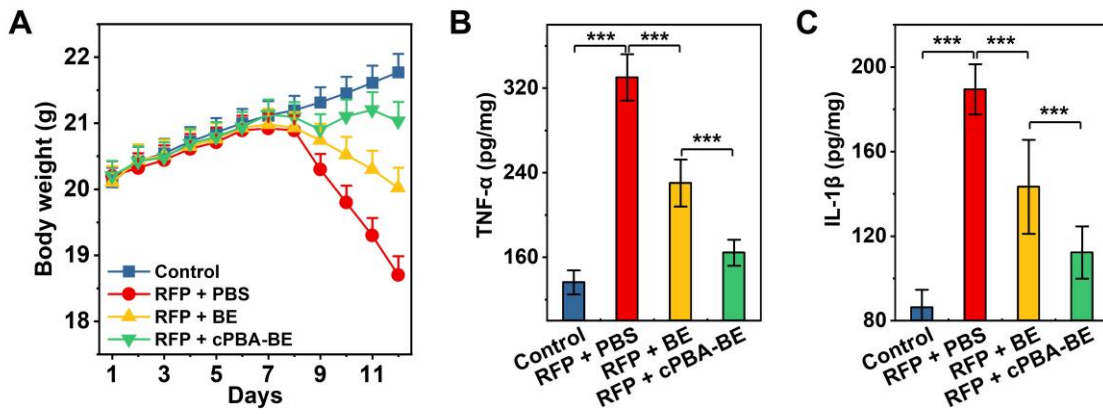
**Figure S12.** Accumulation of cPBA-BE-Cy7.5 in major organs of AIH mice or normal mice.



**Figure S13.** The expression levels of TNF- $\alpha$  (A) and IL-1 $\beta$  (B) of liver tissues in AIH mice. All data are presented as mean  $\pm$  SD (n = 5). \*\*\*p < 0.001.



**Figure S14.** Biomarkers of kidney function in AIH mice. A, Organ index of kidney in AIH mice. B-C, The concentration of CREA (B) and UREA (C). All data are presented as mean  $\pm$  SD (n = 5). \*p < 0.05, \*\*p < 0.01 and \*\*\*p < 0.001; ns, no significance.



**Figure S15.** A, Body weight changes of RIH mice during 12 days. The expression levels of TNF- $\alpha$  (B) and IL-1 $\beta$  (C) of liver tissues in RIH mice. All data are presented as mean  $\pm$  SD (n = 5), \*\*\*p < 0.001.