Electronic Supplementary Material (ESI) for Nanoscale.


# Sensitizing Chemotherapy for Glioma with Fisetin mediated by Microenvironment-responsive nano-drug delivery system

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**Fig. S1. Synthesis route of PEG-SS-PLA**

**Fig. S2. Synthesis route of cRGD-PEG-PLA.**

**Fig.S3. Structural identification of PEG-SS-PLA(a) and cRGD-PEG-PLA(b).**

**Fig.S4. Zeta potential of Fis-DOX/cRGD-NPs**

**Fig. S5. Cell viability study of the nanocomposites by CCK8 assay in U87 cells.**
Synergistic effects of DOX and Fisetin in the carrier system on cytotoxicity in U87 cells. CCK-8 assay was used to assess the cytotoxicity of blank NPs, DOX/NPs, and Fis-DOX/NPs from 0 μg/ml to 0.5 μg/ml at 24 h (a) and 48 h (b). N=3.

**Fig. S6. Analysis of cell cycle in U87-MG cells.** Synergistic effects of DOX and Fisetin in the carrier system cell cycle arrest in U87 cells. (a) Flow cytometric analysis. U87 cells were treated with blank NPs, DOX/NPs, and Fis-DOX/NPs at 0.125 µg/ml for 24 h. (b) Populations of cells at G0/G1, S, and G2/M phases were displayed as percentages of the whole cell population.

**Fig. S7. Apoptosis assay of U87-MG cells.** Synergistic effects of DOX and Fisetin in the NPs carrier system on tumor cell apoptosis. U87 cells were treated with blank NPs, DOX/NPs and Fis-DOX/NPs at concentrations of 0 μg/ml and 0.0625 μg/ml for 24 h. (a)(b) Cells were collected and stained with Annexin V and PI for flow cytometric analysis.

**Fig. S8.** Western blot analysis of U87-MG Cell.

**Fig. S9.** Flow cytometry analysis of the uptake of Dox in (a) GL-261 cells and (b) U87-MG after different treatments.

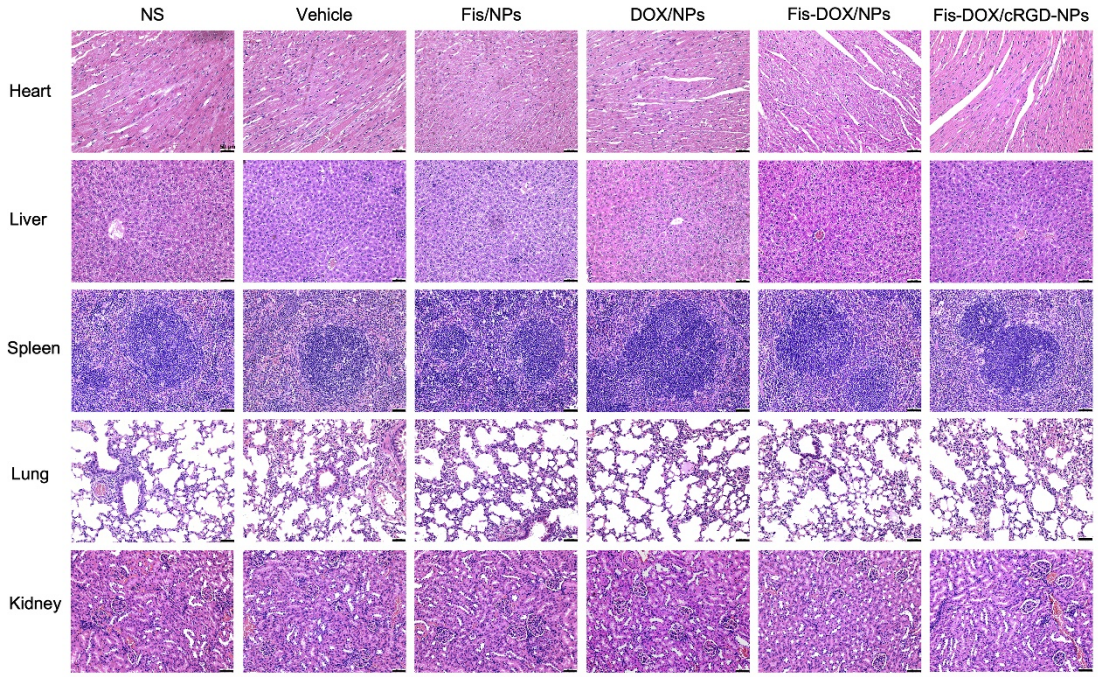


**Fig. S10.** Toxicity assessment in H&E staining with pathological section.

**Fig. S11.** Toxicity assessment in serologic biochemical analysis.

**Fig. S12.The raw image of Western blot of GL261 cells**.

**Fig. S13. The raw image of Western blot of U87 cells**.