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Tumor-responsive nanomedicine based on Ce^{3+}-modulated up-/downconversion dual-mode emission for NIR-II imaging-guided dynamic therapy

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1. Materials

RE_2O_3 (RE = Er, Gd, Yb, Ho, 99.99%), cerium chloride ($CeCl_3 \cdot 7H_2O$, 99.99), hydrochloric acid (HCl), ammonium chloride (NH_4Cl) and ammonium hydroxide ($NH_3 \cdot H_2O$) were purchased from Sinopharm Chemical Reagent Co., Ltd; Trifluoroacetic acid (CF_3COOH, 90%) and sodium trifluoroacetate (CF_3COONa, 90%) (from Beijing Chemical Regent Co.); Oleic acid (OA, 90%), 1-octadecene (ODE, 90%), cyclohexane, methanol (CH_3OH), ammonium fluoride (NH_4F), sodium hydroxide (NaOH), glutathione (GSH), calcein AM, fluorescein isothiocyanate (FITC), propidium iodide (PI), manganese(II) chloride tetrahydrate ($MnCl_2 \cdot 4H_2O$), cetyltrimethyl ammonium bromide (CTAB) and ammonium nitrate (NH_4NO_3) (from Tianjin Kermel Chemical Co., Ltd.) 4',6-diamidino-2-phenylindole (DAPI), 3-4,5-dimethylthiazol-2-yl-2,5-diphenyl tetrazolium bromide (MTT) (from Sigma-Aldrich); Dimethyl sulfoxide (DMSO), copper(II) nitrate trihydrate ($Cu(NO_3)_2 \cdot 3H_2O$), sodium alginate (SA), tetraethyl orthosilicate (TEOS), Methylene blue (MB), 1,3-diphenylisobenzofuran (DPBF), calcein acetoxymethyl ester (Calcein AM), propidium iodide (PI), 2,7-dichlorofluorescin diacetate (DCFH-DA). All chemical reagents are used without any further purification.

2. Characterization

UC and DC fluorescence spectra were collected on a Steady-state transient fluorescence spectrometer. The crystal phase of samples, N_2 adsorption-desorption isotherms, pore-size distributions, UV-vis absorption spectra and Fourier-transform Infrared (FT-IR) spectra were all carried out according to our previously mentioned characterization.

3. Synthesis of OA-stabilized LDNPs

For $NaGdF_4$:Yb,Ce,Ho core nanoparticles, 1.0 mmol $RECl_3$ including 0.49 mmol $GdCl_3$, 0.2 mmol $YbCl_3$, 0.3 mmol $CeCl_3$ and 0.01 mmol $HoCl_3$ was respectively added into a flask containing OA (6 mL) and ODE (15 mL). Subsequently, the system was gradually heated to 120 °C and stirred under vacuum for 30 min. After the temperature was up to 156 °C, the system was continuously stirred for 30 min. Then cooled down to room temperature. 10 mL CH_3OH solution including 0.1 g NaOH and 0.1482 g NH_4F were added into the above-cooled mixture, then the system was also heated to 120 °C and stirred under vacuum for 30 min. Subsequently, after the aimed temperature of 280 °C was achieved, 60 min of stirring was carried out under an N_2 atmosphere. Finally, the products were centrifugated and re-dispersed in cyclohexane.

For the preparation of core-shell, as-prepared $NaGdF_4$:Yb,Ce,Ho core nanoparticles (1 mmol), 0.5 mmol of $RE(CF_3COO)_3$ (RE = 0.78Gd + 0.2Yb + 0.02Er) and 1 mmol CF_3COONa was added to another flask containing OA and ODE (1:1, 15 mL). The solution was gradually heated to 120 °C under vacuum with stirring for 30 min and maintained at 290 °C for 1 h in an inert atmosphere of N_2. After the solution was cooled down to room temperature, multi-time centrifugations were carried out with cyclohexane and ethanol. Similarly, the resultant products were stored in cyclohexane.

For the synthesis of LDNPs, using the same core-shell preparation method, the obtained above samples and $RE(CF_3COO)_3$ (RE = (0.3-x)Gd + 0.2Yb + xCe, 0.5 mmol) and 1 mmol CF_3COONa were mixed into another clean three-neck flask containing 15 mL of OA and 15 mL of ODE. Repeated similar steps, we can get the resultant sample (LDNPs). The $NaGdF_4$:Yb,Ce,Ho@$NaGdF_4$:Yb,Er@$NaGdF_4$:0.2Yb,0.4Ce nanoparticles were designated as

LDNPs and used for subsequent preparation and characterization.

4. Synthesis of LDNPs@mSiO$_2$

2 mL of LDNPs cyclohexane solution was added to 20 mL of an aqueous solution containing 0.1 g of CTAB. Then the solution was vigorously stirred to form a homogeneous solution for 10 h. Before the system was heated to 70 °C with vigorously stirring, 40 mL of the deionized water, 300 μL of NaOH solution (2 M), and 6 mL of ethanol should be added. After the addition of TEOS (180 μL), the mixture was stirred vigorously for 10 min. The resultants were collected, and then dissolved in 50 mL of ethanol containing 0.3 g of NH4NO3 and refluxed for 2 h to remove CTAB.

5. Synthesis of LDNPs@CMSNs

Firstly, LDNPs@mSiO$_2$ (100 mg) and 0.8 mmol of $MnCl_2 \cdot 4H_2O$ were dispersed in 40 mL of the aqueous solution. Secondly, 2 mL of $NH_3 \cdot H_2O$ (25%) was added into another 40 mL of the aqueous solution containing NH_4Cl (20 mmol) and $Cu(NO_3)_2 \cdot 3H_2O$ (0.8 mmol). After mixing by stirring, and transferring into a Teflon-lined autoclave, the temperature was increased to 180 °C for 0.5 h. The resultant was centrifuged with deionized water several times and dried in a vacuum.

6. Preparation of SA/LDNPs@CMSNs

20 mg of LDNPs@CMSNs and 120 mg of SA were dissolved in 100 mL of PBS (pH=7.2) and stirred for 0.5 h. Afterward, SA/LDNPs@CMSNs were collected. Next, 10 mg of SA/LDNPs@CMSNs were added in 20 mL of PBS containing 0.1 mg of FITC to acquire FITC-labelled SA/LDNPs@CMSNs for further preparation and characterization; Then, the solution was stirred overnight; Finally, FITC-decorated SA/LDNPs@CMSNs was obtained

by centrifugation and washing and with PBS several times.

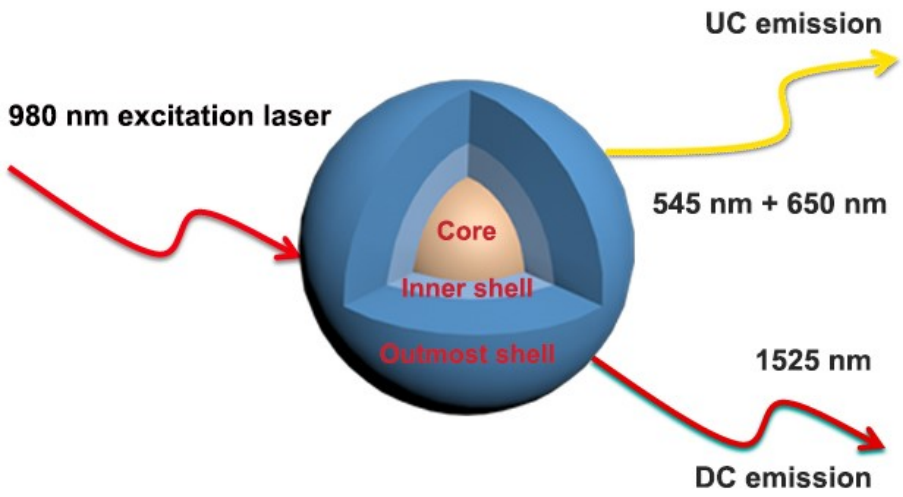

Fig. S1. Structure diagram of $NaGdF_4$:Yb,Ce,Ho core@$NaGdF_4$:Yb,Er inner shell@ $NaGdF_4$:Yb,Ce outmost shell nanoparticles.

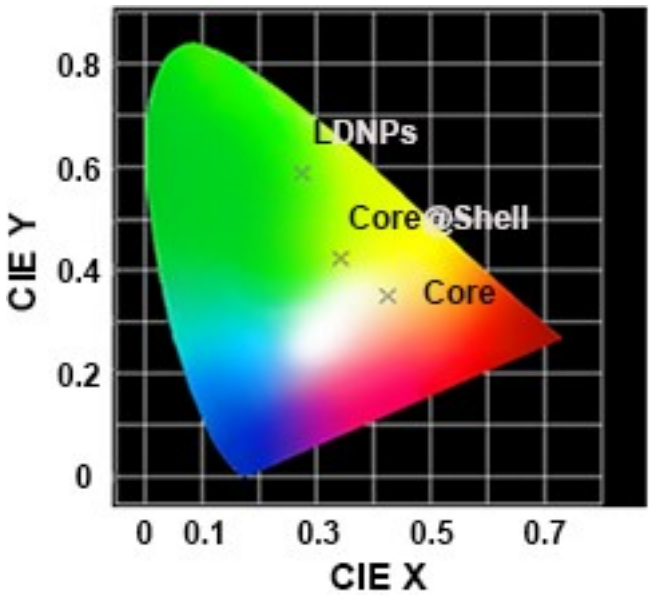

Fig. S2. Corresponding CIE image of the $NaGdF_4$:Yb,Ce,Ho core nanoparticles, LDNPs and $NaGdF_4$:Yb,Ce,Ho@$NaGdF_4$:Yb,Er nanoparticles.

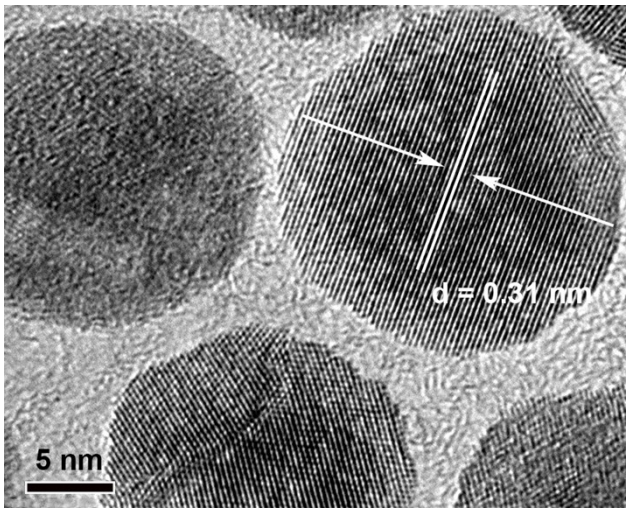

Fig. S3. High resolution-TEM image of $NaGdF_4$:Yb,Ce,Ho core nanoparticles.

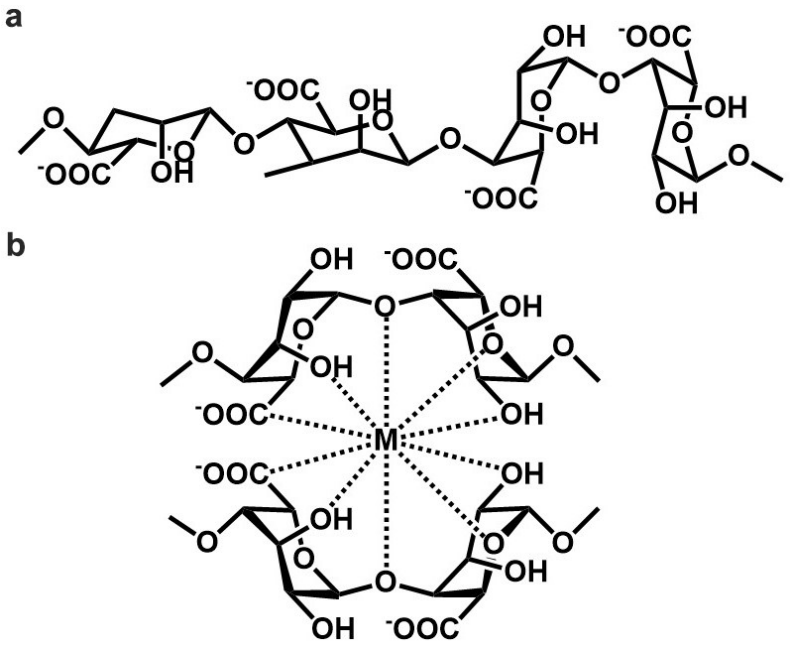

Fig. S4. The chemical structure of SA natural macromolecule (a) and the coordination effect between the SA and metal ions (b).

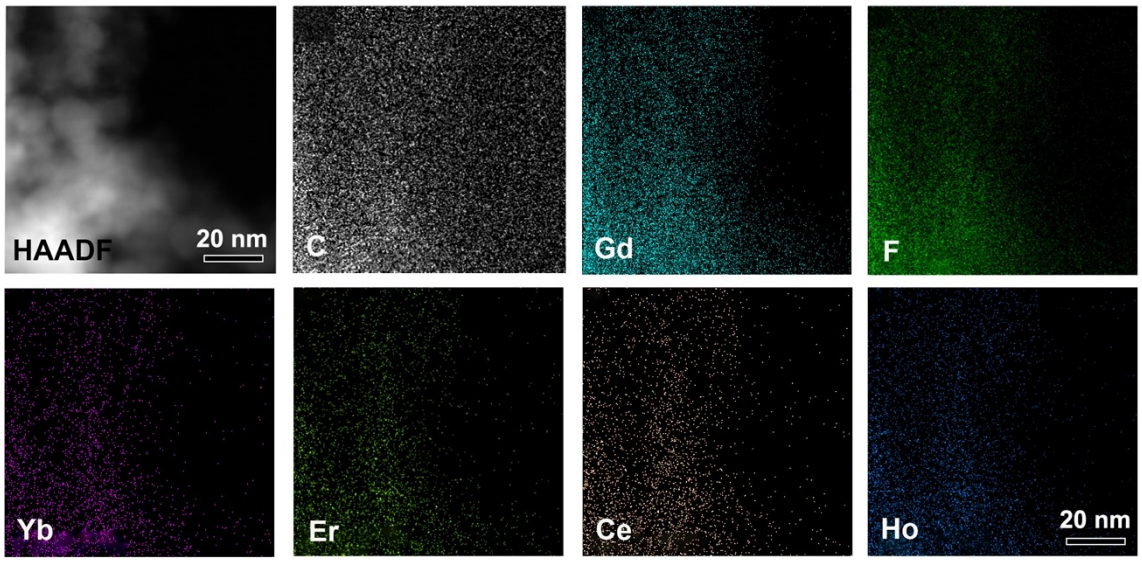

Fig. S5. STEM image and corresponding elemental mapping images of LDNPs@CMSNs.

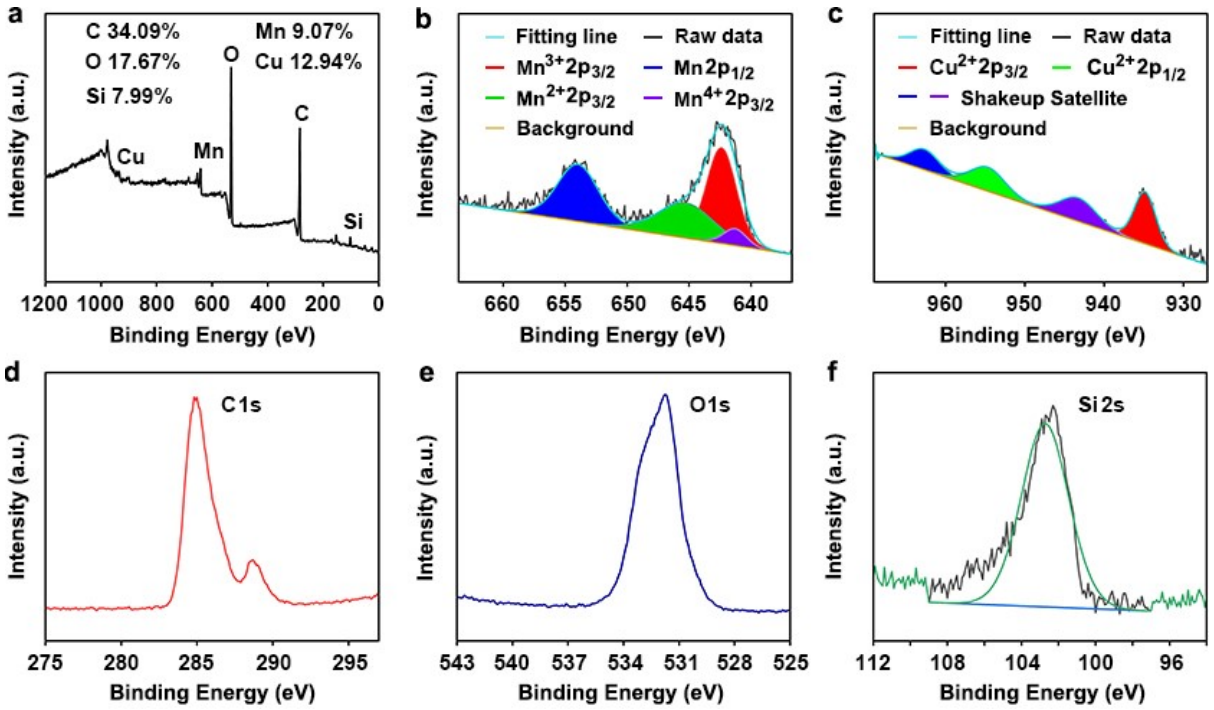

Fig. S6. XPS spectra of LDNPs@CMSNs: survey spectrum (a), Mn 2p (b), Cu 2p (c), C 1s (d), O 1s (e), Si 2s (f).

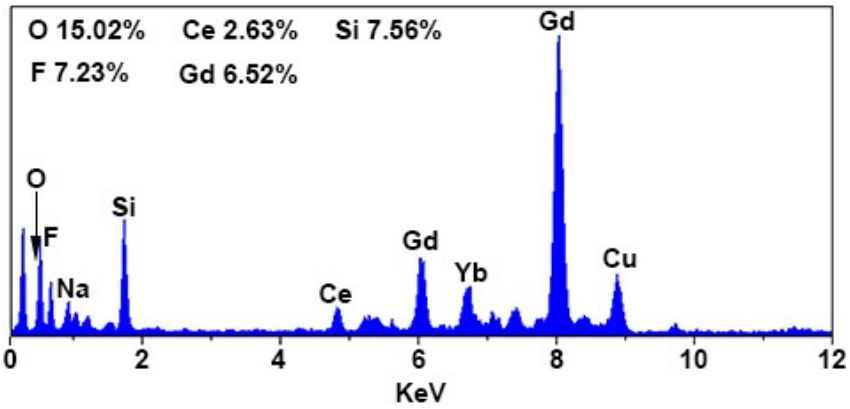

Fig. S7. EDS spectrum of LDNPs@mSiO_2.

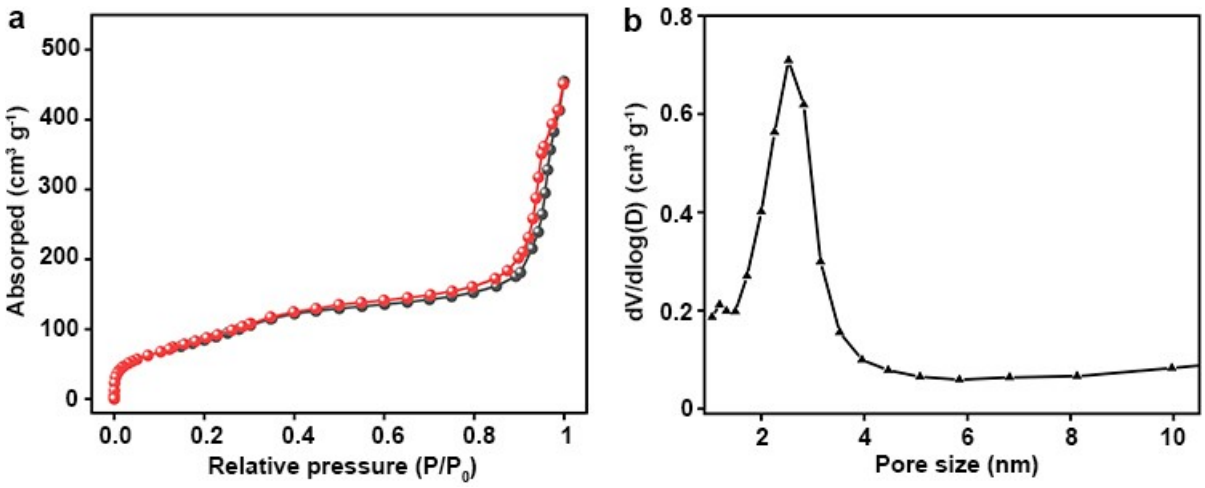

Fig. S8. N_2 adsorption-desorption isotherms (a) and corresponding pore-size distribution (b) of the LDNPs@mSiO_2.

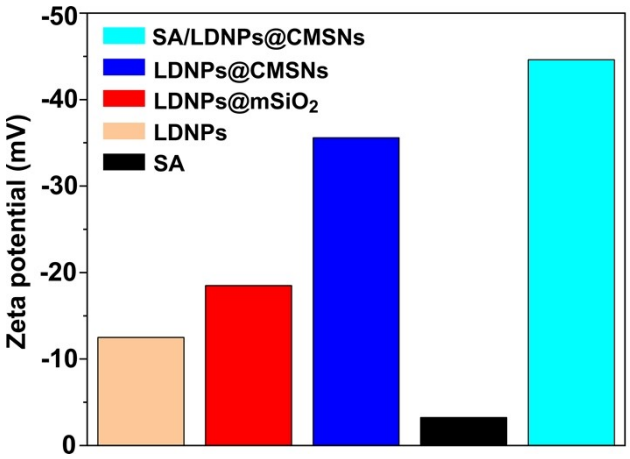

Fig. S9. The Zeta potentials of different samples.

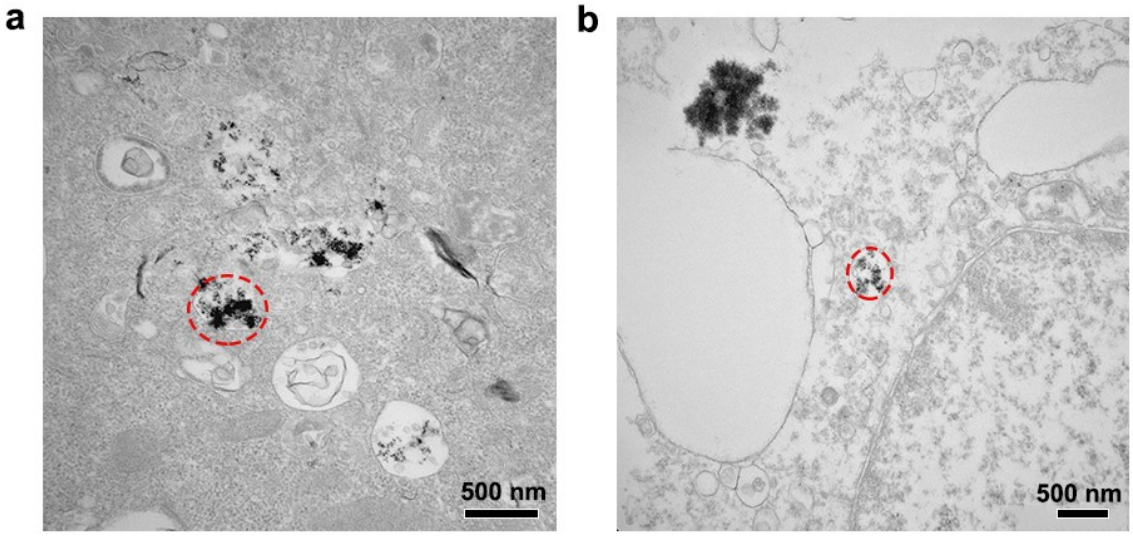

Fig. S10. Bio-TEM images of HeLa cells incubated with SA/LDNPs@CMSNs for 0.5 h (a) and 12 h (b).

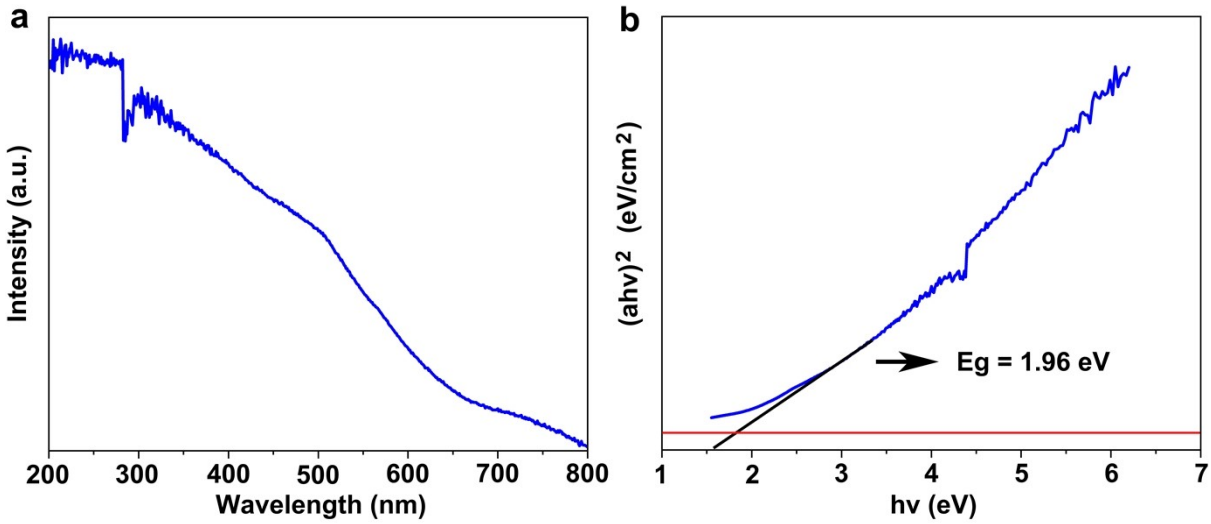

Fig. S11. UV-vis diffuse absorbance spectra (a), the corresponding plots of $(\alpha h\nu)^2$ (b) of samples.

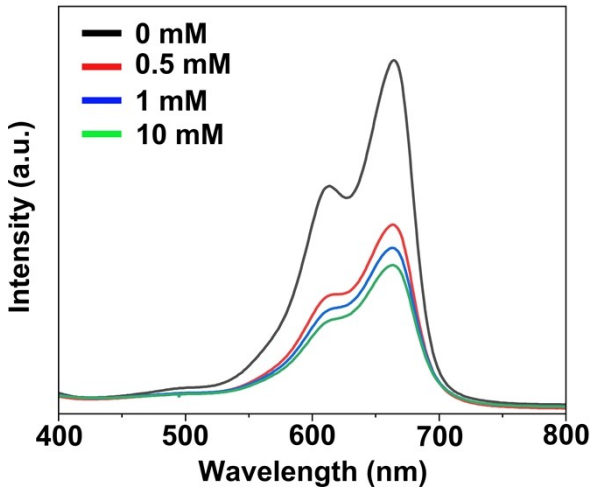

Fig. S12. The absorption spectra of MB solutions with GSH (10 mM) and different concentrations of H_2O_2-treated SA/LDNPs@CMSNs (500 μg/mL).

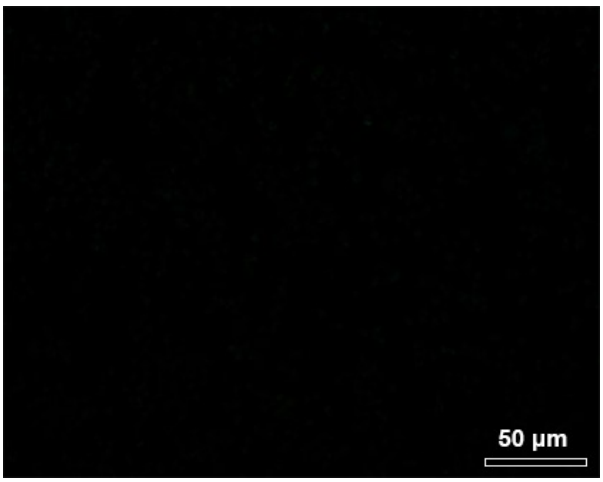

Fig. S13. The CLSM image of HeLa cells incubated with oxidized DCFH-DA.

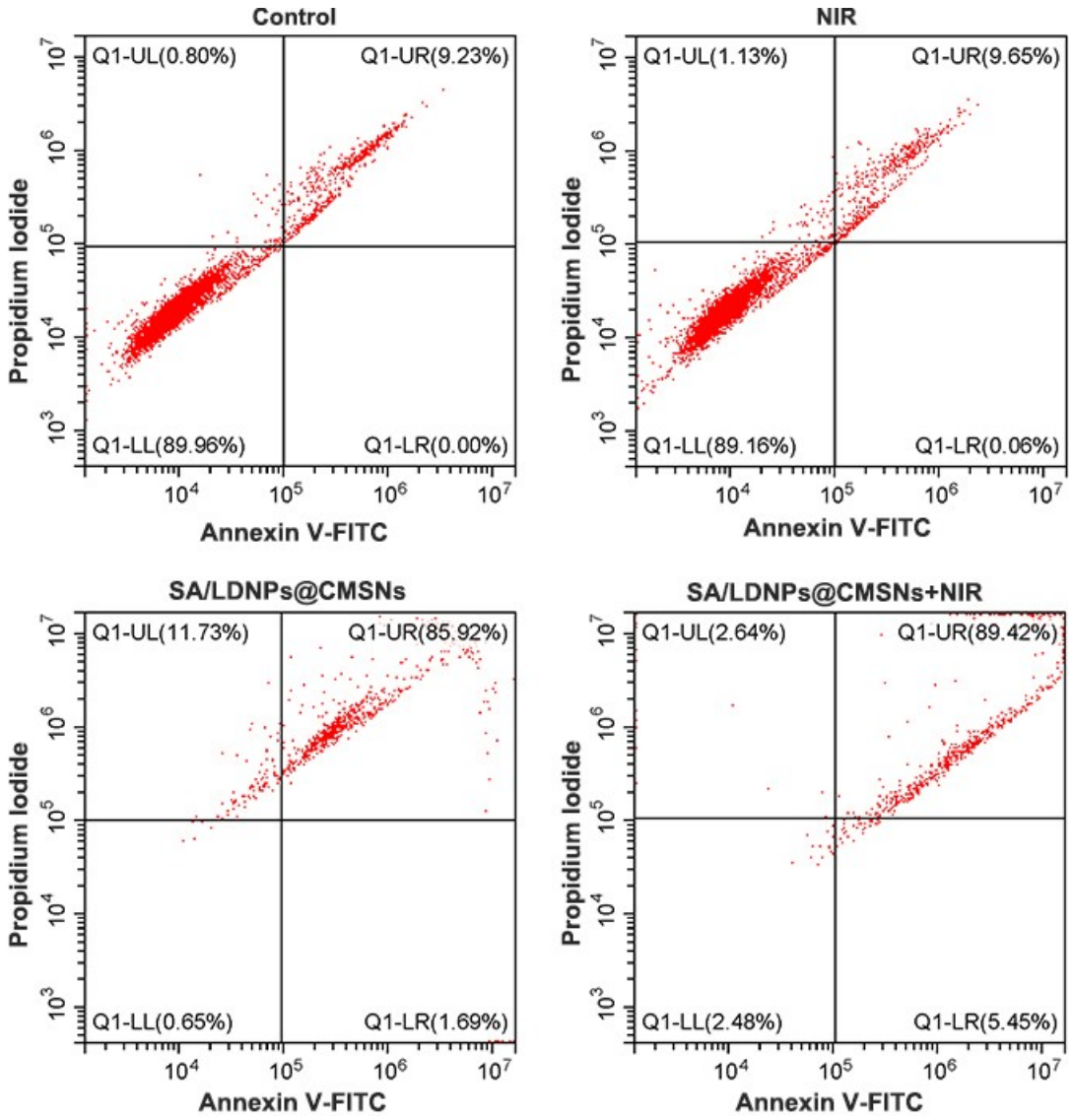

Fig. S14. Flow cytometry analysis of the effects of different formulations for 24 h on HeLa cell apoptosis.