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Supplementary Materials for

Highly bioactive zeolitic imidazolate framework-8–capped nanotherapeutics for efficient reversal of reperfusion-induced injury in ischemic stroke

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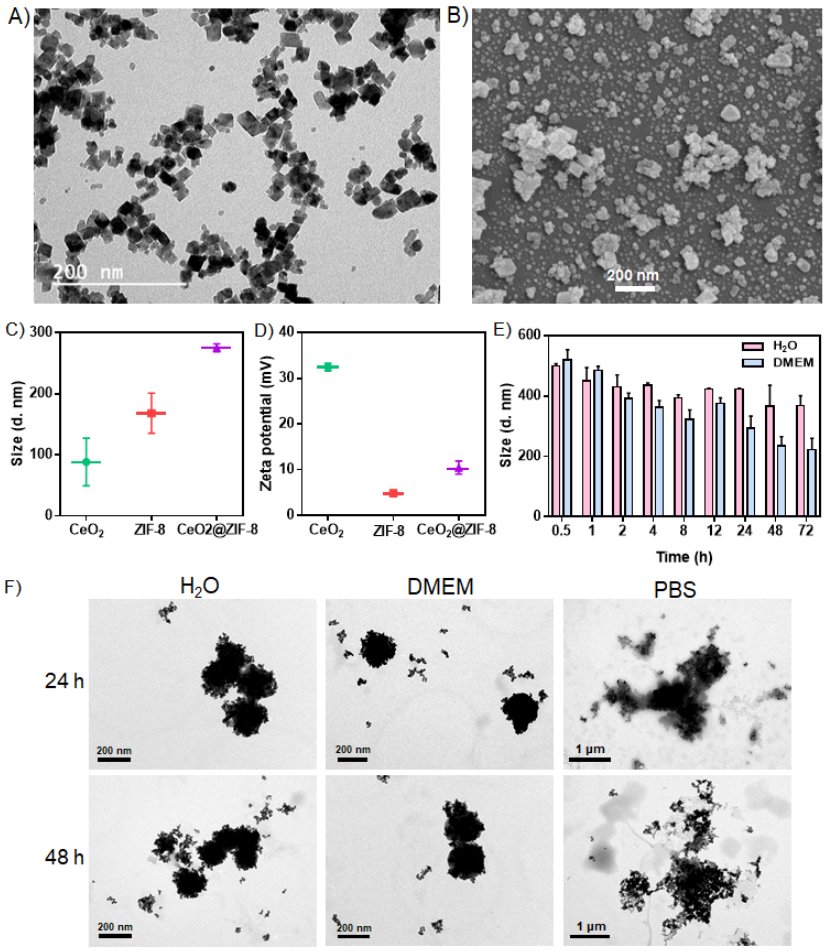


Fig. S1. Characterization of the synthetic nanomaterials. TEM image (**A**) and SEM image (**B**) of CeO_2 polyhedron. The size distribution (**C**) and zeta potential (**D**) of CeO_2, ZIF-8 and CeO_2@ZIF-8 nanomaterials. (**E**) Stability of CeO_2@ZIF-8 in aqueous solution and DMEM medium. (**F**) TEM images of CeO_2@ZIF-8 in H_2O, DMEM (with 10% FBS), PBS (pH 7.4) after shaking for 24 h and 48 h.

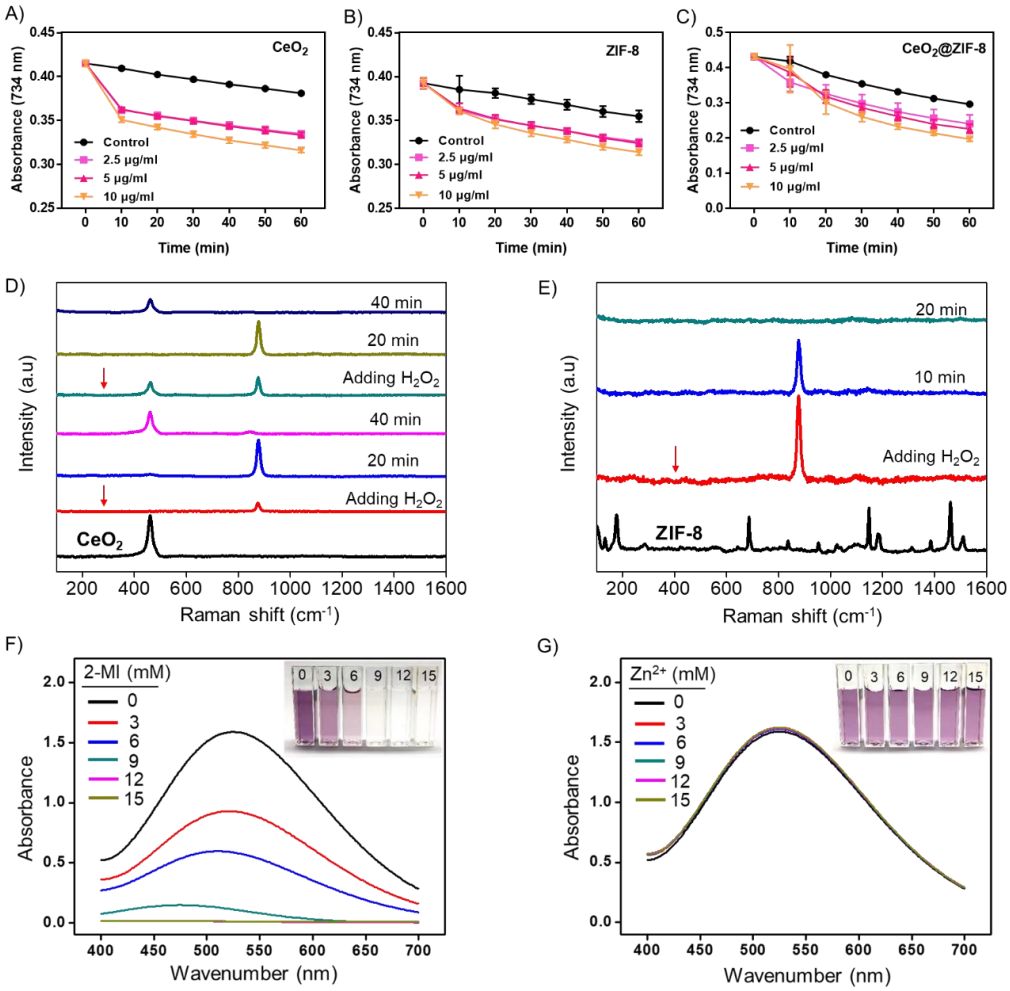
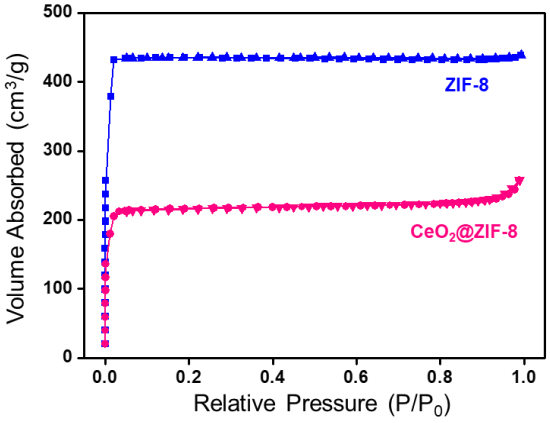


Fig. S2. Examination of free radical scavenging activity of the nanotherapeutics. Examination of antioxidant activities of CeO_2 (**A**), ZIF-8 (**B**) and CeO_2@ZIF-8 (**C**) by ABTS assay. Raman spectra of CeO_2 (**D**) and ZIF-8 (**E**) after reaction with H_2O_2 at various time points. The $^{\bullet}OH$ scavenging ability of 2-methylimidazolate (2-MI) (**F**) and $Zn(NO_3)_2{\cdot}6H_2O$ (Zn^{2+}) (**G**) at indicated concentrations as examined by UV–Vis spectroscopic analysis of salicylic acid (SA) interaction with $^{\bullet}OH$ generated by Fenton reaction with Fe^{2+}/H_2O_2 system for 10 min.

A)



B)

Sample	Surface Area (m^2/g)	Pore Volume (cm^3/g)	Pore Size (nm)
ZIF-8	1325.5741	0.670980	2.0247
CeO_2@ZIF-8	651.2260	0.360747	1.9758

Fig. S3. N_2 adsorption-desorption isotherm and pore property analysis. (**A**) N_2 adsorption-desorption isotherm for ZIF-8 and CeO_2@ZIF-8 NPs. (**B**) The surface area, pore volume and pore size of ZIF-8 and CeO2@ZIF-8.

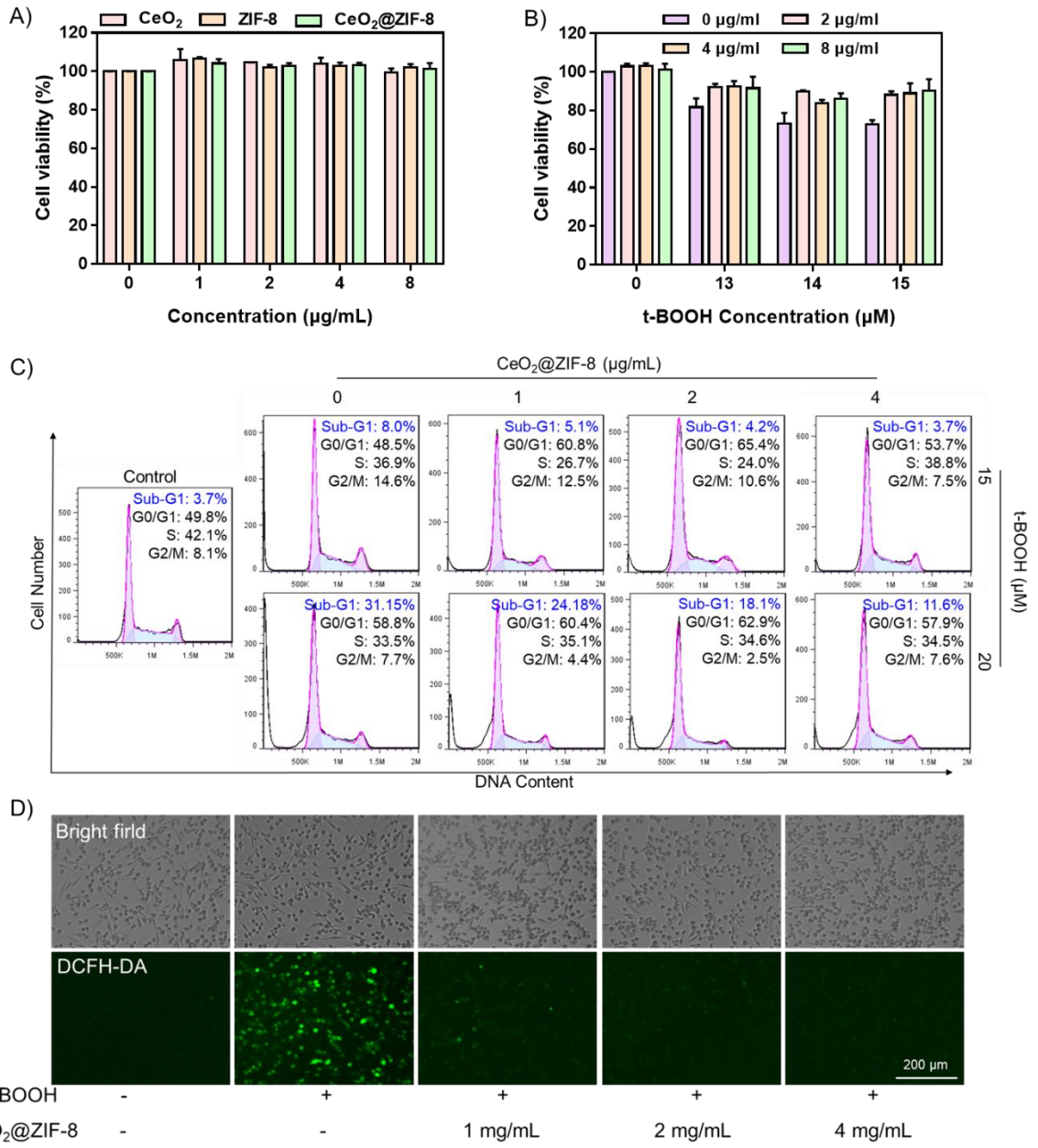


Fig. S4. CeO_2@ZIF-8 inhibits cell apoptosis and ROS overproduction induced by t-BOOH. (**A**) The cell viability of PC-12 cells treated with different concentrations of CeO_2, ZIF-8 and CeO_2@ZIF-8 NPs for 48 h. (**B**) CeO_2@ZIF-8 attenuated t-BOOH-induced cytotoxicity in PC-12 cells damaged with different concentration of t-BOOH. (**C**) CeO_2@ZIF-8 reversed t-BOOH-induced apoptosis in PC-12 cells for 48 h. Cell cycle distribution was analysed by flow cytometric. (**D**) CeO_2@ZIF-8 blocks t-BOOH (15 μM)-induced ROS generation in PC-12 cells for 2 h.

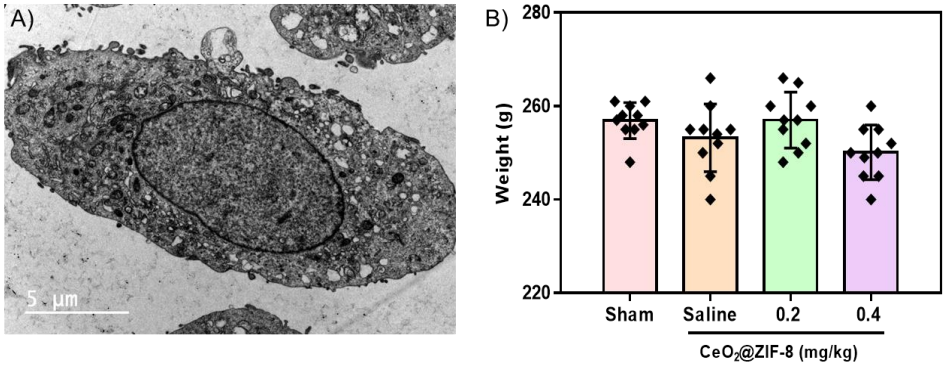


Fig. S5. Change in cell microstructure and mice body weight. (**A**) TEM image of PC-12 cells in control group. (**B**) The body weight of MCAO mice with different treatment (3 days).

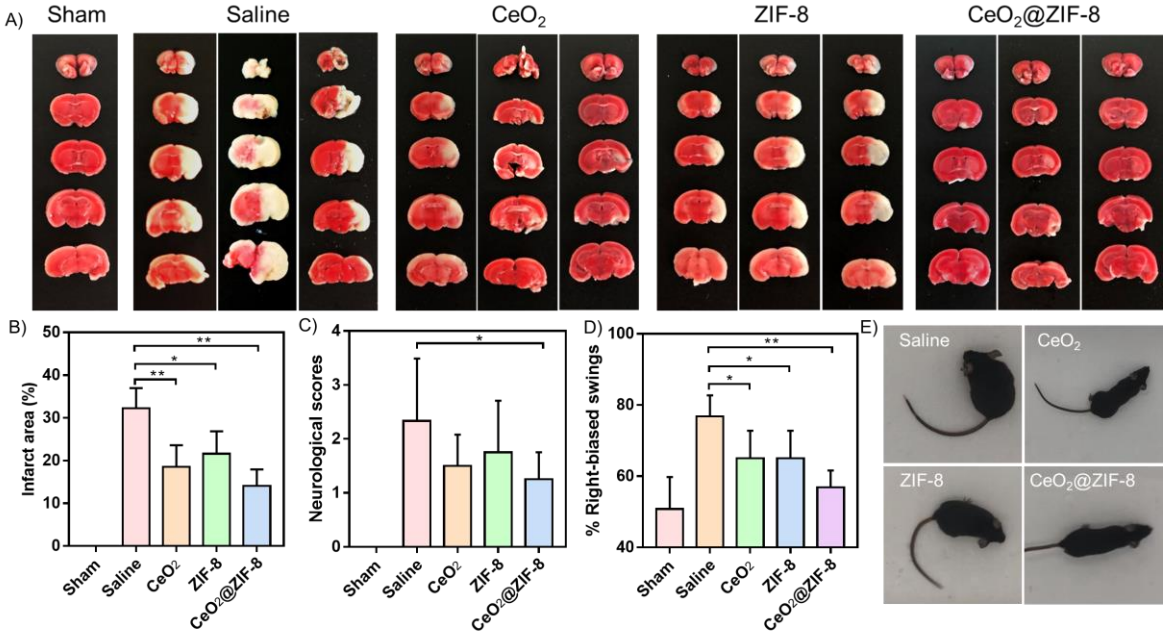


Fig. S6. Brain protection effects of CeO_2@ZIF-8 in C57 MCAO mice. (**A**) Representative images of TTC-stained brain slices after treatment with CeO_2, ZIF-8 and CeO_2@ZIF-8 at 0.4 mg/kg for 3 days in MCAO mice model (n = 4). (**B**) Corresponding infarct areas of different groups analyzed by Image J (n =4). (**C**) Neurological scores of MCAO mice after treatment with CeO_2@ZIF-8 for 3 days (n=4). (**D**) Changes in function and behavior of MCAO mice after different treatments as evaluated by elevated body swing test (EBST). (**E**) Representative images of behavioral recovery of MCAO mice after different treatments. (Photo credit: Guanning Huang, Jinan University).

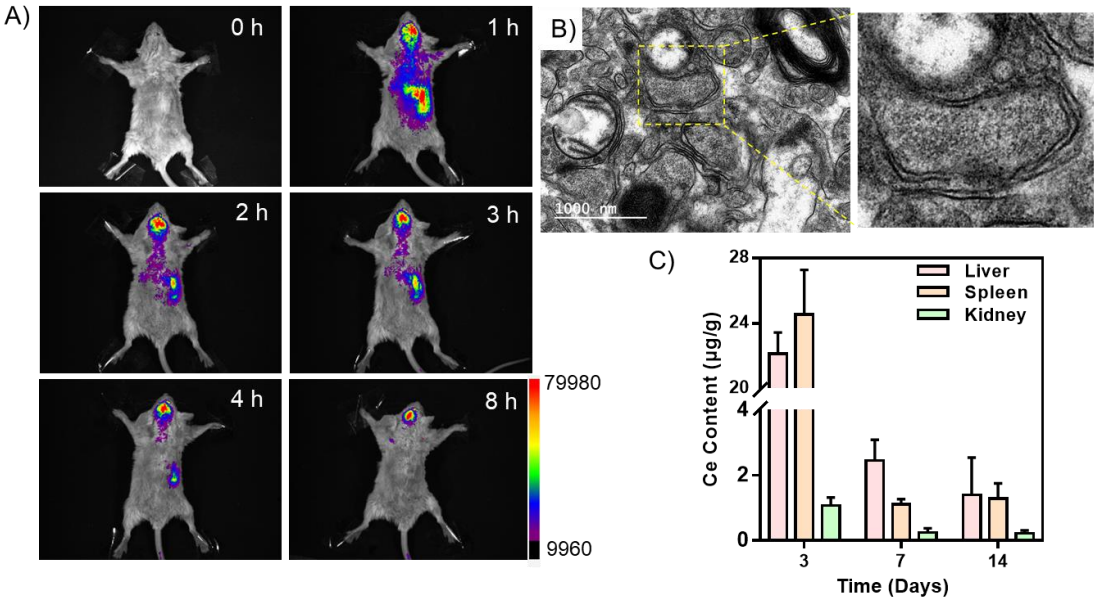


Fig. S7. Fluorescence imaging and biodistribution analysis of CeO_2@ZIF-8 in vivo. (**A**) Fluorescence imaging of accumulation of ICG-labelled CeO_2@ZIF-8 (0.4 mg/kg) in MCAO mice model at different time points. (**B**) TEM image of brain tissue of MCAO mice with saline injection only. (**C**) Biodistribution of Ce in the mice main organs (including liver, spleen and kidney) after intravenous injection with CeO_2@ZIF-8 (0.4 mg/kg) for different periods of time (n =5).

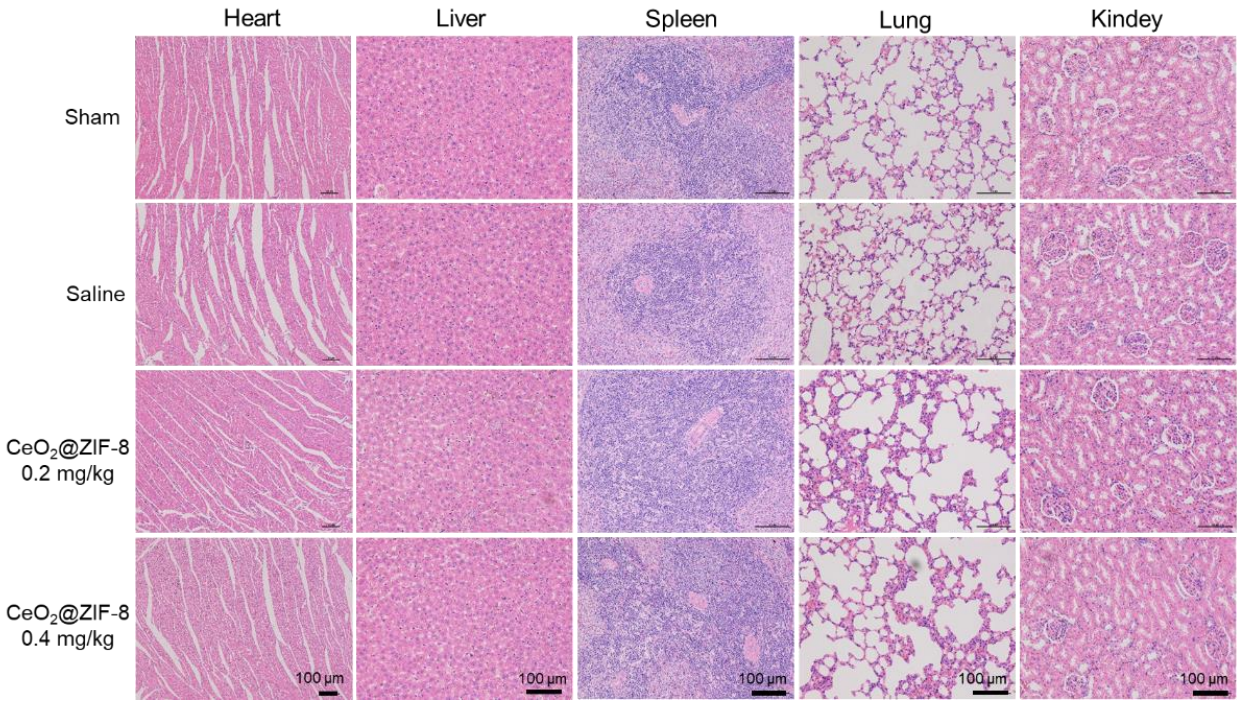


Fig. S8. H&E staining of the heart, liver, spleen, lung, and kidney after treatment with CeO_2@ZIF-8 for 3 days in MCAO mice model.

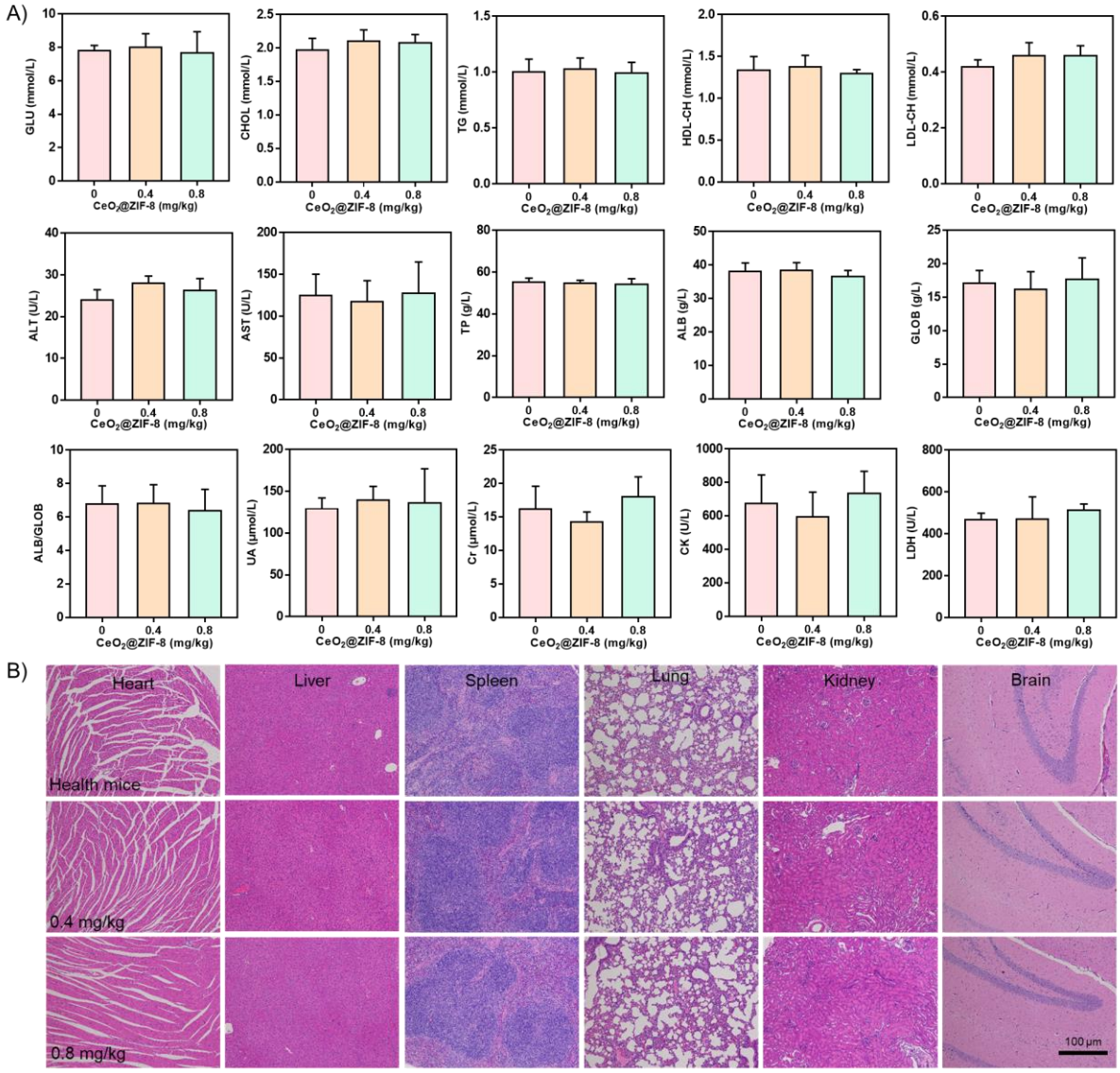


Fig. S9. Toxicity evaluation of CeO_2@ZIF-8 in vivo. (**A**) Haematological analysis of blood glucose, blood fat, the function of liver, kidney and heart in CeO_2@ZIF-8-treated mice for 14 days (n=6). (**B**) H&E staining of the heart, liver, spleen, lung, kidney and brain tissue after treatment with CeO_2@ZIF-8 for 14 days (n=6).

Table S1. Pharmacokinetic parameters of CeO_2 nanopolyhedra and CeO_2@ZIF-8 composite nanomaterials.

Parameter	Unit	CeO_2 NPs	CeO_2@ZIF-8 NPs
		Value	Value
k10	1/h	0.0623	0.0112
k12	1/h	1.8406	0.1078
k21	1/h	0.3210	0.2409
t1/2Alpha	h	0.3129	1.9667
t1/2Beta	h	76.6648	89.7881
C0	μg/ml	2.6253	0.7258
V	(μg)/(μg/ml)	38.0903	137.7729
CL	(μg)/(μg/ml)/h	2.3758	1.5554
V2	(μg)/(μg/ml)	218.3612	61.6702
CL2	(μg)/(μg/ml)/h	70.1104	14.8615
AUC 0-t	μg/ml*h	20.6692	27.7958
AUC 0-inf	μg/ml*h	42.0901	64.2914
AUMC	μg/ml*h^2	4543.2473	8243.7547
MRT	h	107.9408	128.2248
Vss	μg/(μg/ml)	256.4516	199.4431