

## Hypoxia-Augmented and Photothermal-Enhanced Ferroptotic Therapy with High Specificity and Efficiency

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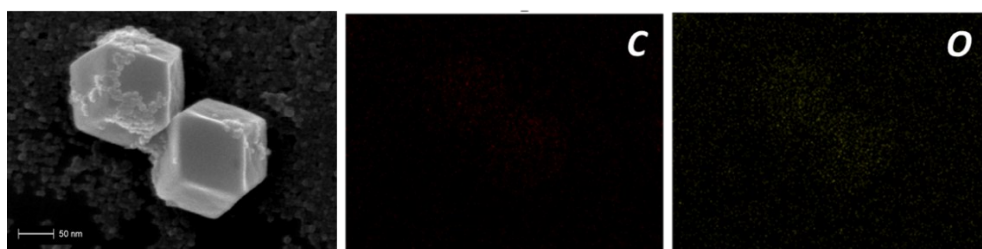


Figure S1. Corresponding elemental mapping of FGGZ.

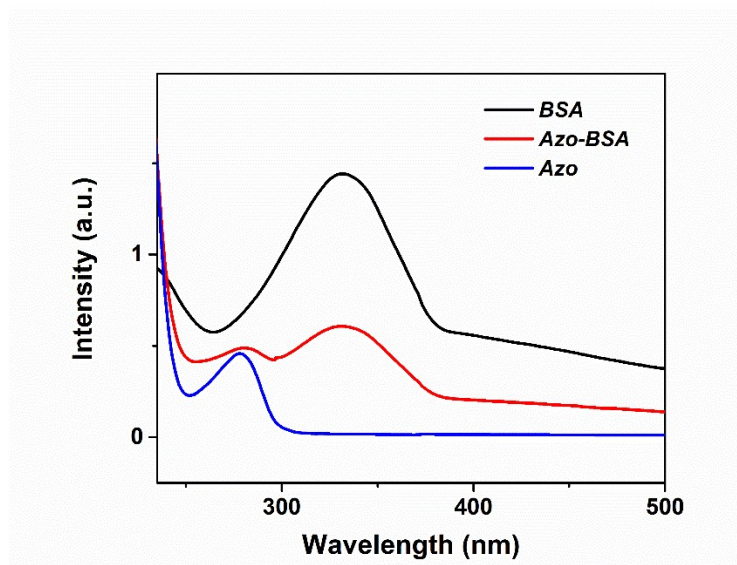


Figure S2. UV/Vis absorption spectra of Azo, BSA and Azo-BSA. Azo exhibited a characteristic absorption peak at 278 nm, and BSA exhibited a characteristic absorption peak at 332 nm. The obvious peaks at 278 nm and 332 nm of Azo-BSA spectrum proved the successful synthesis of Azo-BSA.

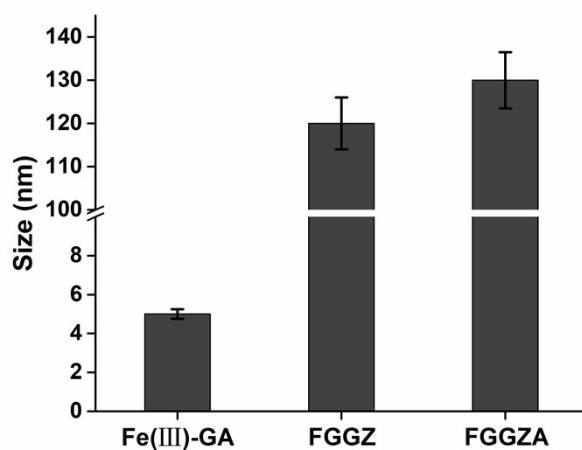


Figure S3. Particle size of Fe(III)-GA, FGGZ and FGGZA.

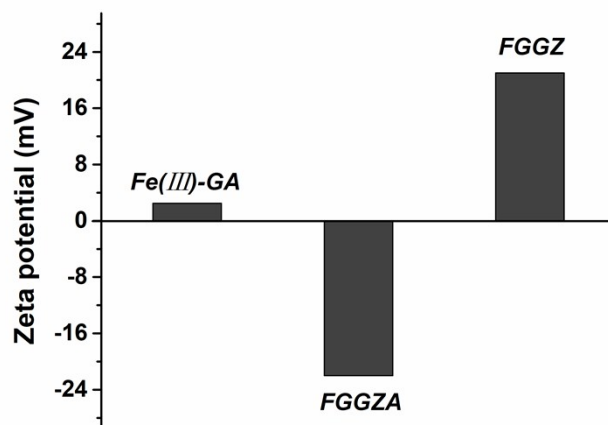


Figure S4. Zeta potential of Fe(III)-GA, FGGZ and FGGZA.

The photothermal conversion efficiency ( $\eta$ ) was given as:

$$\eta = \frac{hS(T_{\max} - T_{\text{surr}}) - Q_s}{I(1 - 10^{-A})}$$

$$hS = \frac{\sum m_i C_{p,i}}{\tau S}$$

$$t = \tau S(-\ln \theta)$$

$$\theta = \frac{T - T_{\text{surr}}}{T_{\max} - T_{\text{surr}}}$$

Where  $m$  is the mass of sample and equal to 1.0 g,  $c$  is the specific heat capacity of water (4.2 J g<sup>-1</sup>),  $T_{\max}$  is the maximum temperature and equal to 45.1 °C,  $T_{\text{surr}}$  is the temperature of ambient surroundings and equal to 26.1 °C. The  $Q_s$  expresses the heat associated with the light absorbance,  $I$  is the laser power density and equal to 1.0 W, and  $A$  is absorption of Fe(III)-GA aqueous solution at 808 nm and equal to 0.8588. The  $t$  is cooling time after irradiation. Finally, the photothermal conversion efficiency is calculated to be 66.5%.

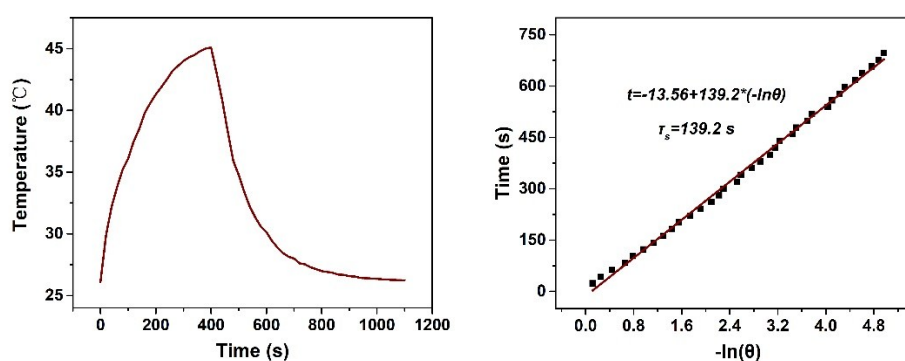


Figure S5. a) Heating and cooling curves of Fe(III)-GA aqueous solution (100  $\mu\text{g mL}^{-1}$ ) under irradiation of 808 nm laser (1 W  $\text{cm}^{-2}$ ). b) Linear time data versus  $-\ln\theta$  obtained from the cooling period.

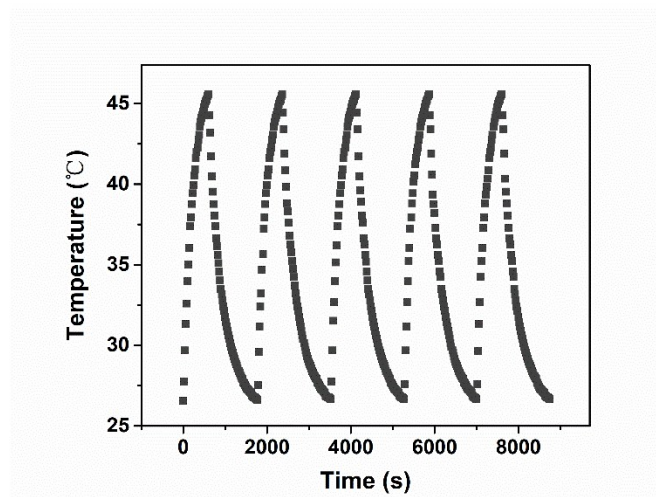


Figure S6. Temperature variations of Fe(III)-GA aqueous solution over five laser on/off cycles irradiated by 808 nm laser.

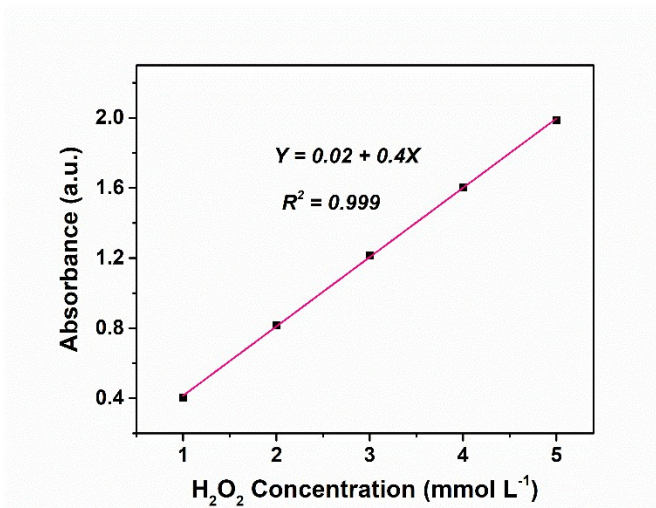


Figure S7. Standard calibration curve of H<sub>2</sub>O<sub>2</sub> aqueous solution.

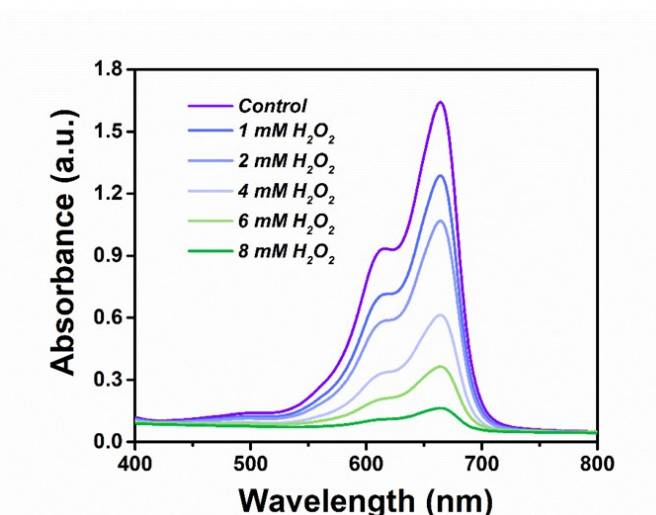


Figure S8. Degradation of MB with different concentration of H<sub>2</sub>O<sub>2</sub>. The degradation of MB significantly increased with the H<sub>2</sub>O<sub>2</sub> concentration increasing.

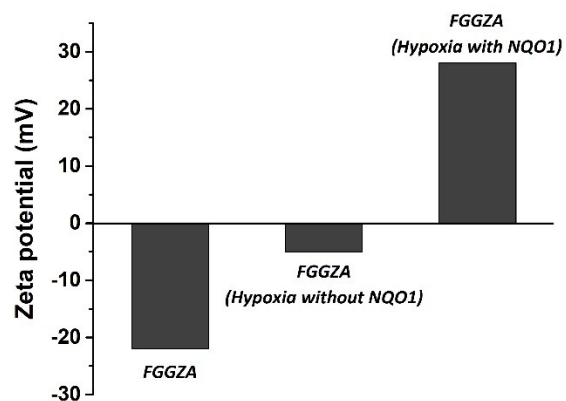


Figure S9. Zeta potential of FGGZA under various conditions.

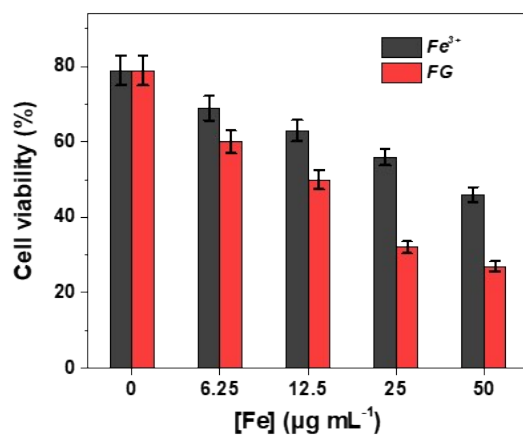


Figure S10. The cell viability of MCF-7 cells after 24 h of incubation of  $\text{Fe}^{3+}$  and  $\text{Fe(III)-GA}$ .

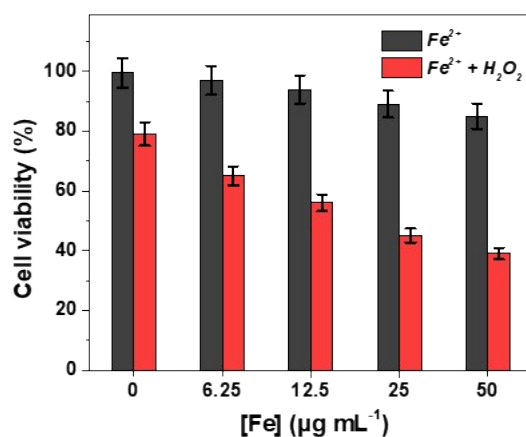


Figure S11. The cell viability of MCF-7 cells after 24 h of incubation of  $\text{Fe}^{2+}$  plus  $\text{H}_2\text{O}_2$  compared with  $\text{Fe}^{2+}$ .

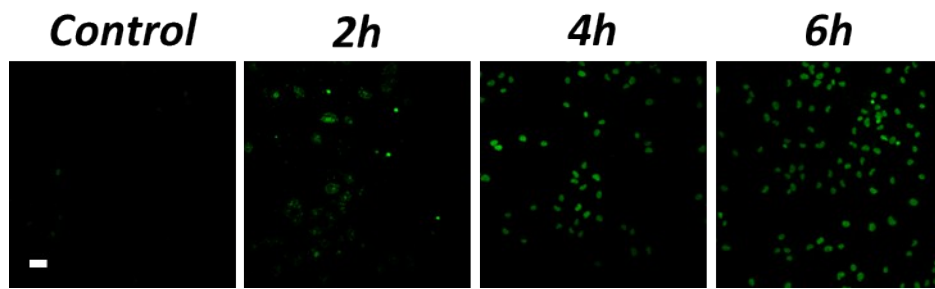


Figure S12. Qualitatively analysis of generated ROS in MCF-7 cells after incubation with  $\text{Fe}^{2+}$  measured by CLSM. (Scale bar, 40 nm)

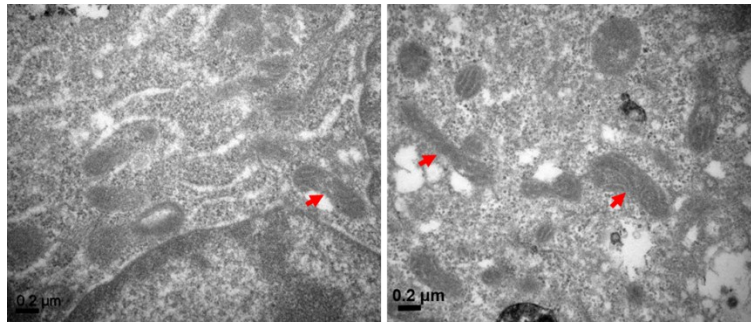


Figure S13. TEM image of MCF-7 cells treated with FGGZA plus NIR showing intact nucleus with complete structure and shrunken mitochondria with dense membrane.

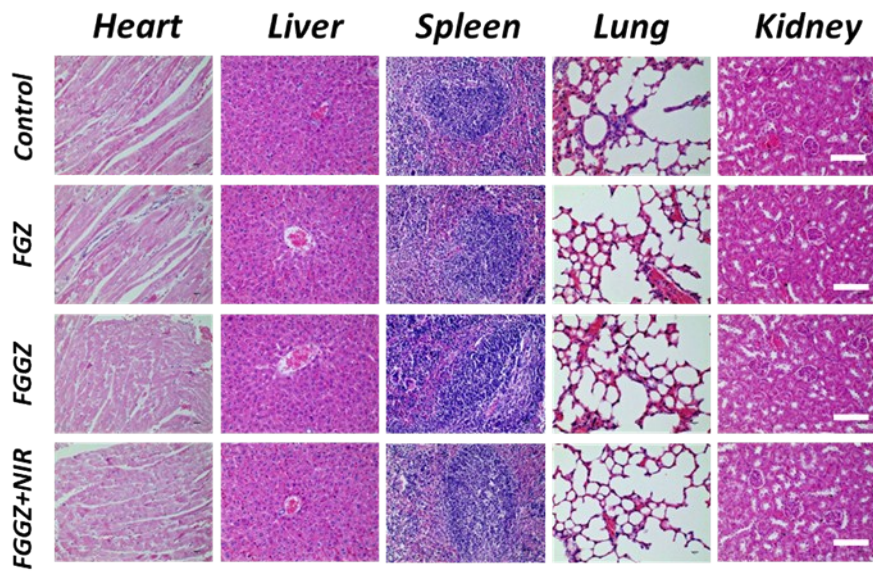


Figure S14. H&E stained images of major organ slices exposed to different groups. (bar = 100  $\mu\text{m}$ ).