

Supplementary Information

Self-assembled nanomedicine combining berberine derivative and doxorubicin for enhanced antitumor and antimetastatic efficacy *via* mitochondrial pathways

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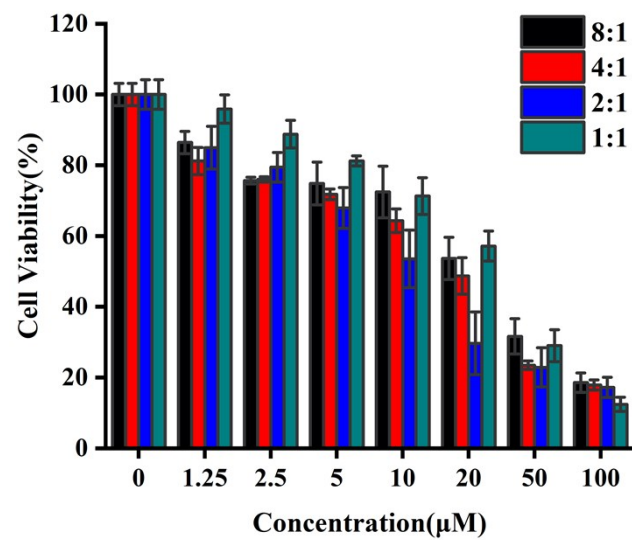


Figure S1. *In vitro* anti-tumor activity of different molar ratio of self-assembled BD NDs on MCF-7 cells.

Table. S1. IC50 values of different molar ratio of BD NDs on MCF-7 cells.

Formulation	8:1	4:1	2:1	1:1
IC 50 (μ M)	30.78	21.47	9.766	47.62

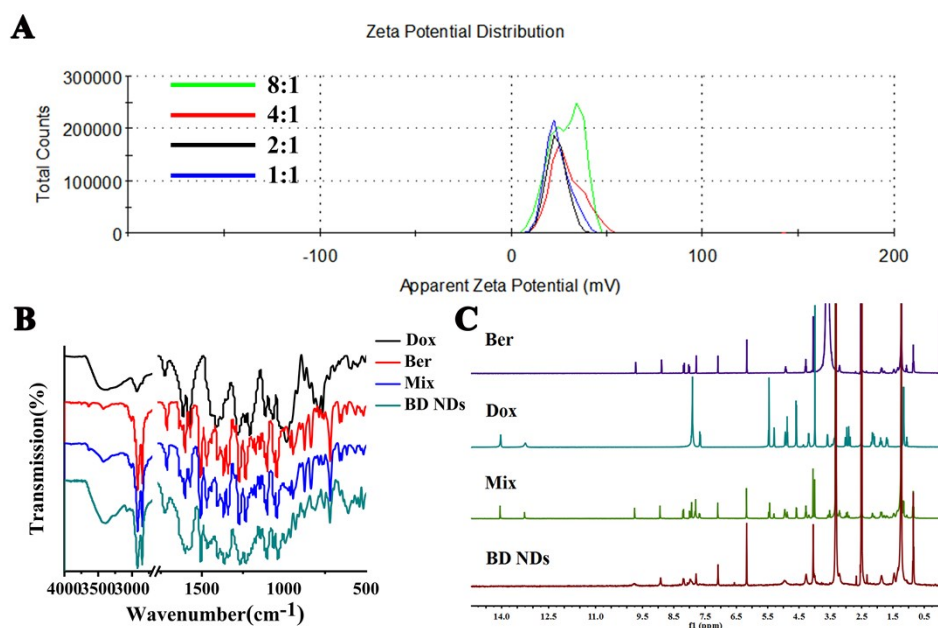


Figure S2. (A) Zeta potential of different molar ratio of BD NDs (Ber/Dox = 1:1, 2:1, 4:1 and 8:1). (B) FT-IR spectra and (C) ¹H NMR spectra of Ber, Dox, Ber/Dox Mix, and BD NDs (without FA and HA modified).

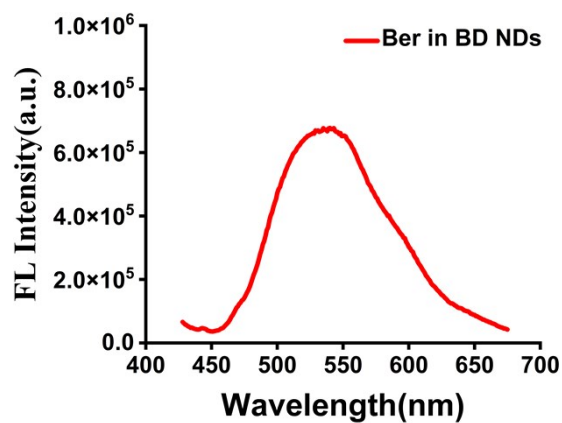


Figure S3. The fluorescence of Ber in nanodrugs.

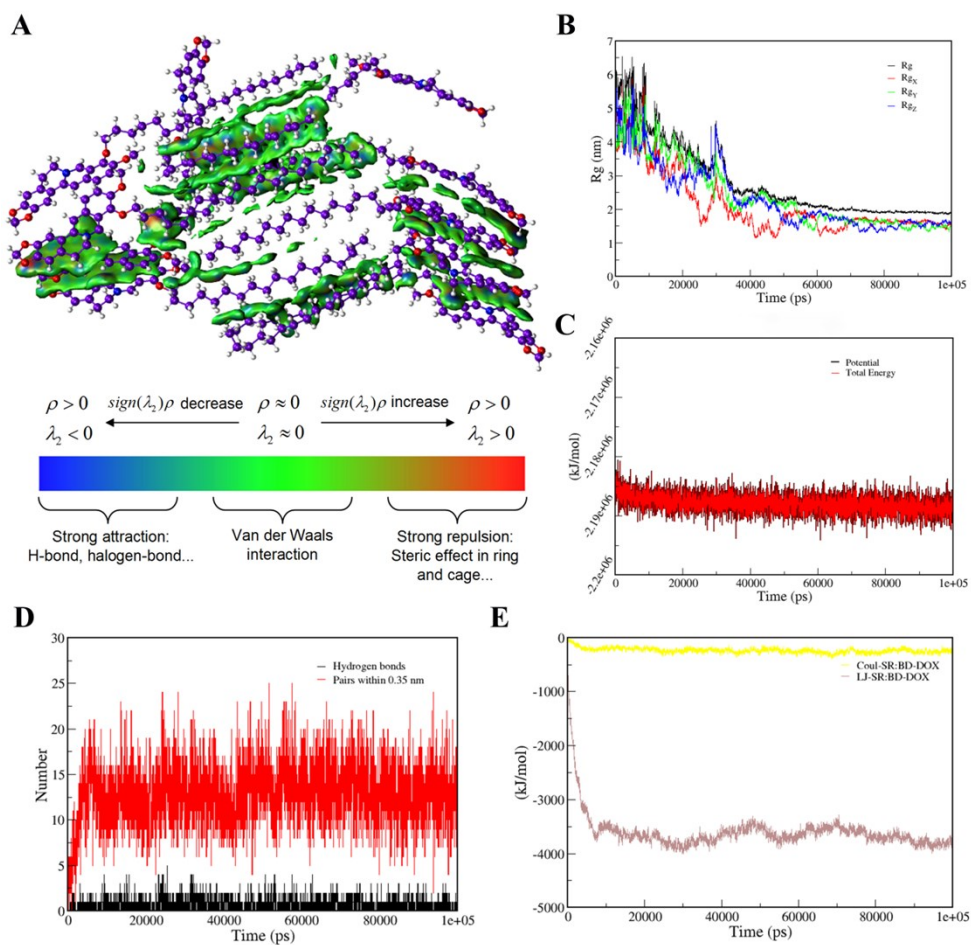


Figure S4. (A) Intermolecular interaction of Ber molecules. (B) R_g fluctuation of versus time for Ber/Dox system in the self-assembled simulation. (C) Total energy of Ber/Dox system. (D) Hydrophobic interaction between Ber and Dox. (E) Coulomb energy short-range (Coul-SR) and Lennard-Jones energy short-range (LJ-SR) between Ber and Dox.

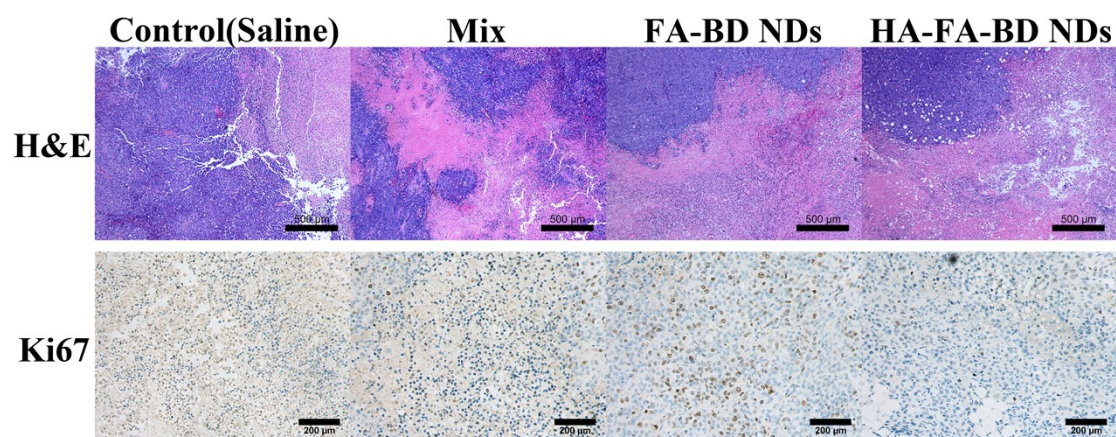


Fig. S5. H&E and ki67 staining of tumor tissues. Scale bar are 500 μm and 200 μm, respectively.

Drug loading (DL) test

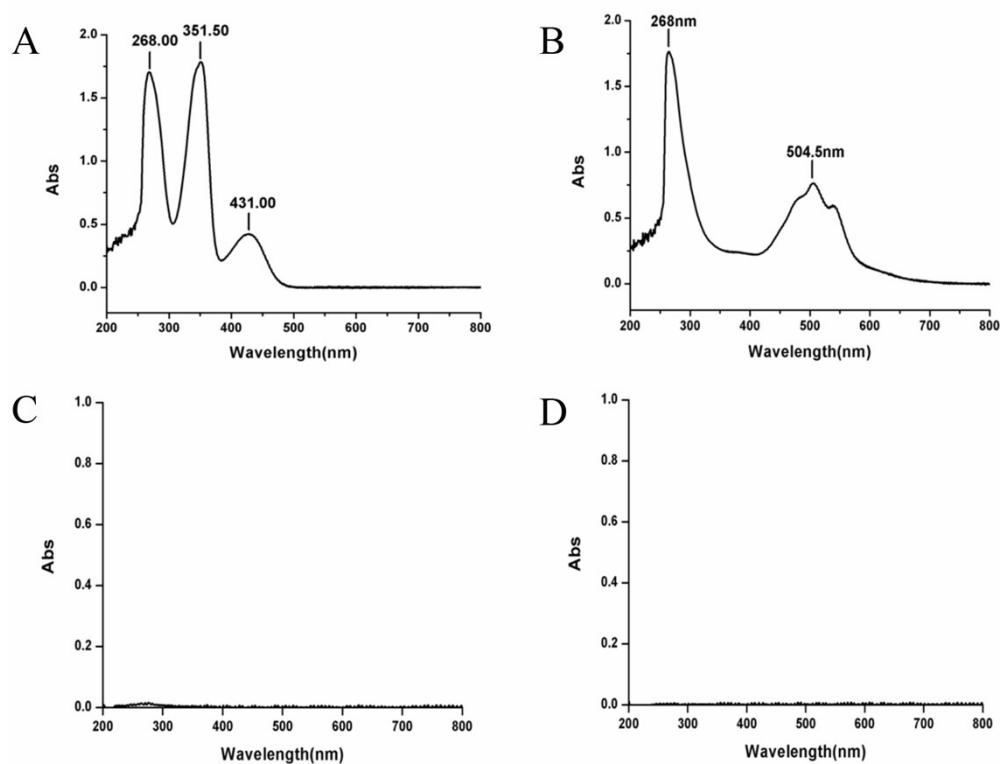


Figure S6. UV-Vis spectrum of (A) Ber, (B) Dox (C) DSPE-PEG-FA and (D) HA.

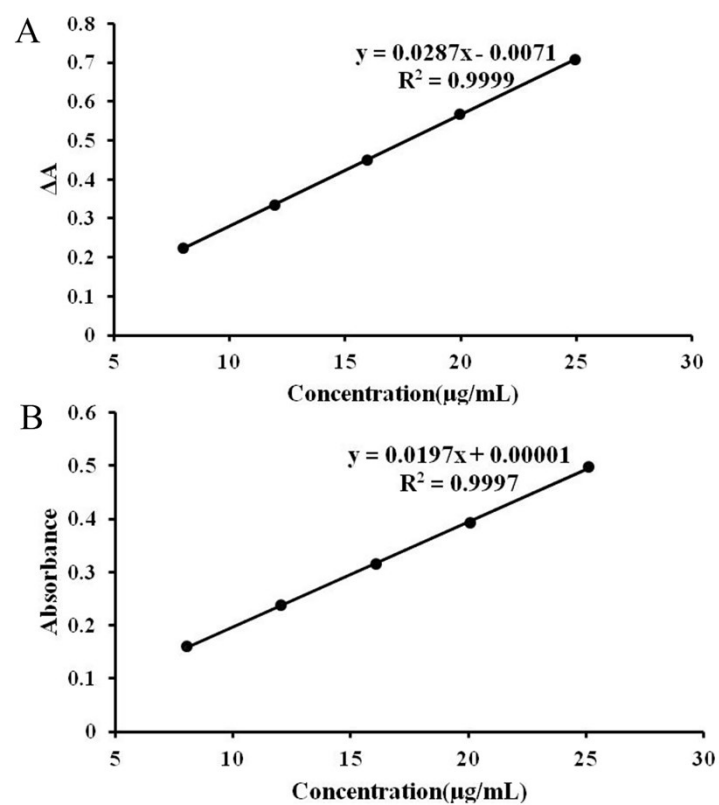


Figure S7. The fitted standard curve between concentration and absorbance of (A) Ber and (B) Dox, which would be further used in the drug loading measurement.

Table. S2. The drug loading (DL) of FA-BD NDs.

Batch	ΔA measured between 351.5 and 557.5 nm	Ber concentration ($\times 25 \mu\text{g/mL}$)	A measured at 504.5 nm	Dox concentration ($\times 4 \mu\text{g/mL}$)	DL (%)
1	0.384	340.679	0.079	100.241	82.237
2	0.383	339.808	0.079	100.241	82.208
3	0.383	339.808	0.079	100.241	82.208
Mean $\pm$ SD	0.383 $\pm$ 0.001	340.098 $\pm$ 0.503	0.079 $\pm$ 0.000	100.241 $\pm$ 0.000	82.22 $\pm$ 0.02

Table. S3. The drug loading (DL) of HA-FA-BD NDs

Batch	ΔA measured between 351.5 and 557.5 nm	Ber concentration ($\times 25 \mu\text{g/mL}$)	A measured at 504.5 nm	Dox concentration ($\times 4 \mu\text{g/mL}$)	DL (%)
1	0.470	66.495	0.148	30.049	68.208
2	0.468	66.216	0.148	30.049	68.144
3	0.468	66.216	0.148	30.049	68.144
Mean $\pm$ SD	0.469 $\pm$ 0.001	66.309 $\pm$ 0.161	0.148 $\pm$ 0.000	30.049 $\pm$ 0.000	68.17 $\pm$ 0.04