Electronic Supplementary Material (ESI) for Inorganic Chemistry Frontiers.

NIR-triggered Biodegradable MOF-coated Upconversion Nanoparticles for Synergetic Chemodynamic/Photodynamic Therapy with Enhanced Efficacy

Man Zou[a,b], Yajie Zhao[b, c], Binbin Ding[b,c], Fan Jiang[b, c], Yeqing Chen[a], Ping'an Ma[b,c]*, Jun Lin*[a,b,c]*

[a]*School of Applied Physics and Materials, Wuyi University, Jiangmen, Guangdong 529020, P. R. China.*

[b]*State Key Laboratory of Rare Earth Resource Utilization, Changchun Institute of Applied Chemistry, Chinese Academy of Sciences, Changchun, 130022, P. R. China*

[c]*University of Science and Technology of China, Hefei, 230026, P. R. China*

Corresponding Authors:

[*]Yeqing Chen: yqchenwyu@126.com

[*]Ping'an Ma: mapa675@ciac.ac.cn

[*]Jun Lin: jlin@ciac.ac.cn

pH-Responsive Cu^{2+} Release

In order to measure the release behavior of Cu^{2+}, UCZF (10 mg) was dispersed in PBS solution (5 mL, pH = 6.5 and 7.4). Then, the supernatant was removed at a predetermined time point. ICP was used to characterize the copper ion released from UCZF. The supernatant was diluted 10 times before testing.

GSH Depletion

GSH indicator was used to detect the depletion of GSH. In short, GSH solution (0.01 mM, pH=6.5) was stirred with PBS, UZ and UCZ respectively. After centrifugation, the change of GSH absorbance at 412 nm was detected by UV-Vis.

ROS Generation

1, 3-Diphenylisobenzofuran (DPBF) probe was used to detect the production of extracellular $^1O_2$. The specific process is as follows, 2 mg UCZRF is uniformly dispersed in 2 mL PBS solution containing 20 μL DPBF (10 mm), ultrasonically processed in the dark; then irradiated under 980 nm near-infrared laser (1 W cm^{-2}) for different periods of time (0 , 2, 4, 6 and 8 min). The other group was not irradiated by 980 nm near infrared as a control group. The characteristic absorption of DPBF was detected by ultraviolet-visible absorption spectrum. Measure the hydroxyl radicals (•OH) produced by the Fenton-like reaction with MB, mix MB (10 mg mL^{-1}) with all materials were mixed in PBS buffer (pH=6.5) containing GSH (1 mM) and H_2O_2 (1 mM), and also use UV-visible absorption spectroscopy to detect the characteristic absorption of MB.

Cell uptake and localization of UCZRF

Cell uptake and localization were certified by intracellular fluorescence. First, 4T1 cells seeded in a 12-well plate at a density of 10^5 cells per well are incubated with UCZRF (60 μg mL^{-1}) for 1 h, 4 h and 6 h. Then wash three times and fix for 15-20 min. Next, incubate with DAPI for 10 min after washing, and finally the cells were washed repeatedly with PBS and image with a fluorescence microscope.

Intracellular ROS Detection

For in vitro ROS detection, ROS production was detected by a cell permeable dye 2',7'-dichlorofluorescin diacetate (DCFH-DA), which is non-fluorescent and could be easily oxidized to green fluorescent 2',7'-dichlorofluorescein (DCF) by intracellular ROS. Briefly, 4T1 cells were seeded into 6-well culture plates at a density of 0.8×10^5 cells per well and treated with (a) PBS; (b) UZRF only; (c) UCZRF only; (d) 980 nm laser + UZRF; (e) 980 nm laser + UCZRF. After 12 h of incubation in the dark, the culture media were replaced by fresh culture media, and exposed to a 980 nm laser (1 W cm^{-2}) for 5 min. Then, the ROS probe was added to each well and the mixture was incubated for 30 min at 37 °C. Finally, the cells were washed repeatedly with PBS. The fluorescence was routinely detected by exciting at 485 nm and measuring emission at 545 nm with an inverted florescence microscope system (Nikon Ti–S).

Cell Viability Assays

L929 cells were cultured in DMEM (or 1640) at 37 °C under 5% CO_2. In total, 6000 cells were seeded into 96 well plates and incubated with different concentrations (0, 3.75, 7.5, 15, 30, 60 μg mL^{-1}) of UCZRF dispersed in DMEM (or 1640) for 12 h. Relative cell viabilities were detected by the standard 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. Then, for in vitro therapy, 4T1 cells were incubated with UZRF, UCZRF, UZRF+ and UCZRF+ for 4 h, and then the irradiation group was irradiated with a 980 nm laser at a power density of 1 W cm^{-2} for 5 min. The cell viability was calculated using a typical MTT assay.

Antitumor Study

Female Balb/c mice were purchased from the Center of Experimental Animals, Jilin University (Changchun, China). The animal experiments were performed under the criteria of The National Regulation of China for Care and Use of Laboratory Animals. Thirty mice (about 20 g) were subcutaneously injected with 1×10^6 4T1 cells to obtain tumor bearing mice and were separated into six groups [control, light irradiation (NIR), UZRF, UZRF+, UCZRF and UCZRF+ treated groups]. Each group contained six mice, and all materials are used at a concentration of 5.0 mg kg^{-1} body weight. Nanoparticles were injected intravenously on the first. Laser (980 nm) (1W cm^{-2}, 5 min) was used during the irradiation treatment after 24 h post injection. The tumor sizes were measured every 2 days and body weights were recorded at the same time. The tumor volume was estimated by $L \times W^2 /2$,

where L and W refer to the length and width of the tumor, respectively.

Histological Examination

After 14 days of treatment, the heart, liver, spleen, lung and kidney of the control and UCZRF plus NIR treated mice were excised and dehydrated with buffered formalin. Finally, all types of dehydrated tissues were embedded in liquid paraffin to obtain stained slices for H&E staining by optical microscope.

List of Abbreviations in This Study

Full Name	**Abbreviations**
Rose Bengal	RB
Cu-doped ZIF-8	Cu/ZIF-8
$NaYF_4$:20% Yb,2% Er@ZIF-8@F127	UZF
$NaYF_4$:20% Yb,2% Er@ZIF-8/RB@F127	UZRF
$NaYF_4$:20% Yb,2% Er@Cu/ZIF-8@F127	UCZF
$NaYF_4$:20% Yb,2% Er@Cu/ZIF-8/RB@F127	UCZRF

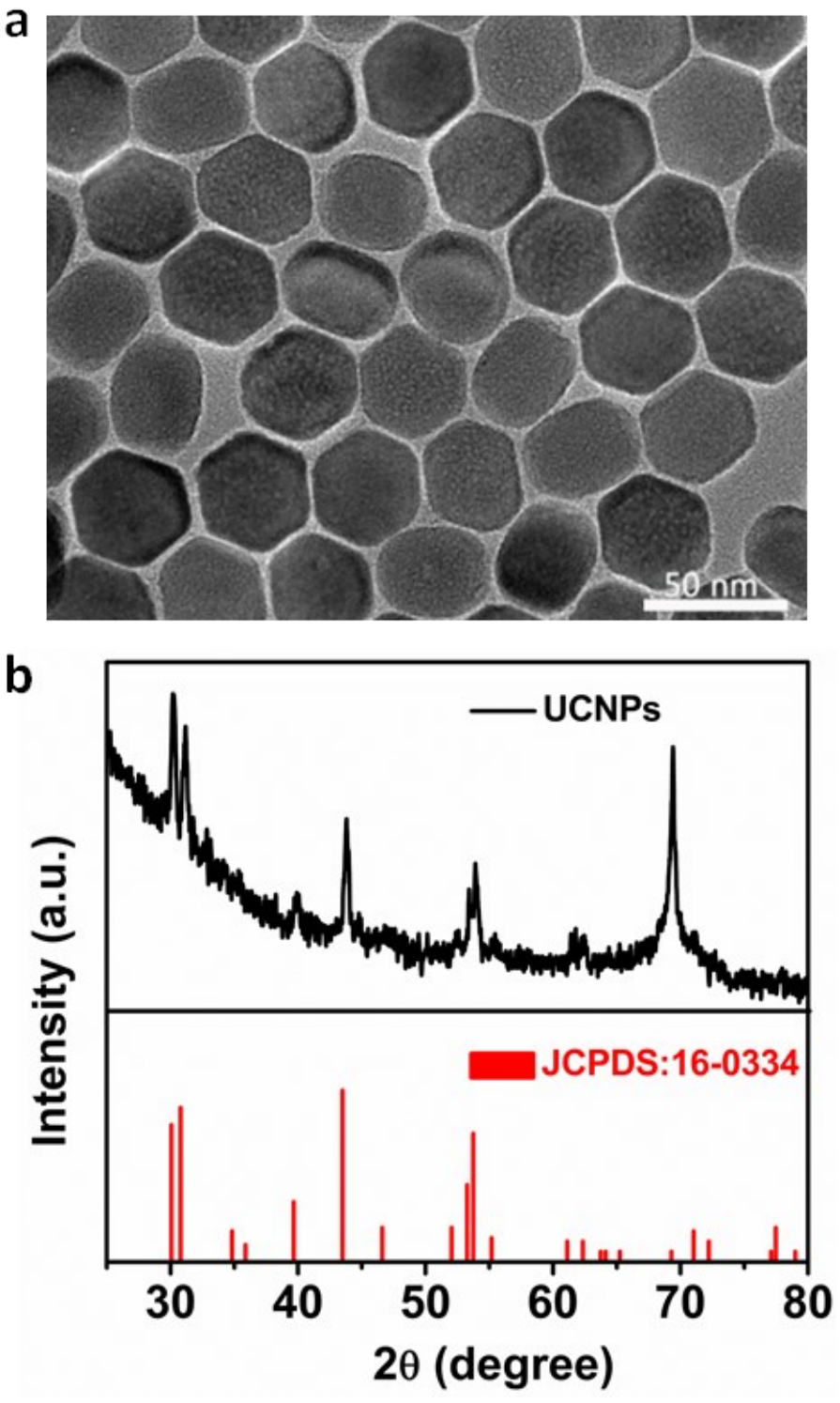

Figure S1. (a) TEM images of UCNPs. (b) XRD patterns of UCNPs.

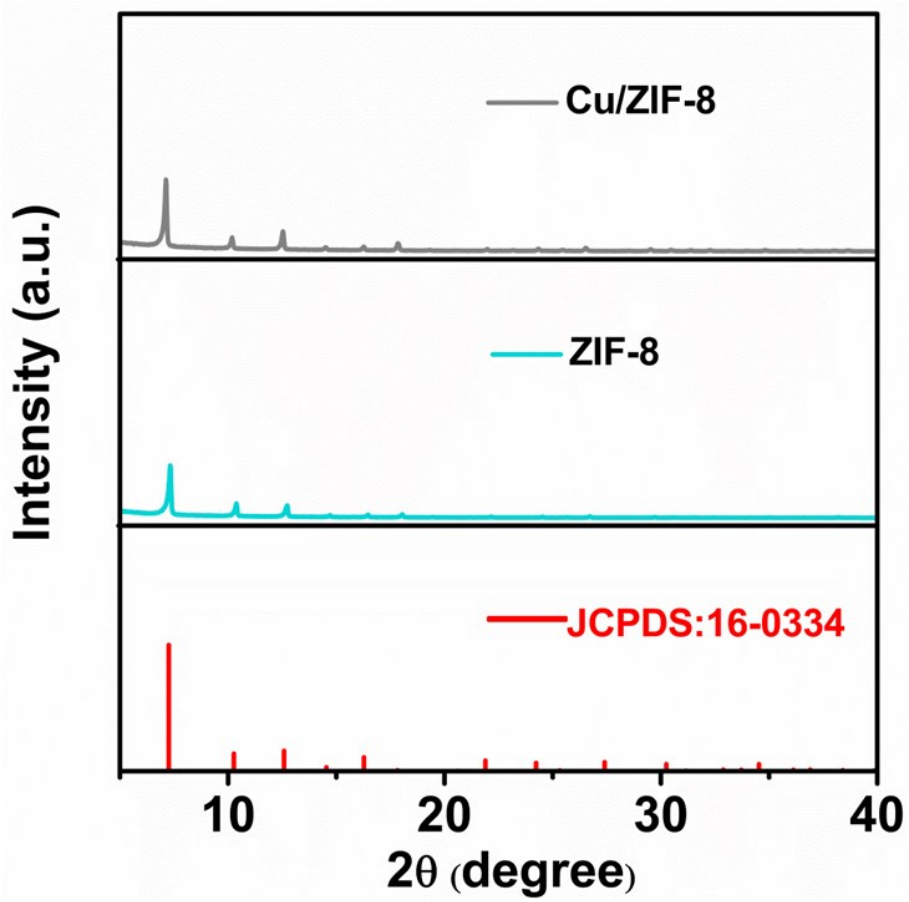

Figure S2. XRD patterns of Cu/ZIF-8 and ZIF-8, which could be well indexed to the ZIF-8 (JCPDS No. 43-0144).

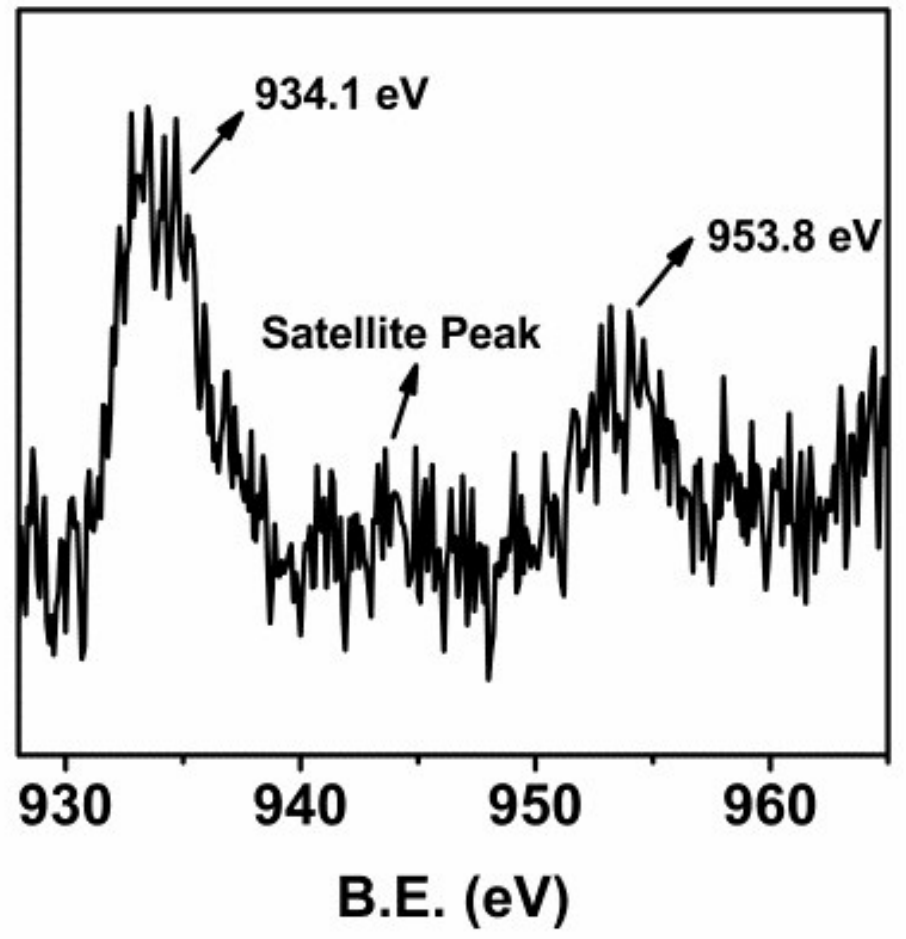

Figure S3. High-resolution XPS Cu^{2+} spectra of UCZRF. The peaks are located at 934.1 and 953.8 eV of Cu^{2+}, respectively.

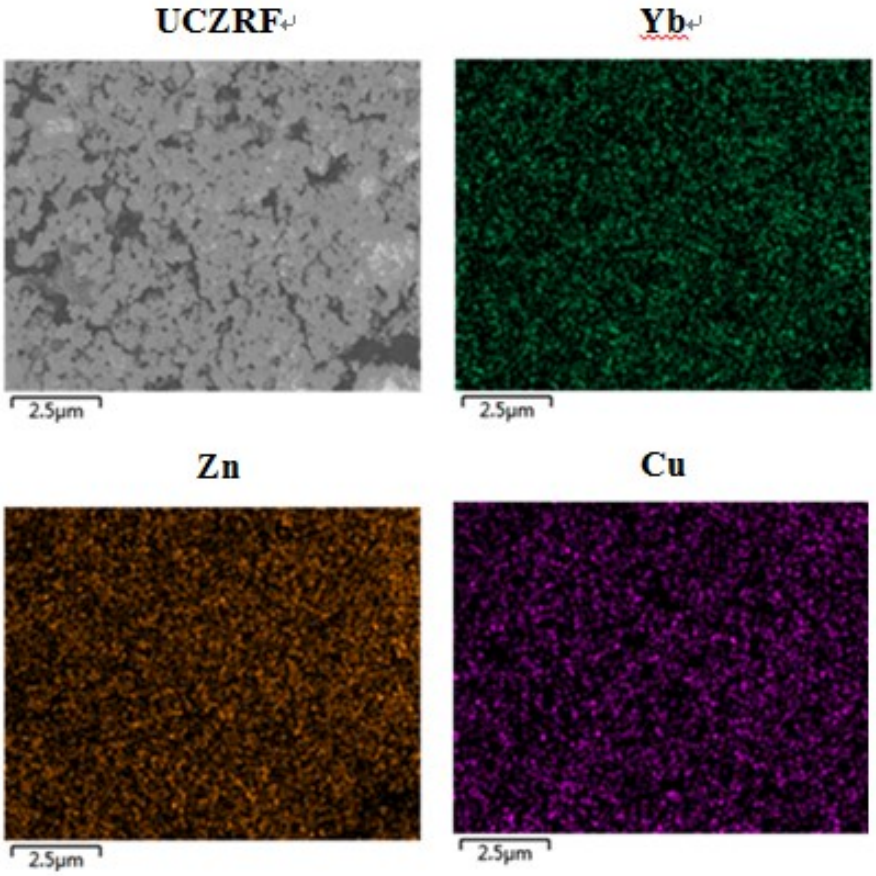

Figure S4. SEM images of UCZRF and the element mappings of Yb, Zn, and Cu.

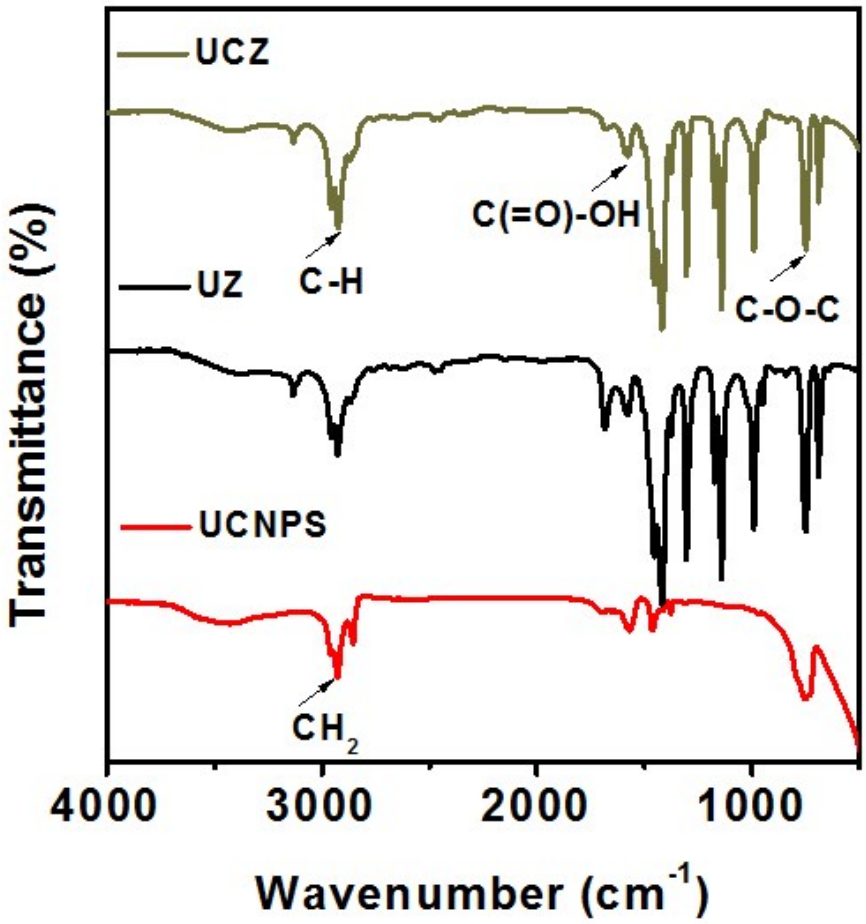

Figure S5. FT-IR spectra of the UCNPs, UZ, and UCZ.

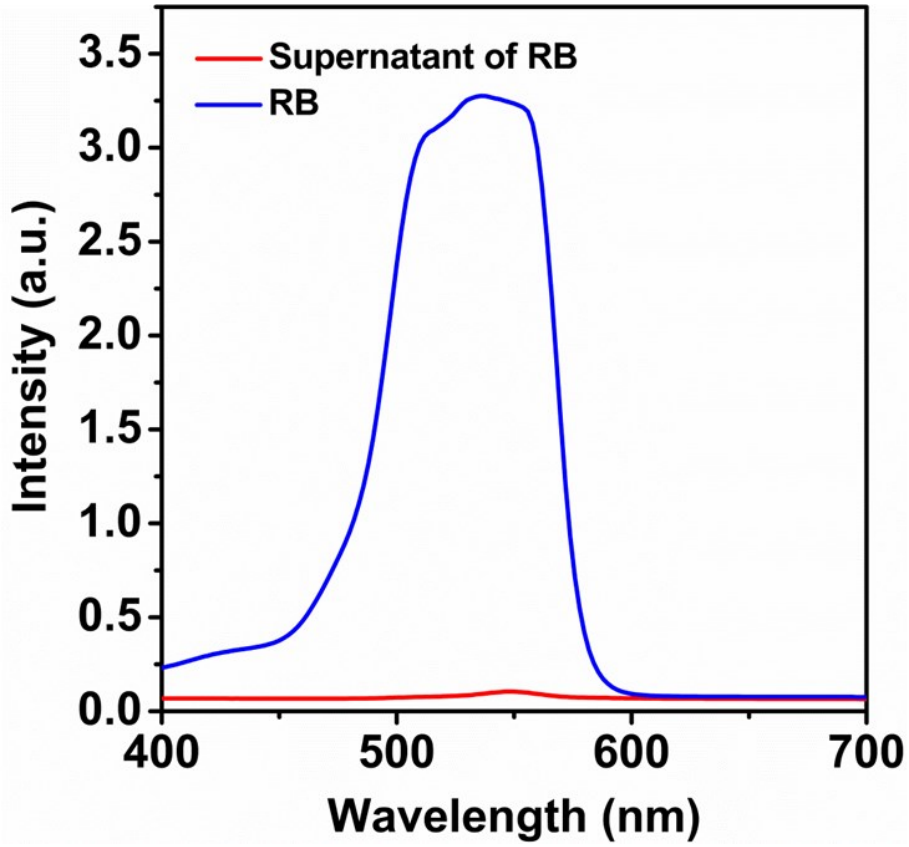

Figure S6. UV−vis absorption spectra of pure RB and supernatant of RB.

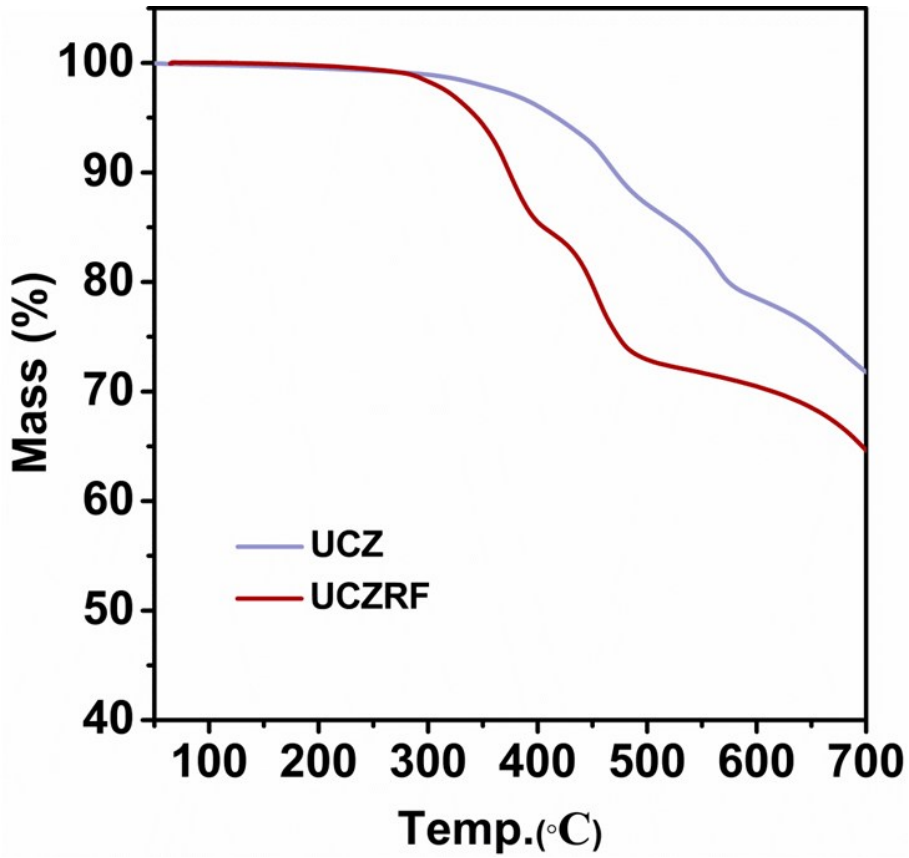

Figure S7. TGA curves of UCZ and UCZRF.

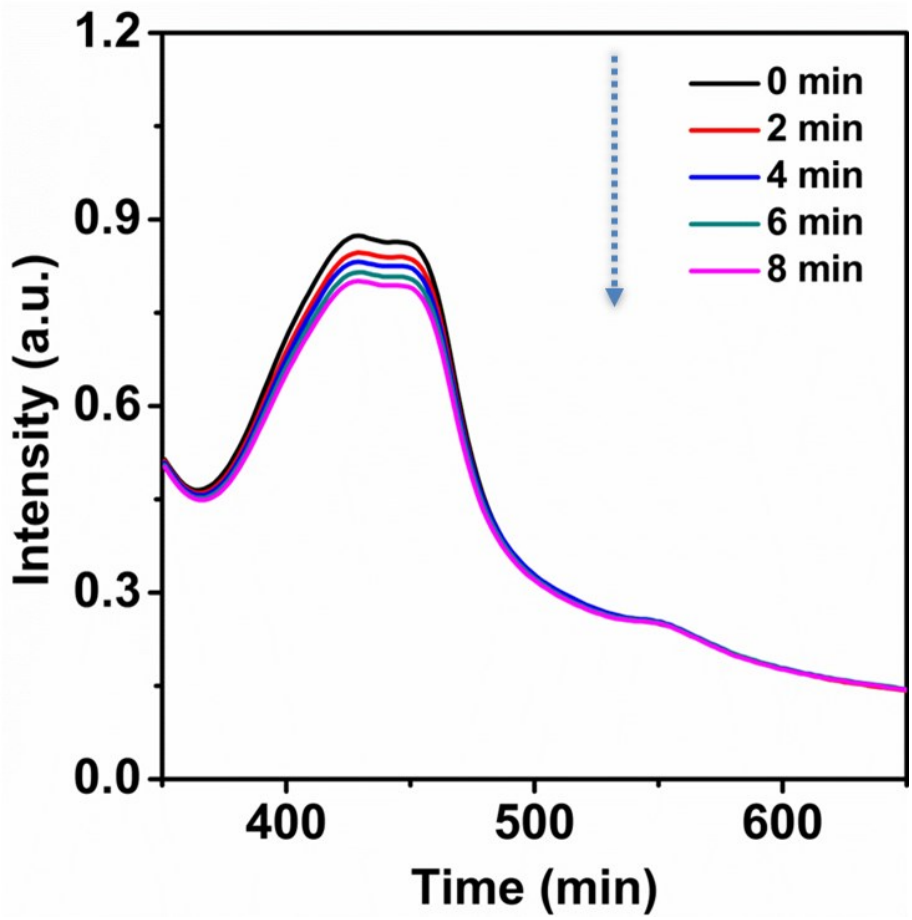

Figure S8. Absorbance changes of DPBF treated with UCZRF without 980 nm laser irradiation at different times.

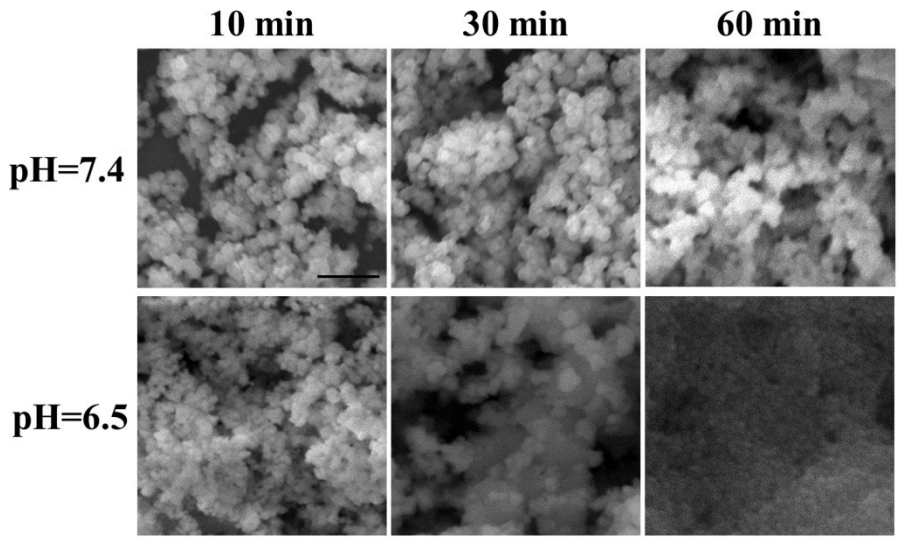

Figure S9. SEM images of UCZRF after immersed in PBS solution (pH = 6.5 and 7.4) for different time intervals. Scale bar indicates 200 nm. The crystal decomposed after soaking in PBS buffer with pH = 6.5 for 10 min.

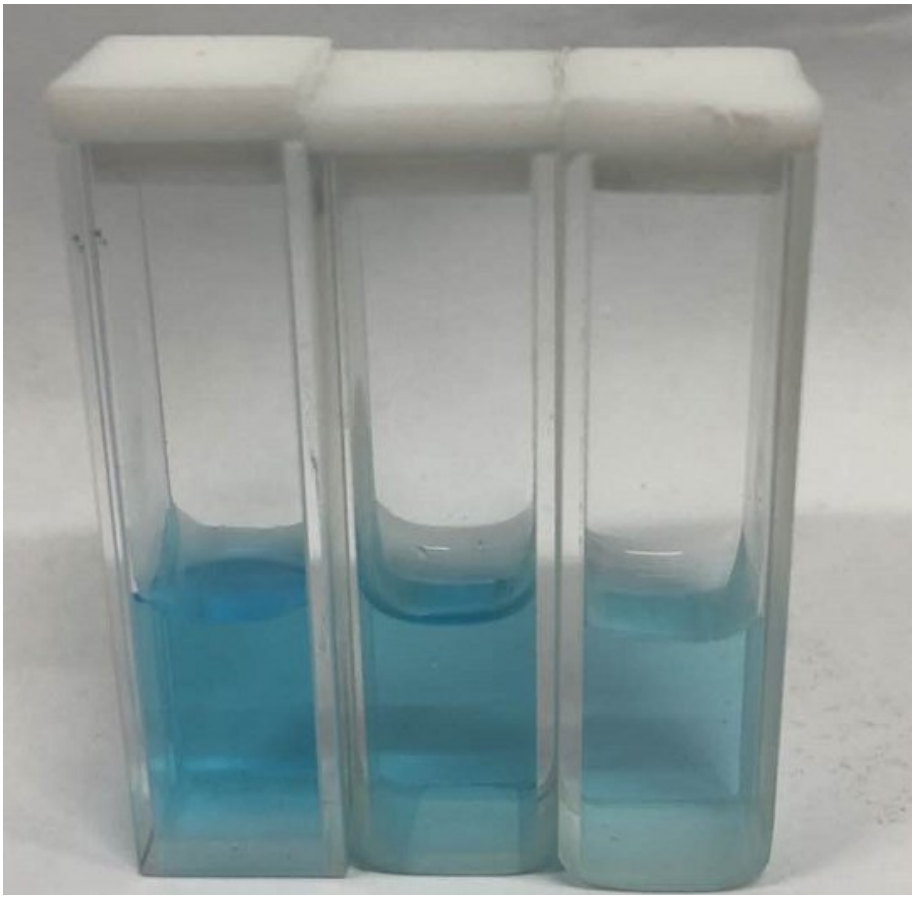

Figure S10. Degradation process of MB after incubation with various conditions (H_2O_2, H_2O_2+UCZRF, H_2O_2+UCZRF+GSH).

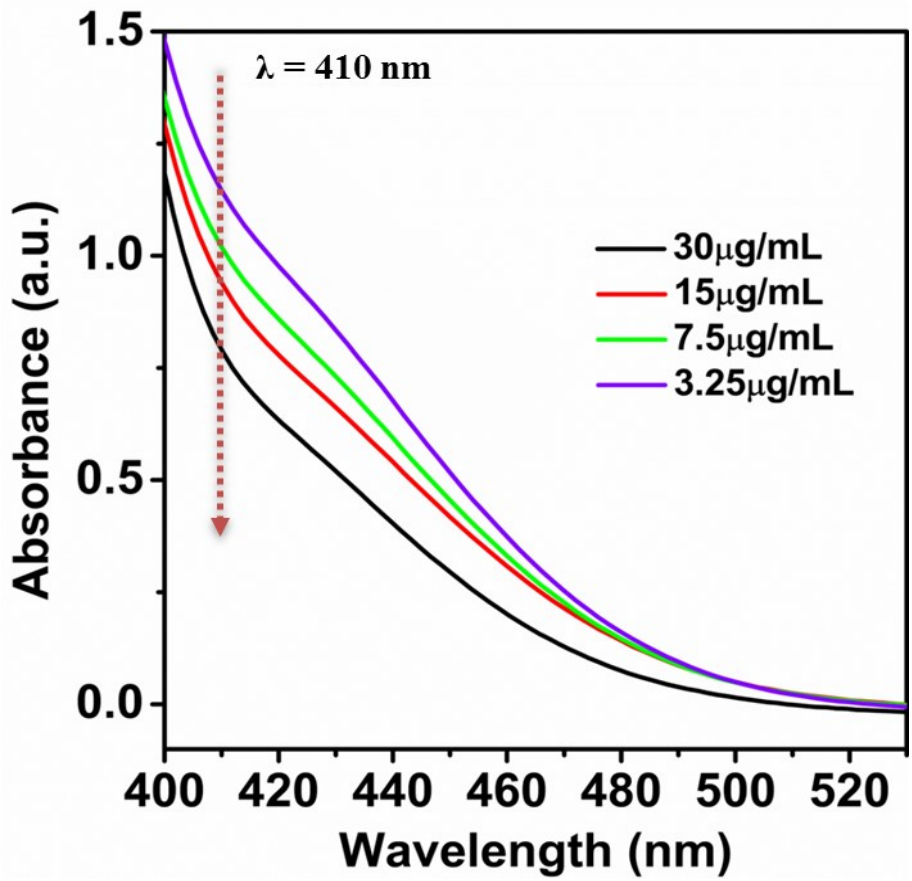

Figure S11. Absorbance changes of DNTB treated in different concentrations of UCZRF (3.25, 7.5, 15, and 30 μg/mL).

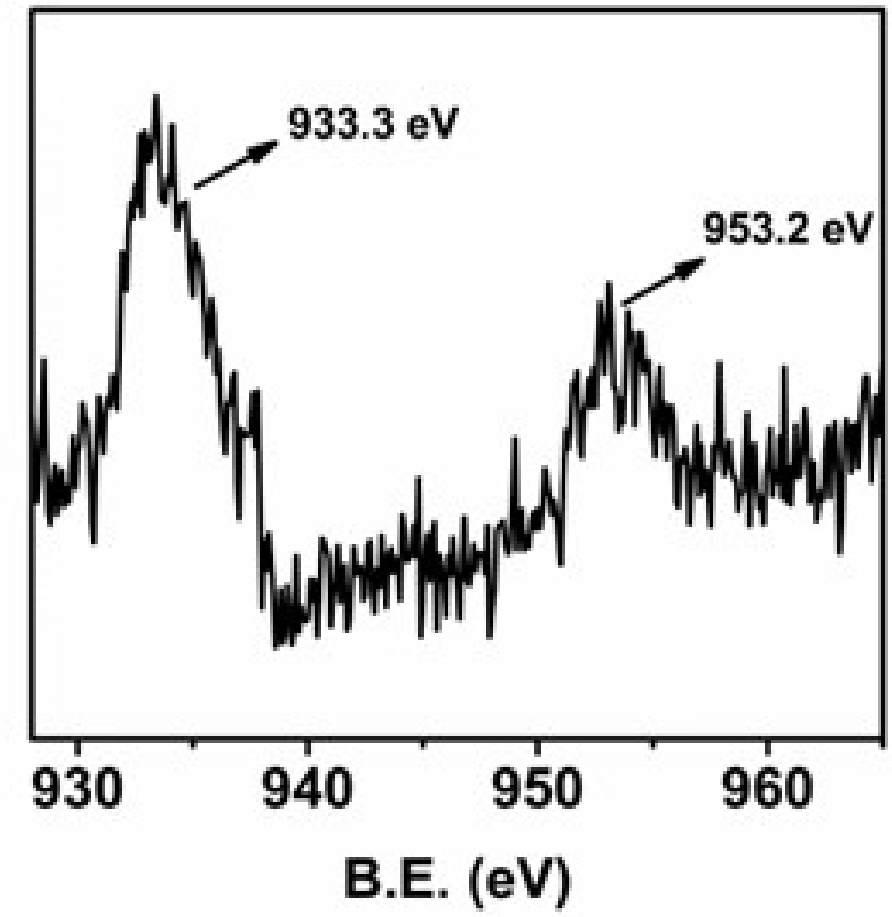

Figure S12. High-resolution XPS Cu^{2+} spectra of UCZRF after incubating with GSH. Compared with UCZRF, the binding energy shifted from 934.1 and 953.8 eV of Cu^{2+} to 933.3 and 953.2 eV, respectively. Besides, the satellite peak at around 942.3 eV dissappears, indicating the existance of Cu^{+}.

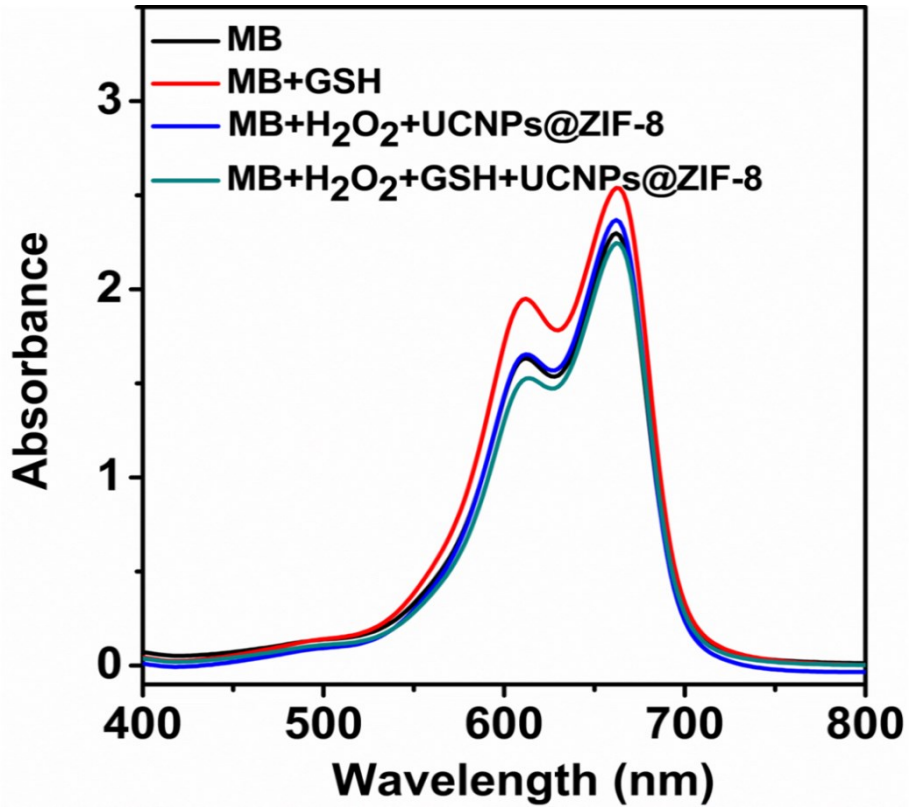

Figure S13. The UV-vis absorption spectra of MB under different treating conditions.

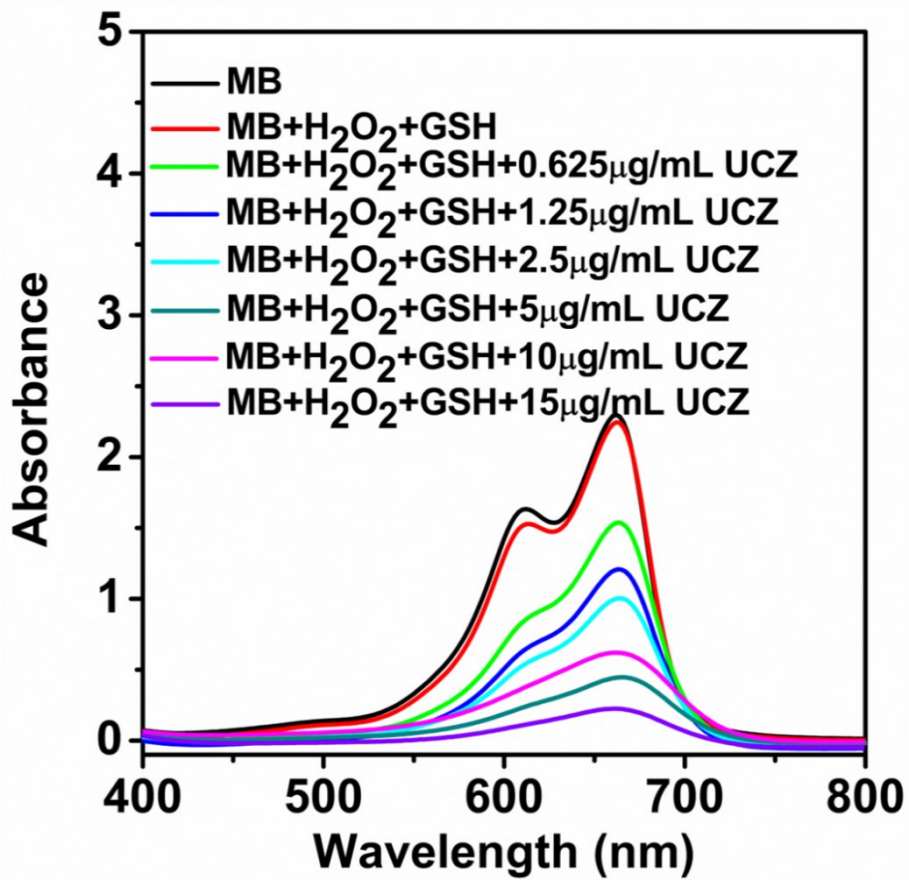

Figure S14. The absorption spectra of MB treated by UCZRF in different concentrations (0, 0.625, 1.25, 2.5, 5, 10, and 15 μg/mL).

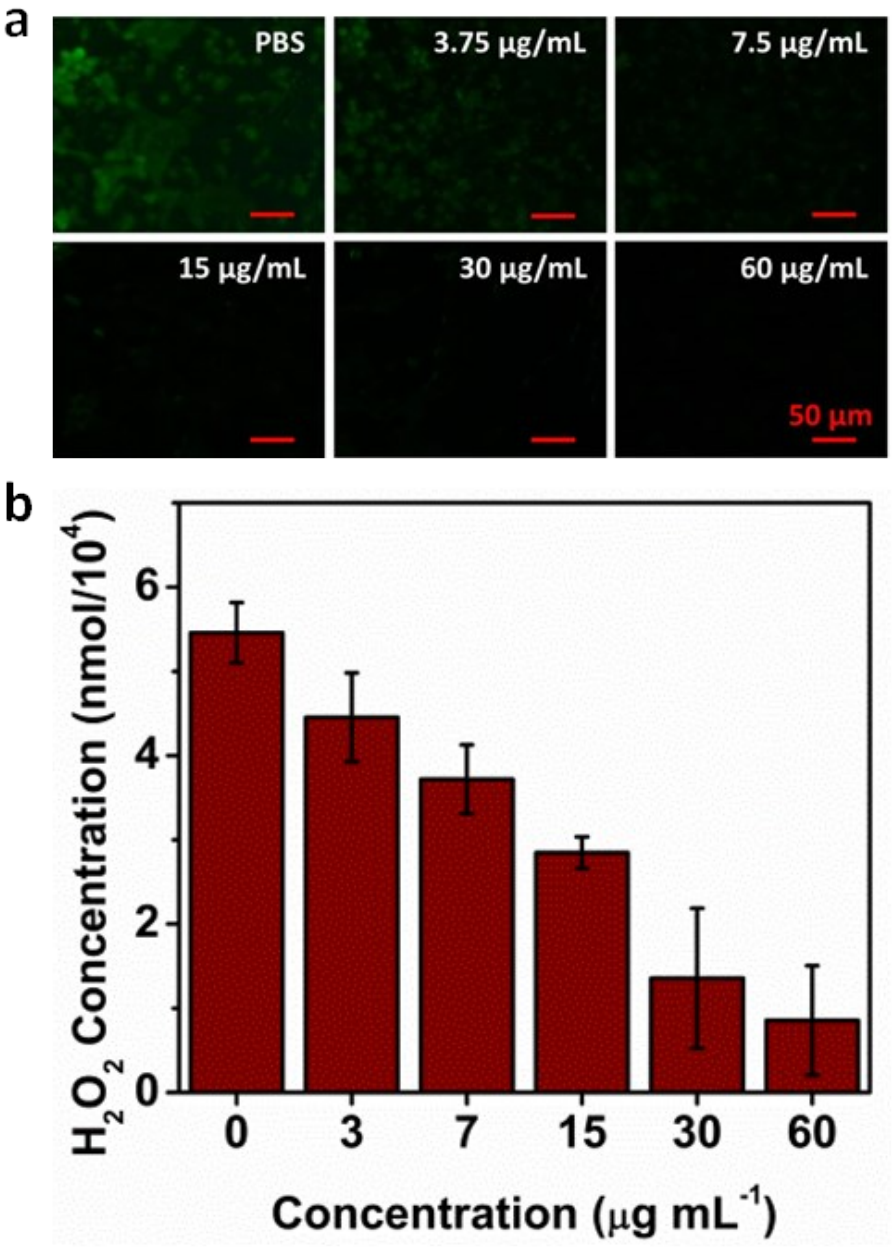

Figure S15. (a) Intracellular GSH detections of 4T1 cells with various concentrations (0, 3.75, 7.5, 15, 30, 60 μg/mL) and (b) H_2O_2 detections of 4T1 cells with various concentrations (0, 3, 7, 15, 30, 60 μg/mL).