Supporting Information

Title: Amplification of oxidative stress with hyperthermia-enhanced chemodynamic process and MTH1 inhibition for tumor sequential nanocatalytic therapy

Authors: Qingcheng Song[1,2 *], Yiran Zhang[3, *], Xiangtian Deng[4, *], Haiyue Zhao[3], Yueyao Zhang[1,2], Junyong Li[5], Wei Chen [1,2 #], Hongzhi Hu[6, #], Yingze Zhang[1,2 #].

[1]Department of Orthopaedic Surgery, Third Hospital of Hebei Medical University, Shijiazhuang, 050051, Hebei, People's Republic of China

[2]Orthopaedic Institution of Hebei Province, Shijiazhuang 050051, Hebei, China

[3]School of Medicine, Nankai University, Tianjin, 300071, China

[4]Trauma medical center, Department of Orthopedics surgery, West China Hospital, Sichuan University, Chengdu 610041, China.

[5]The People's Hospital, Shijiazhuang, 050051, Hebei, People's Republic of China

[6]Department of Orthopedics, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, China

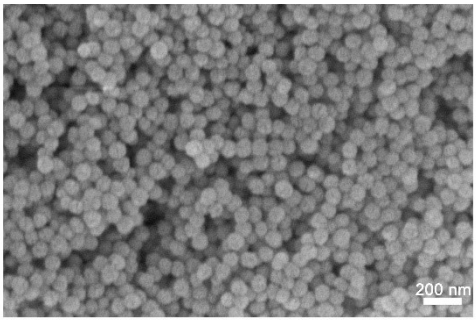

Fig. S1 SEM image of DMSN NPs.

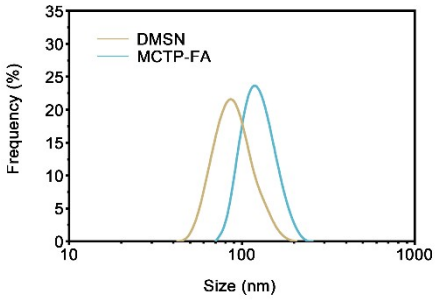

Fig. S2 DLS measurements of DMSN and MCTP-FA NPs.

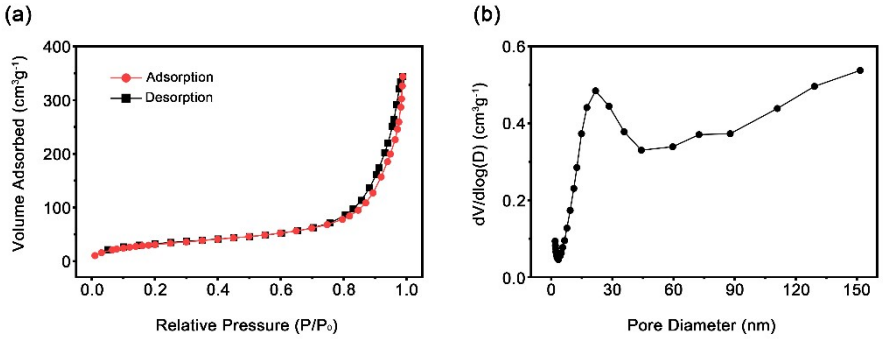

Fig. S3 (a) N_2 adsorption-desorption isotherms and (b) pore size distribution of the DMSN NPs.

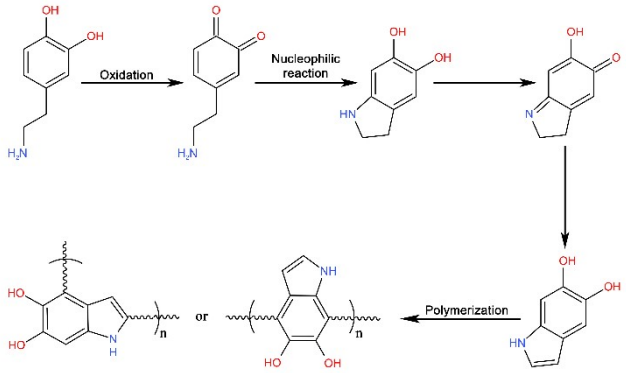

Fig. S4 Schematic illustration of the synthesis of PDA shell through oxidative polymerization.

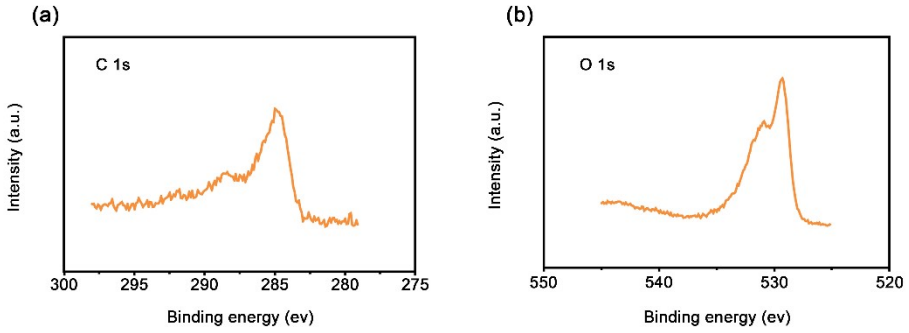

Fig S5 XPS high resolution C 1s (a) spectrum and O 1s (b) spectrum of CeO_2 NPs.

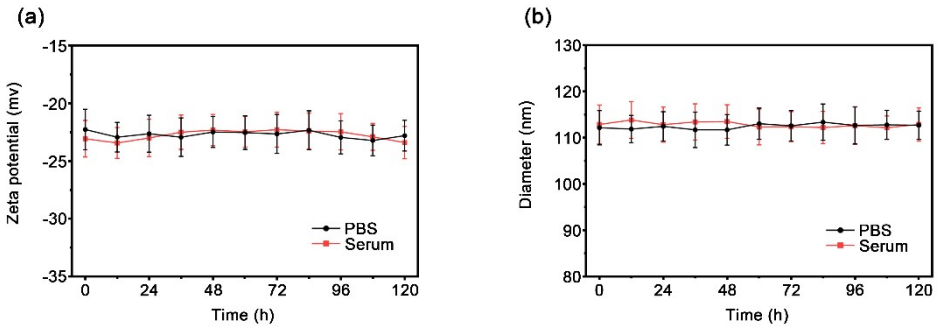

Fig. S6 Zeta potential (a) and DLS (b) changes of MCTP-FA NPs with time in PBS and serum every 12 h (mean ± SD, n = 3).

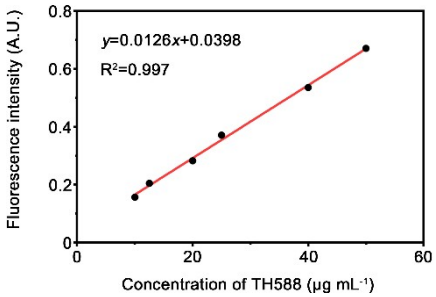

Fig. S7 The standard curve of absorption intensity of TH588 as a function of concentration.

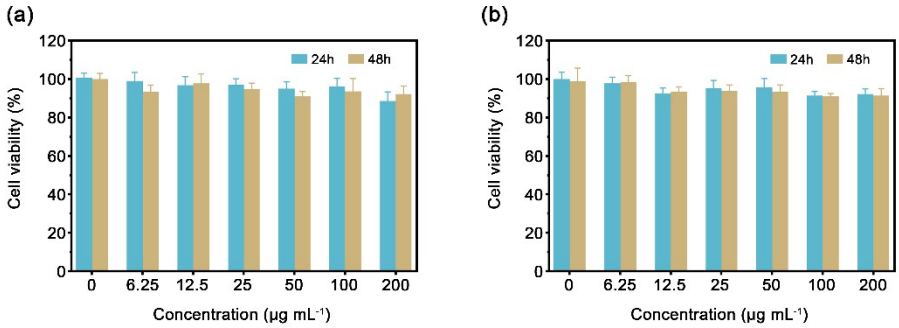

Fig. S8 Cell viabilities of L929 fibroblast cells (a) and HUVEC cells (b) incubated with MCTP-FA NPs at a series of concentrations for 24 h and 48 h.

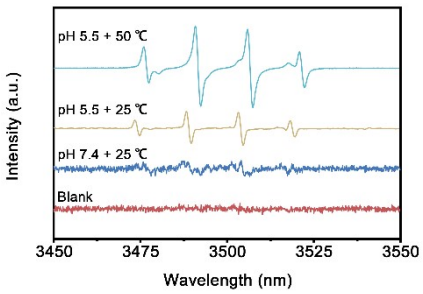

Fig. S9 ESR spectra of ·OH generation in different reaction systems (Blank: ESR spectrum of H_2O).

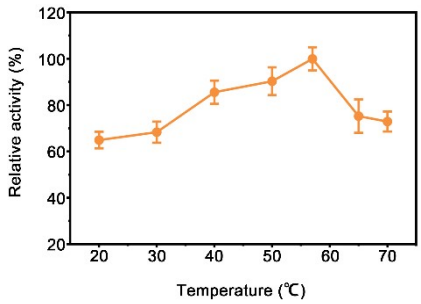

Fig. S10 Effect of temperature on POD-mimic catalytic activity of the MC NPs.

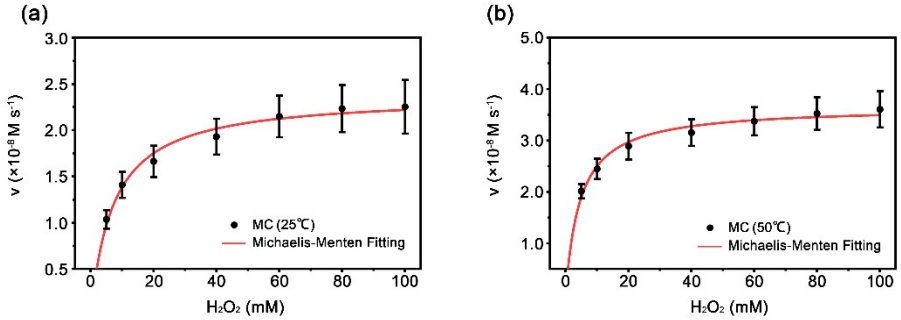

Fig. S11 Michaelis–Menten kinetics for MC NPs with H_2O_2 as the substrate at 25 ℃ (a) and 50 ℃ (b).

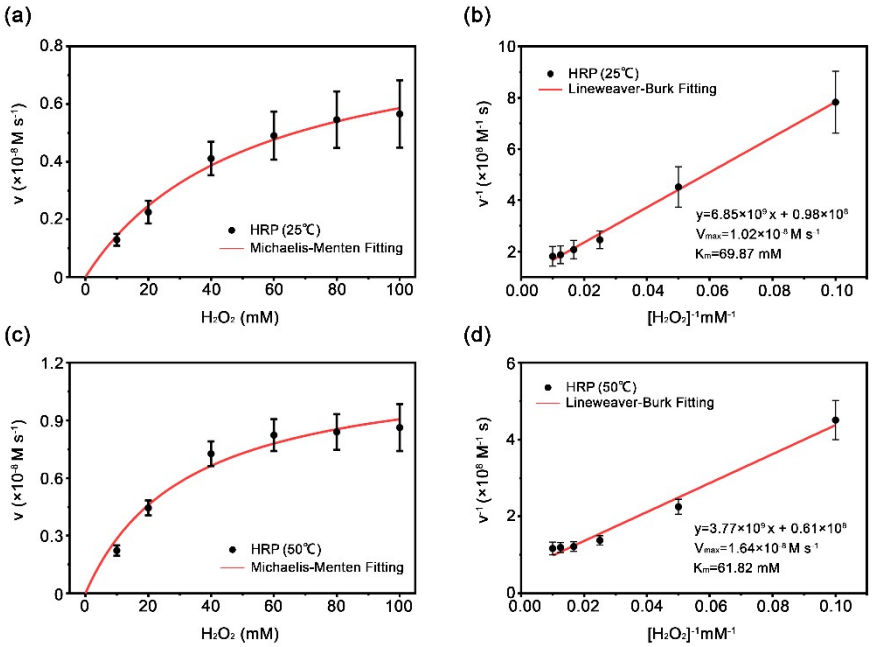

Fig. S12 Michaelis–Menten kinetics and Lineweaver–Burk plotting for HRP with H_2O_2 as the substrate at 25 ℃ (a, b) and 50 ℃ (c, d).

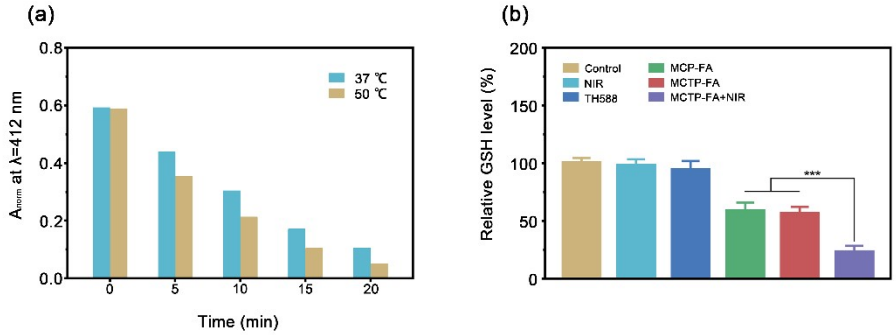

Fig. S13 (a) Effect of temperature on the velocity of GSH consumption. (b) The relative GSH level in MMNG/HOS cells of different treatment groups.

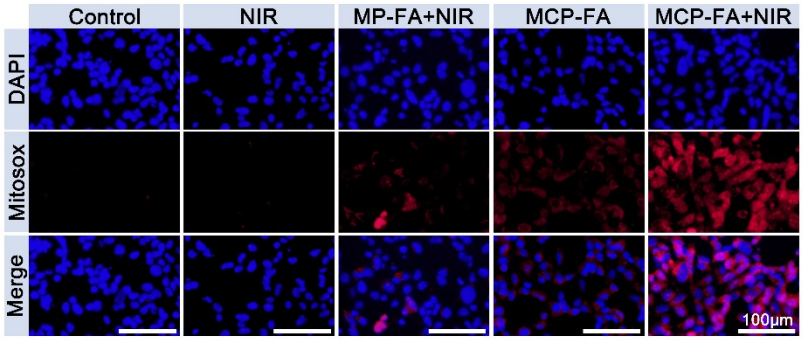

Fig. S14 Fluorescence images of MNNG/HOS cells stained by Mitosox Red after treatment with different formulations.

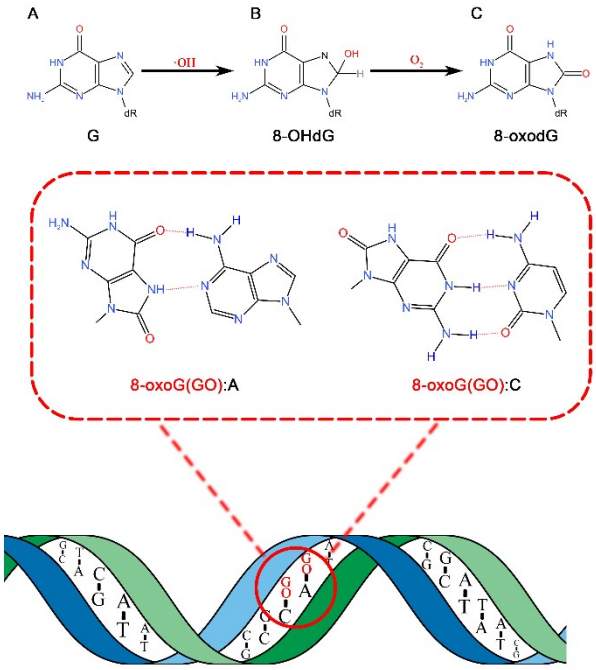

Fig. S15 Formation mechanism of 8-oxoG and changes in base pairing properties.

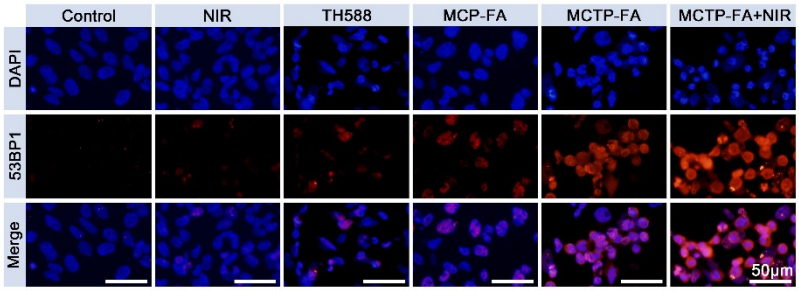

Fig. S16 Immunofluorescence images of 53PB1 after different treatments.

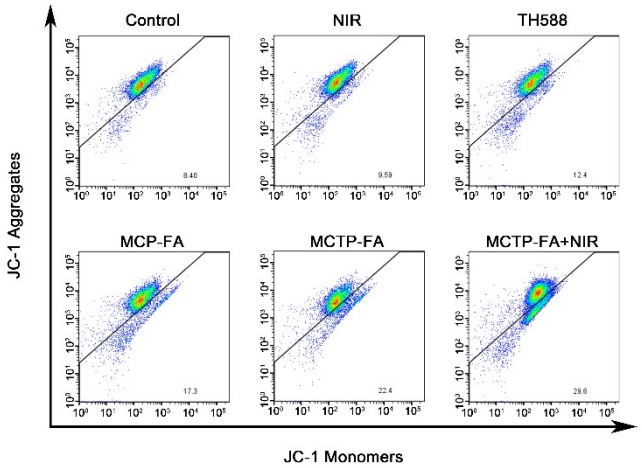

Fig. S17 The decrease of mitochondrial membrane potential after different treatments confirmed by JC-1 analysis.

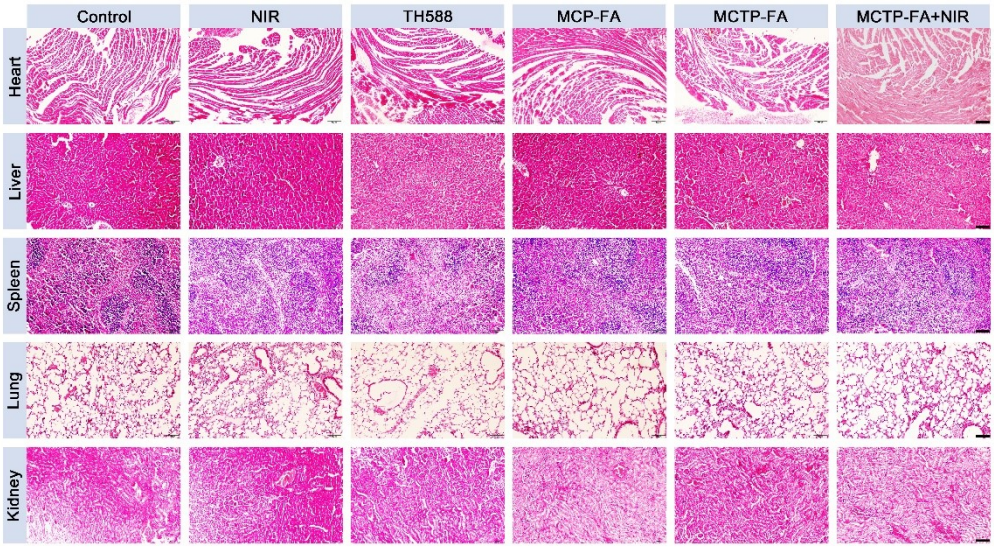

Fig. S18 H&E-stained images of major organs in different groups.

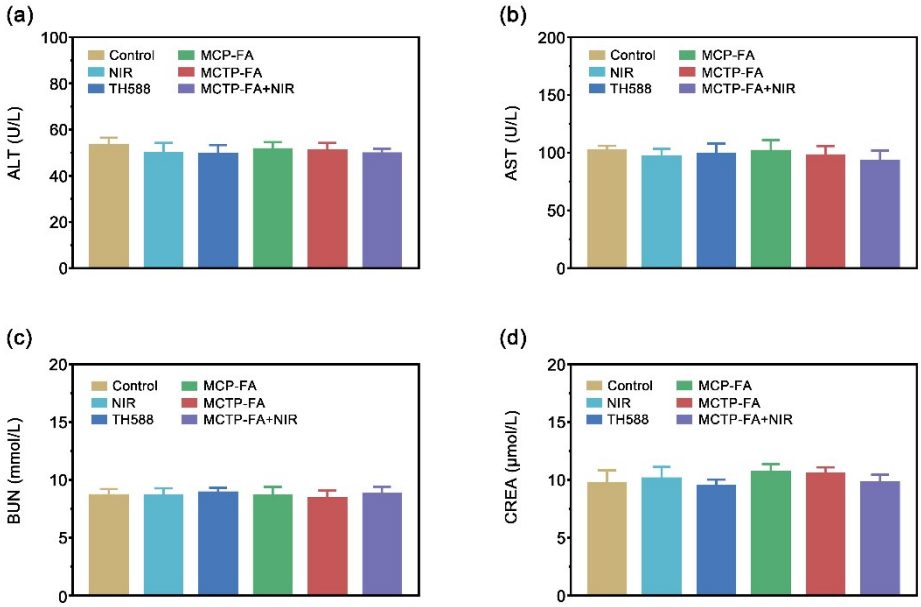

Fig. S19 Biosafety evaluation by blood biochemistry test of mice after intravenous injection with MCTP-FA NPs. (a, b) Serum levels of ALT and AST (liver function index). (c, d) Serum levels of BUN and CREA (kidney function index).

Table S1: Kinetic parameters (K_m, V_{max}) of various nanozymes with H_2O_2 as the substrate for POD-mimic catalysis.

Nanozyme	V_{max} (M s^{-1})	K_m (mM)	Reference
Fe_2O_3	3.05×10^{-8}	86.43	[1]
Fe_3O_4	1.13×10^{-8}	4.94	[2]
Zn-CuO	3.0×10^{-9}	71	[3]
CuO	1.61×10^{-7}	400	[3]
Ala-Fe_3O_4	4.45×10^{-9}	226.6	[4]
PtFe	8.182×10^{-8}	217.6	[5]
$Cu_{2-x}Te$	7.3×10^{-7}	189	[6]
CeO_2	2.63×10^{-8}	32.11	[7]

Reference

1. S. Tanaka, Y. Kaneti, R. Bhattacharjee, M. Islam, R. Nakahata, N. Abdullah, S. Yusa, N. Nguyen, M. Shiddiky, Y. Yamauchi and M. Hossain, *ACS Appl Mater Interfaces*, 2018, **10**, 1039-1049.
2. W. Feng, X. Han, R. Wang, X. Gao, P. Hu, W. Yue, Y. Chen and J. Shi, *Adv Mater*, 2019, **31**, e1805919.
3. A. Nagvenkar and A. Gedanken, *ACS Appl Mater Interfaces*, 2016, **8**, 22301-22308.
4. K. Fan, H. Wang, J. Xi, Q. Liu, X. Meng, D. Duan, L. Gao and X. Yan, *Chem Commun*, 2016, **53**, 424-427.
5. S. Li, L. Shang, B. Xu, S. Wang, K. Gu, Q. Wu, Y. Sun, Q. Zhang, H. Yang, F. Zhang, L. Gu, T. Zhang and H. Liu, *Angew Chem Int Ed Engl*, 2019, **58**, 12624-12631.
6. M. Wen, J. Ouyang, C. Wei, H. Li, W. Chen and Y. Liu, *Angew Chem Int Ed Engl*, 2019, **58**, 17425-17432.
7. S. Dong, Y. Dong, T. Jia, S. Liu, J. Liu, D. Yang, F. He, S. Gai, P. Yang and J. Lin, *Adv Mater*, 2020, **32**, e2002439.