Electronic Supplementary Material (ESI) for Chemical Science.

Supplementary Information (ESI)

A MXene-derived redox homeostasis regulator perturbs the Nrf2 antioxidant program for reinforced sonodynamic therapy

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I. Methods

Reagents

V_2AlC MAX powder was purchased from 11 technology Co., Ltd. (Changchun, China). The mPEG-DSPE (M_W = 5000) and DSPE-PEG-Cy5 (M_W = 5000) were ordered from ToYong Biotechnology. Hydrofluoric acid (HF, 40%) was purchased from Aladdin Reagent. The ammonium hydroxide solution (NH_4OH, 25%) was purchased from Beijing Chemicals, Inc.. Ultrapure (UP) water was prepared by Milli-Q-Plus system (18.2 MΩ cm^{-1}) and used through all the experiments. Dialysis bags were ordered from Spectrumlabs and Shanghai yuanye Bio-Technology Co., Ltd. Methyl thiazolyl tetrazolium (MTT) was purchased from Sigma-Aldrich. Reactive Oxygen Species Assay Kit, PARP1 Rabbit Polyclonal Antibody (KO Validated) were purchased from Beyotime Biotechnology. Nrf2 Polyclonal Antibody, HO-1 Monoclonal Antibody, NQO1 Monoclonal Antibody, Caspase3 Polyclonal Antibody, and β-actin Monoclonal Antibody (KD/KO validated), Fluorescein (FITC)-conjugated Affinipure Goat Anti-Mouse IgG(H+L), Cy3-conjugated Affinipure Goat Anti-Rabbit IgG(H+L), HRP-conjugated Affinipure Goat Anti-Mouse IgG(H+L), and HRP-conjugated Affinipure Goat Anti-Rabbit IgG(H+L) were purchased from Proteintech Group, Inc.. DAPI solution and Crystal violet were purchased from Beijing Solarbio Science & Technology Co. Ltd.. Cell Meter Intracellular GSH Assay Kit was purchased from AAT Bioquest. Annexin V-FITC Apoptosis Detection Kit was purchased from Bioss Inc.. Dulbecco's Modified Eagle Medium (DMEM, high glucose) and Penicillin/streptomycin were purchased from Hyclone Laboratories, Inc.. QuantiChrom Glutathione Assay Kit was purchased from BioAssay Systems. Super ECL Detection Reagent, Hifair II 1st Strand cDNA Synthesis SuperMix for qPCR (gDNA digester plus) and Hieff qPCR SYBR Green Master Mix (Low Rox Plus) was purchased from Yeasen Biotechnology (Shanghai) Co., Ltd.. Primers were ordered from Sangon Biotech (Shanghai) Co., Ltd.. RNAiso Plus was purchased from TAKARA BIO INC. Quick Start Bradford protein assay Kit was purchased from Bio-Rad Laboratories, Inc. All other reagents were of analytical grade and used as received.

Synthesis of V_2C Mxenes

V_2C MXenes were prepared by etching V_2AlC powders (mesh number: 400) with HF. Briefly, 1 g of V_2AlC powder was added to 25 mL of HF (40%) within 10 min. Afterwards, the mixture was stirred at 35 °C. One day later, the mixture was further stirred at 50 °C for 2 days. After that, the V_2C MXenes can be obtained by washing with ultrapure water until the pH of the mixture was adjusted to 6. The mixture was further freeze-dried to result in black V_2C MXenes.

Synthesis of VCQDs

0.21 g of V_2C MXenes were suspended in ultrapure water (31 mL). The mixture was sonicated for 3 h under air atmosphere and 2 mL of ammonium hydroxide solution (25%) was further added. Then, above dispersion was further transferred to a Teflon-lined, stainless-steel autoclave (50 mL) and heated in an oven at 120 ℃ for 6 h. Subsequently, the reactor was cooled to room temperature naturally. The suspension was filtered through a 0.22 μm microporous membrane to remove the large tracts, and a yellow solution was separated. The mixture was further dialyzed in a dialysis bag with a molecular weight cut off of 3.5 kDa, and the VCQDs were obtained by freeze-drying.

Synthesis of PMQDs

4 mg of VCQDs were mixed with 10 mg of mPEG-DSPE in 5 mL of UP water and sonicated for 30 min. Afterwards, PMQDs were purified *via* dialysis in a dialysis bag with a molecular weight cut off of 7 kDa for further use.

Synthesis of Cy5-PMQDs

4 mg of VCQDs were mixed with 10 mg of DSPE-PEG-Cy5 in 5 mL of UP water and sonicated for 30 min. Afterwards, Cy5-PMQDs were purified *via* dialysis in a dialysis bag with a molecular weight cut off of 7 kDa for further use.

Characterization

UV-vis diffuse reflectance spectra were carried out on a Shimadzu UV 3600 spectrophotometer. UV-vis-NIR absorbance measurements were carried out on a JASCO V-550 UV-vis-NIR spectrophotometer. TEM and HR-TEM imaging were carried out on a FEITECNAI G220 high-resolution transmission electron microscope. ζ potential measurements were performed on Malvern Nano ZS-90 at 25℃. Fluorescence spectra were recorded on a JASCO FP-6500 spectrofluorometer. XPS measurements were performed on a Thermo Fisher Scientific ESCALAB 250Xi XPS system. For XPS analysis, sample (10 mg) was pelletized into a self-supporting wafer. High resolution XPS spectra were fitted using Gaussian-Lorentzian component profiles after subtraction of a Shirley background using XPS PEAK41 software. For C 1s XPS analysis, the C 1s peak in the C 1s region could be fit with four peaks at 282.20 eV, 284.55 eV, 285.90 eV, and 288.50 eV. The component centered at 282.20 were consistent with C-V species. The peak centered at 284.55 eV was assigned to graphitic carbon species. The peak centered at 285.90 eV was assigned to C-O species. The peak centered at 288.50 eV was assigned to O-C=O species. For V 2p XPS analysis, the binding energies of six peaks including $V^{\delta+}$ $2p_{1/2}$, $V^{\delta+}$ $2p_{3/2}$, V^{4+} $2p_{1/2}$, V^{4+} $2p_{3/2}$, V^{5+} $2p_{1/2}$, and V^{5+} $2p_{3/2}$ species were confined at 513.60 eV ($V^{\delta+}$ $2p_{3/2}$), 516.10 eV (V^{4+} $2p_{3/2}$), 517.40 eV (V^{5+} $2p_{3/2}$), 521.10 eV ($V^{\delta+}$ $2p_{1/2}$), 523.50 eV (V^{4+} $2p_{1/2}$), and 524.90 eV (V^{5+} $2p_{1/2}$), respectively. For O 1s XPS analysis, the O 1s peak in the O 1s region could be fit with four peaks at 529.90 eV, 531.50 eV, 532.00 eV, and 533.20 eV. The components centered at 529.90 eV and 531.50

eV were consistent with mixed vanadium oxide (VO_x) and V-O species. The peak centered at 532.00 eV was assigned to COOH species. The peak centered at 533.20 eV was assigned to C-O species.The fitting was performed by fixing the peak position for individual species. Confocol imaging was carried out on a Nikon A1R confocal microscope. Powder X-ray diffraction (XRD) measurement was conducted by BRUKER D8 ADVANCE X-ray diffractometer equipped with CuKα radiation (λ=0.15406 nm). ESR analysis was conducted by BRUKER A300 electron spin resonance spectrometer by using DMPO or TEMP as trapping agents. Electrochemical impedance spectrum (EIS) was performed on a CHI660E electrochemical workstation (Beijing Chinese Science Days Technology Co., Ltd.).

ROS-generating ability of VCQDs

Electron spin resonance (ESR) was adopted to explore the generation of $^1O_2$ and •OH by using TEMP and DMPO as the trapping agents, respectively. VCQDs with various concentrations were mixed with trapping agents and exposed to US irradiation (1 MHz, 0.5 W/cm^2, duty cycle: 50%). The characteristic peak signals were detected by an ESR spectrometer. In these experiments, the intensity of the ESR signal was measured as the peak-to-peak height of the second line of ESR spectrum. ESR settings: microwave power: 19.23 mW, microwave frequency: 9.853616 GHz, center field: 3510.00 G, modulation frequency: 100.00 kHz; modulation amplitude: 1.00 G. The concentration of the trapping agents was 33 mM.

GSH depletion ability of VCQDs

The depletion of GSH was detected by UV-vis spectra. VCQDs with various concentrations were mixed with GSH (1 mM) at room temperature. 6 h later, 50 μL of above mixture was added into 0.45 mL of PBS, and 2 μL of 5, 5'-dithiobis-(2-nitrobenzoic acid) (DTNB) (10 mg/mL) was subsequently added. Finally, the UV-vis spectra were measured.

Cell culture

MDA-MB-231 cells and Hacat cells were obtained from the American Type Culture Collection (ATCC) and cultured at 37 °C under 5% CO_2 in an incubator (SANYO). Media was Dulbecco's Modified Eagle Medium (DMEM, high glucose) containing FBS (10%), and penicillin/streptomycin (1%, W/V).

Cellular experiments

MDA-MB-231 cells were incubated with various concentrations of PMQDs (0-60 μg/mL) for 24 h, followed by US irradiation (1 MHz, 1 W/cm^2, duty cycle: 50%) for 1min.

Cellular uptake

MDA-MB-231 cells with a density of 5×10^4 cells per well were seeded in a 6-well plate and incubated overnight. After 24 h attachment, cells were treated with PMQDs (60 μg/mL) for different periods and cellular fluorescence imaging was performed on a Nikon A1R confocal microscope.

Cell viability study

The cell viabilities were determined by a standard methyl thiazolyl tetrazolium (MTT) assay. Briefly, MDA-MB-231 cells (1×10^4 cells per well) were seeded in 96-well plates and incubated overnight. After incubating with PMQDs (0-60 μg/mL) for 24 h, US irradiation (1 MHz, 1 W/cm^2, duty cycle: 50%, 1 min) was conducted, and incubated for another 24 h. Then, MTT was added to the culture medium and incubated for 4 h at 37 °C in 5 % CO_2. Then, 200 μL of DMSO was added to dissolve the formazan crystals, and microplate reader (Bio-Rad) was used to measure the absorbance at 570 nm. To investigate the cytotoxivity of PMQDs towards normal cells, Hacat cells (1×10^4 cells per well) were seeded in 96-well plates and incubated overnight. After incubating with PMQDs (0-100 μg/mL) for 48h, MTT was added to the culture medium and incubated for 4 h at 37 °C in 5 % CO_2. Then, 200 μL of DMSO was added to dissolve the formazan crystals, and microplate reader (Bio-Rad) was used to measure the absorbance at 570 nm.

Colony formation assay

MDA-MB-231 cells (5×10^5 cells per well) were seeded in 6-well plates and incubated overnight. After incubating with PMQDs (0-20 μg/mL) for 24 h, US irradiation (1 MHz, 1 W/cm^2, duty cycle: 50 %, 1 min) was conducted. Single-cell suspension from various groups (2.5×10^3 cells/ml, 2 ml/well)) were seeded in 6-well plates and incubated for 14 days, and the culture medium was changed once every three days. After being washed with PBS twice, cells were fixed with 4% paraformaldehyde for 20 minutes at room temperature. Then, the cells were stained with crystal violet. Images were collected by an EPSON scanner.

ROS detection

Intracellular ROS level was detected by flow cytometry (BD LSRFortessa Cell Analyzer) and fluorescence microscopy (Nikon A1R) with DCFH-DA. Briefly, MDA-MB-231 cells (5×10^5 cells per well) were seeded in 6-well plates and incubated overnight. After incubating with PMQDs (0-60 μg/mL) for 24 h, cells were stained with DCFH-DA for 20 min at 37 ℃ in 5% CO_2, and US irradiation (1 MHz, 1 W/cm^2, duty cycle: 50%, 1 min) was conducted. Then, the cells were collected for fluorescence intensity detection.

GSH detection by Cell Meter Intracellular GSH Assay

MDA-MB-231 cells (5×10^5 cells per well) were seeded in 6-well plates and incubated overnight. After incubating with PMQDs (0-60 μg/mL) for 24 h, intracellular GSH content was measured using Cell Meter

Intracellular GSH Assay Kit according to manufacturer's protocol using flow cytometer (BD LSRFortessa Cell Analyzer).

GSH detection by Quantichrom glutathione assay

MDA-MB-231 cells (5×10^5 cells per well) were seeded in 6-well plates and incubated overnight. After incubating with PMQDs (0-60 μg/mL) for 24 h, cells were lysed by homogenization in 1 mL of cold PBS containing 1 mM EDTA. After centrifuging at 10,000 g for 15 min at 4°C, the supernatant was collected. The concentration of GSH in supernatant was detected by Quantichrom glutathione assay according to manufacturer's instructions.

Apoptosis assay

Cell apoptosis assays were performed using the Annexin V-FITC Apoptosis Detection Kit following the manufacturer's instructions. MDA-MB-231 cells (5×10^5 cells per well) were seeded in 6-well plates and incubated overnight. After incubating with PMQDs (0-60 μg/mL) for 24 h, US irradiation (1 MHz, 1 W/cm^2, duty cycle: 50%, 1 min) was conducted. Afterwards, cells were stained with Annexin V-FITC and Propidium Iodide (PI) for 15 min at 37 ℃ in 5% CO_2, and subsequently collected and analyzed by flow cytometry (BD LSRFortessa Cell Analyzer).

Western blotting

Samples were first lysed in RIPA buffer supplemented with protease inhibitor cocktail at 4 °C, and the protein concentration was determined by a Quick Start Bradford protein assay Kit. Afterwards, 25 μg of protein from each sample was resolved by SDS-PAGE (8 %-10 % SDS-PAGE gels), and subsequently transferred to the polyvinylidene difluoride (PVDF) membranes. Membranes were then blocked in 5 % skim milk in TBST and probed with specific primary antibodies. HRP-conjugated secondary antibodies (1:10000) and ECL Chemiluminescence Detection Kit was used for protein detection. The level of β-actin immunoreactivity was used as a control to monitor equal protein loading**.**

Immunofluorescence assays

To visualize proteins, samples were subjected to immunofluorescence. Cells grown on coverslips and fixed with formalin at room temperature for 20 min. After PBS rinses and permeabilization in 0.5% Triton/PBS for 10 min, samples were blocked in 3% BSA/PBT for 2 hour. Subsequently, cells on glass cover slips were incubated with anti-Nrf2 antibodies (1:500) at 4 °C for 12 h, and labelled with Cy3-conjugated secondary antibodies (1:100) at 4 °C for 12 h. Finally, samples were stained with DAPI for 10 min and imaged by a confocal microscope (Nikon A1R). The colocalization were analyzed by Fuji Software.

qRT-PCR

Total RNA was extracted from cells with RNAiso Plus. Then, cDNA was synthesized with Hifair II 1st Strand cDNA Synthesis SuperMix for qPCR (gDNA digester plus). The qRT–PCR was performed using Hieff qPCR SYBR Green Master Mix (Low Rox Plus). and triplicate samples were run on a Agilent MX3000P qPCR system according to the manufacturer's protocol. The threshold cycle (C_t) values for each gene were normalized to those of β-actin, and the $2^{-\Delta\Delta Ct}$ method was used for quantitative analysis. Primer sequences are listed below.

HO-1: CCAGGCAGAGAATGCTGAGTTC and AAGACTGGGCTCTCCTTGTTGC;

NQO-1: CCTGCCATTCTGAAAGGCTGGT and GTGGTGATGGAAAGCACTGCCT;

β-actin: CACCATTGGCAATGAGCGGTTC and AGGTCTTTGCGGATGTCCACGT.

Animal and tumor-bearing mouse model

All animal experiments were performed in accordance with the NIH guidelines for the care and use of laboratory animals (NIH Publication No. 85-23 Rev. 1985) and approved by the Jilin University Animal Care and Use Committee. Balb/c nude mice (6 weeks) were obtained from Laboratory Animal Centre of Jilin University (Changchun, China), and all animal care and handling procedures were in accordance with the guidelines approved by the ethics committee of Jilin University. The tumor-bearing mouse model was established first. MDA-MB-231 cells (2×10^6 cells) were suspended in 100 μL of cell culture medium and subcutaneously injected on the back of mice. Then, tumor volume was calculated as (tumor length) × (tumor width)^2 × 0.5.

***In vivo* imaging of Cy5-PMQDs**

Mice were intravenously injected with Cy5-PMQDs with a concentration of 10 mg kg^{-1}. Afterward, mice were anesthetized and imaged at various expected time points. Additionally, mice were sacrificed and major organs and tumors were collected and imaged. Related images were analyzed using ImageJ Software.

Biodistribution analysis

Tumor-bearing mice were intravenously injected with PMQDs with a concentration of 10 mg kg^{-1} and sacrificed at different time points. Tumors and major organs were harvested for the quantitative analysis of the biodistribution of PMQDs. Typically, tumors and major organs were surgically removed from the mice at various expected time points and dissolved in aqua regia. The mixtures were heated at 80 °C for 2 h, and the V amounts in the above samples were assessed *via* ICP-MS.

***In vivo* SDT efficacy**

Tumor-bearing mice were randomly divided into four groups and defined as control, US, PMQDs, and PMQDs + US, respectively. Then, mice were intravenously injected with PMQDs with a concentration of 10 mg kg^{-1}. At 12 h after i.v. injection of PMQDs, the tumors of mice in the groups of US and PMQDs + US were treated with US

irradiation (1 MHz, 2 W/cm^2, duty cycle: 50%, 3 min) and repeated daily for 3 days. Tumor volumes were measured by using calipers after various treatments. The tumor sizes and body weights were recorded for 15 days. Then, mice were sacrificed and tumors were collected for tumor mass measurement. Moreover, the major organs including heart, liver, spleen, lung, and kidney were fixed with paraformaldehyde (4%), dehydeated, embedded in paraffin, sectioned, and stained with hematoxylin and eosin (H&E). Slides were observed on an Olympus BX-51 optical system for histological analysis.

Histological analysis

Tumor-bearing mice were randomly divided into four groups and defined as control, US, PMQDs, and PMQDs + US, respectively. Then, mice were intravenously injected with PMQDs with a concentration of 10 mg kg^{-1}. At 12 h after i.v. injection of PMQDs, the tumors of mice in the groups of US and PMQDs + US were treated with US irradiation (1 MHz, 2 W/cm^2, duty cycle: 50%, 3 min) and repeated daily for 3 days. Afterwards, mice were sacrificed and tumors were collected for histological analysis. Harvested tumors were fixed with paraformaldehyde (4%), dehydeated, embedded in paraffin, sectioned, and stained with hematoxylin and eosin (H&E) or (colorimetric TUNEL apoptosis assay kit, Beyotime). Slides were observed on an Olympus BX-51 optical system.

Immunofluorescence staining

Sections were blocked in 5% goat serum for 2 h and then stained overnight at 4 °C with Nrf2 Polyclonal Antibody, HO-1 Monoclonal Antibody, and NQO1 Monoclonal Antibody. Afterwards, fluorescein (FITC)-conjugated secondary antibody (Affinipure Goat Anti-Mouse IgG) or Cy3-conjugated secondary antibody (Affinipure Goat Anti-Rabbit IgG) were incubate with sections for 2 h. Finally, samples were imaged by a confocal microscope (Nikon A1R).

***In vivo* toxicity assessment**

Healthy mice were treated with PMQDs (0 mg kg^{-1}, 10 mg kg^{-1}, 25 mg kg^{-1} or 50 mg kg^{-1}), and the body weight of mice were monitored continuously. 15 days later, blood of mice in all groups were collected and the samples were used to perform blood routine tests. Moreover, the major organs were harvested, fixed with paraformaldehyde (4%), dehydeated, embedded in paraffin, sectioned, and stained with hematoxylin and eosin (H&E).

Statistical analysis

All data were expressed as mean ± standard deviation (SD) and performed in at least 3 specimens. The qRT-PCR results were expressed as the mean ± error. Student's t-test was used for a comparison between two groups by using Graphpad Prism 9.0 software. A P-value < 0.05 was considered statistically significant.

II. Figures

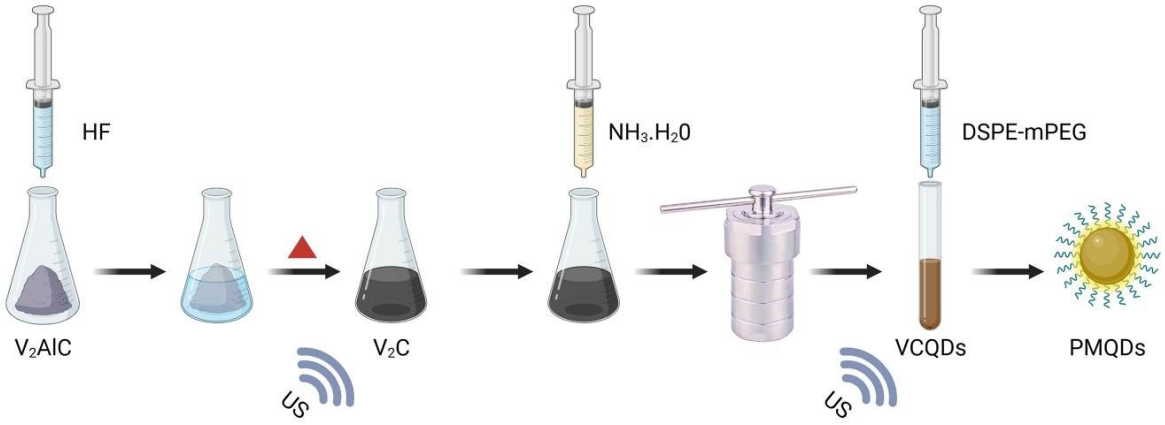

Fig. S1. Schematic illustration of the synthetic process of PMQDs. Created with BioRender.com.

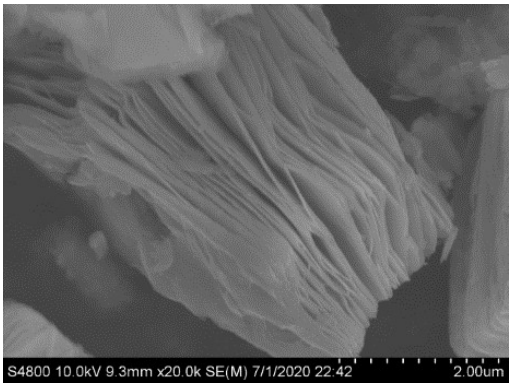

Fig. S2. Typical SEM image of V_2C MXene.

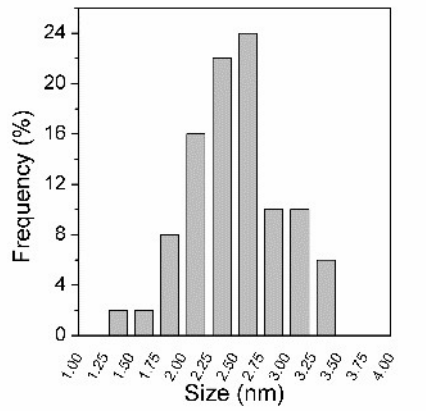

Fig. S3. Size distributions of VCQDs. The average size is 2.51 nm.

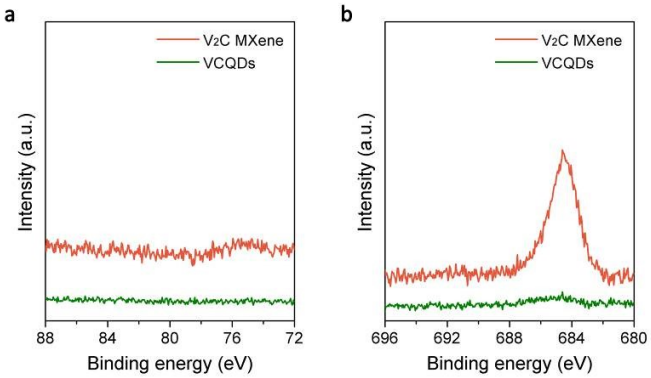

Fig. S4. High-resolution Al 2p (a) and F 1s (b) XPS spectra of V_2C MXene and VCQDs.

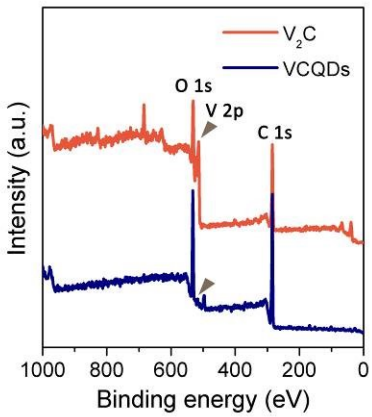

Fig. S5. XPS survey spectra of V_2C MXene and VCQDs.

Fig. S6. Typical digital photograph of VCQDs with a concentration of 5 mg mL^{-1} in water.

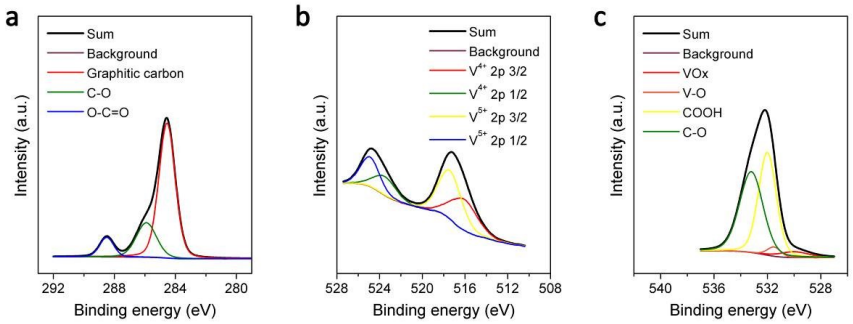

Fig. S7. High-resolution C 1s (a), V 2p (b), and O 1s XPS spectra of VCQDs after dialysis against water for 7 days.

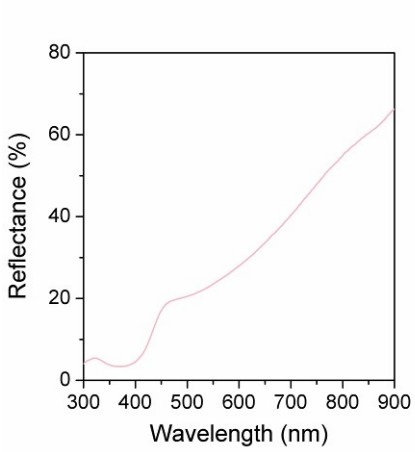

Fig. S8. UV-vis diffuse reflectance spectrum of VCQDs.

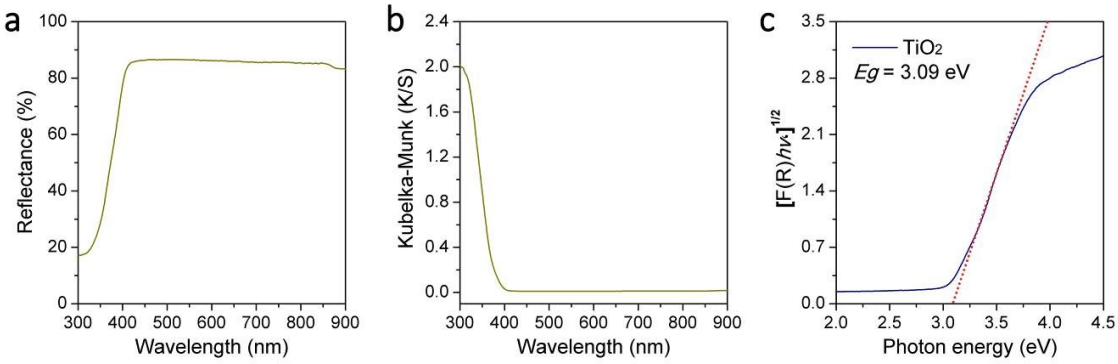

Fig. S9. UV-vis diffuse reflectance spectrum (a), the corresponding absorption spectrum transformed by using Kubelka-Munk function (b), and Tauc plots (c) of TiO_2.

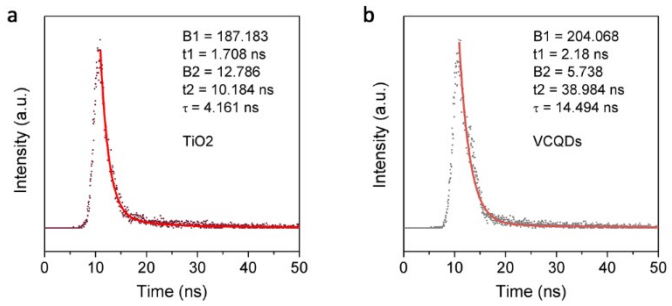

Fig. S10. Luminescence decay curves of (a) nano-TiO_2 and (b) VCQDs.

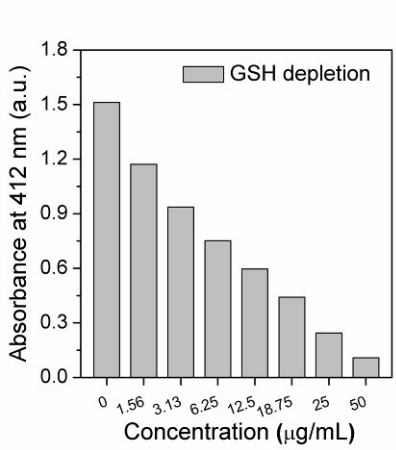

Fig. S11. Concentration-dependent GSH depletion abilities of VCQDs by using DTNB as the indicator of sulphydryl (-SH) in GSH.

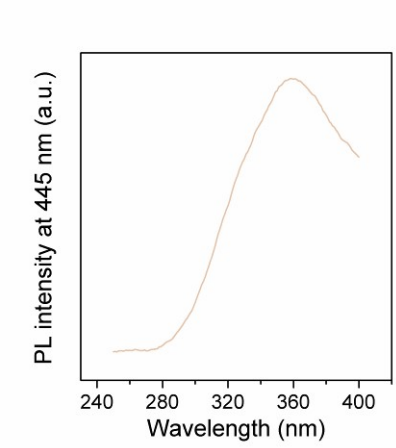

Fig. S12. PLE spectrum of VCQDs. Emissions: 445 nm.

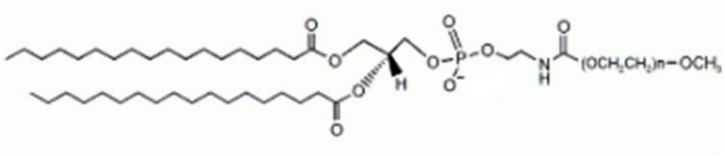

Fig. S13. The structure of mPEG-DSPE.

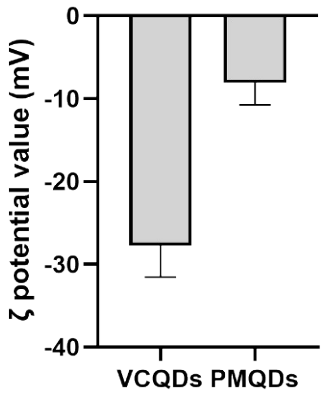

Fig. S14. The ζ potential values of VCQDs and PMQDs.

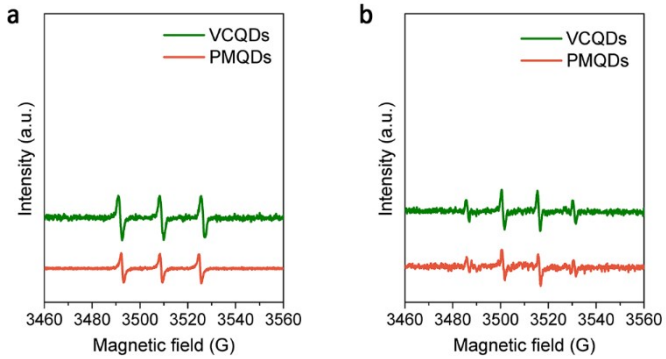

Fig. S15. ESR spectra demonstrating the generation of $^1O_2$ (a) and •OH (b) of VCQDs and PMQDs (50 μg/mL) under US irradiation (1.0 MHz, 0.5 W/cm^2, duty cycle: 50%, 5 min). TEMP and DMPO are used as the trapping agents to investigate the generation of $^1O_2$ and •OH, respectively.

				NQO1			
	Min	**Q1**	**Med**	**Q3**	**Max**	**Upper whisker**	**N**
Normal	289	1152	1776	3102	24622	5564	112
Tumor	138	1307.5	2514.5	5067	18445	10235	112
				HO-1			
	Min	**Q1**	**Med**	**Q3**	**Max**	**Upper whisker**	**N**
Normal	99	271.5	470	843.5	61142	1606	112
Tumor	71	454.5	660.5	1219	5210	1914	112

Fig. S16. Supplementary information of data from the TNMplot database.

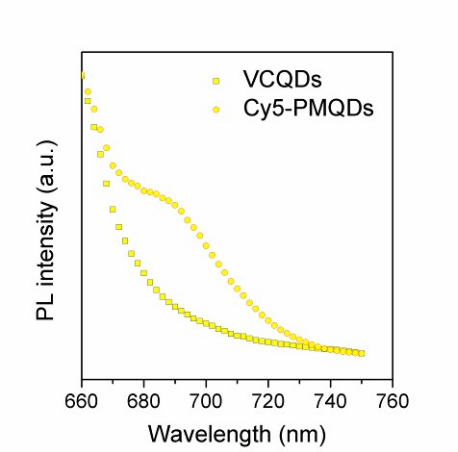

Fig. S17. PL spectra of VCQDs and Cy5-PMQDs. The excitation wavelength was 650 nm.

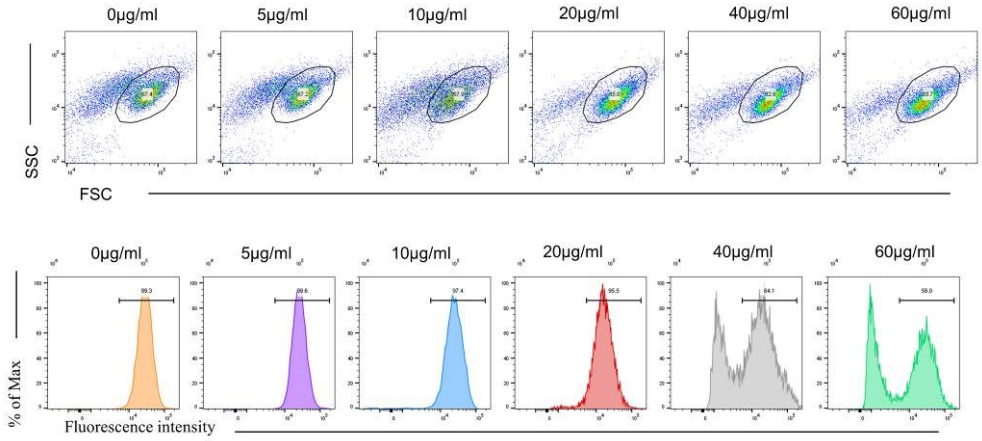

Fig. S18. Flow cytometry results show the intracellular GSH levels of MDA-MB-231 cells after treating with PMQDs by using CellMetrix Intracellular GSH Assay Kit.

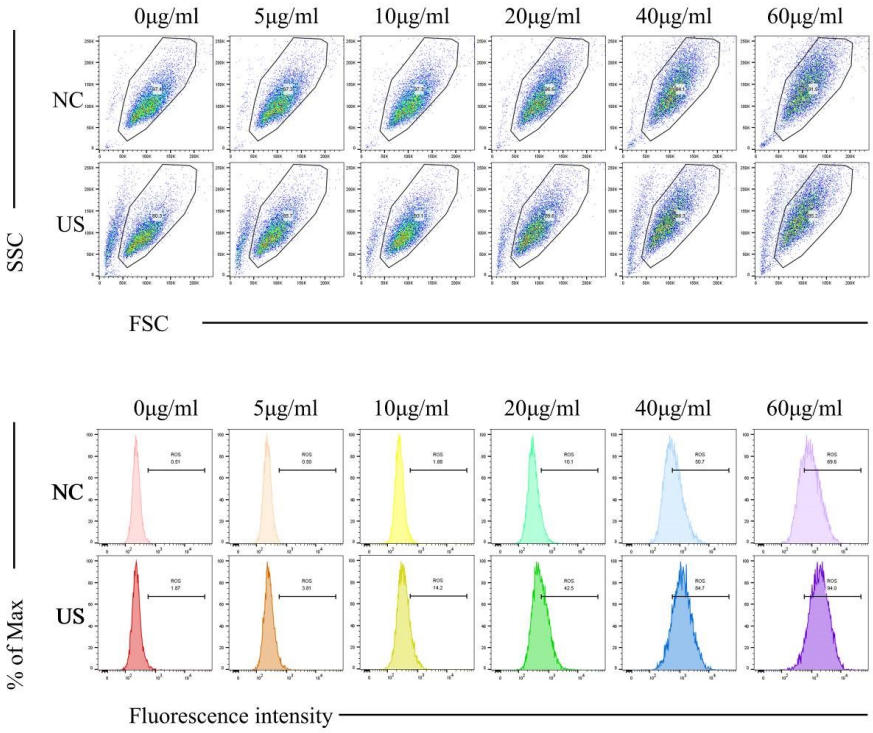

Fig. S19. Flow cytometry results show the intracellular ROS levels of MDA-MB-231 cells after treating with PMQDs upon US (1.0 MHz, 1 W/cm^2, duty cycle: 50%, 1 min) irradiation by using DCFH-DA as the typical fluorescent sensor.

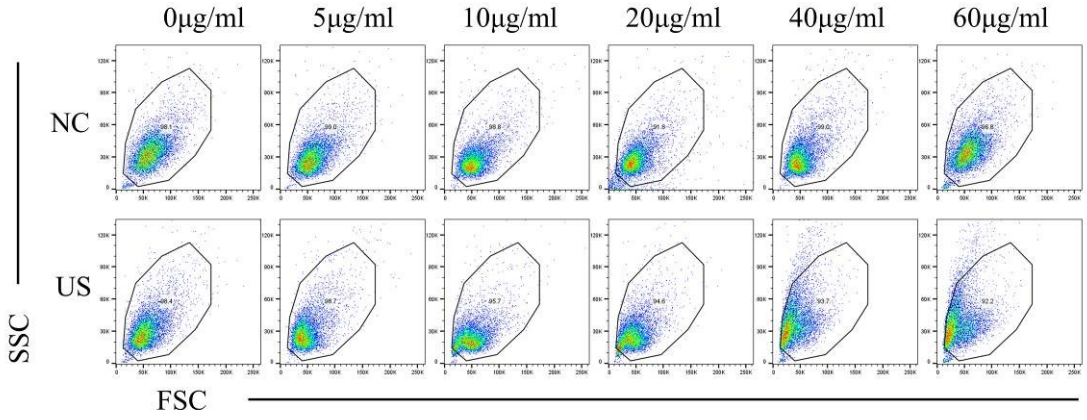

Fig. S20. Apoptosis/necrosis analysis of SDT efficacy based on flow cytometry in MDA-MB-231 cells incubated with PMQDs upon US (1.0 MHz, 1 W/cm^2, duty cycle: 50%, 1 min) irradiation.

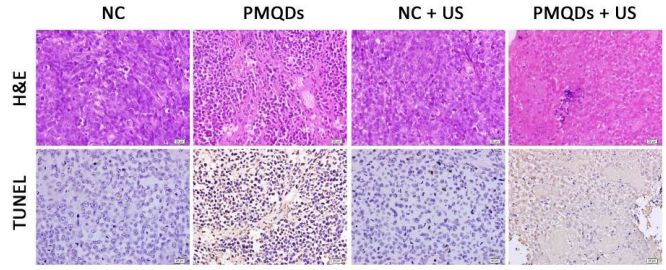

Fig. S21. Enlarged H&E/TUNEL staining images of tumor slices collected from different groups. Scale bars are equal to 20 μm.

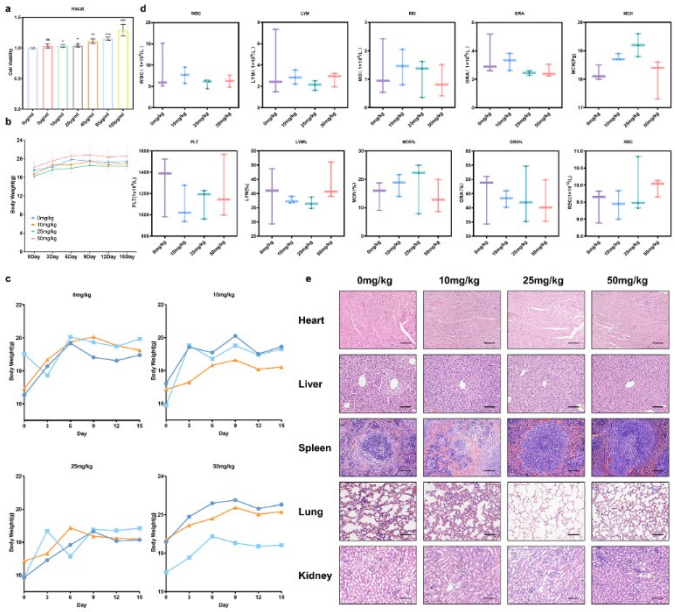

Fig. S22. *In vivo* toxicity assessment. Cytotoxicity of PMQDs towards HaCat cells (a). Bodyweight changes of the mice after various treatments (b,c). Blood routine tests of the mice after various treatments (d). WBC: white blood cells; LYM: lymphocytes; MO: monocytes; GRA: granulocytes; MCH: mean corpuscular hemoglobin; PLT: platelets; LYM%: lymphocyte ratio; MON%: monocyte ratio; GRA%: granulocyte ratio; RBC: red blood cells. H&E staining images of major organs collected from different groups (e). Scale bars are equal to 100 μm.

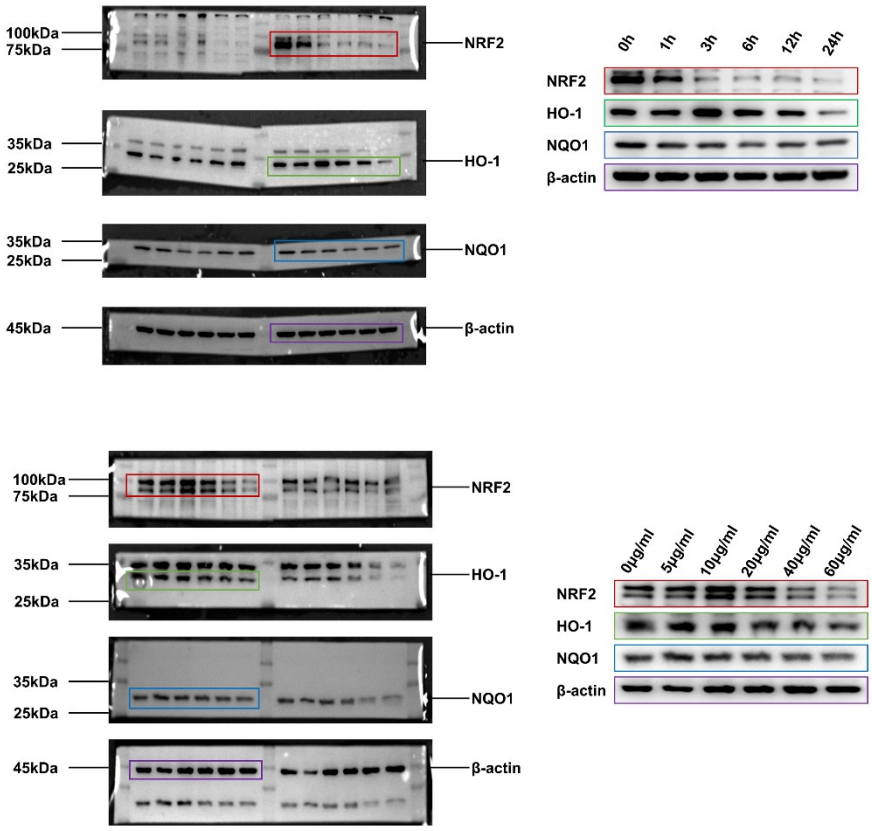

Fig. S23. (Related to Fig. 4i and 4k) Time-dependent and concentration-dependent of western blot analysis of MDA-MB-231 cells treated with PMQDs.

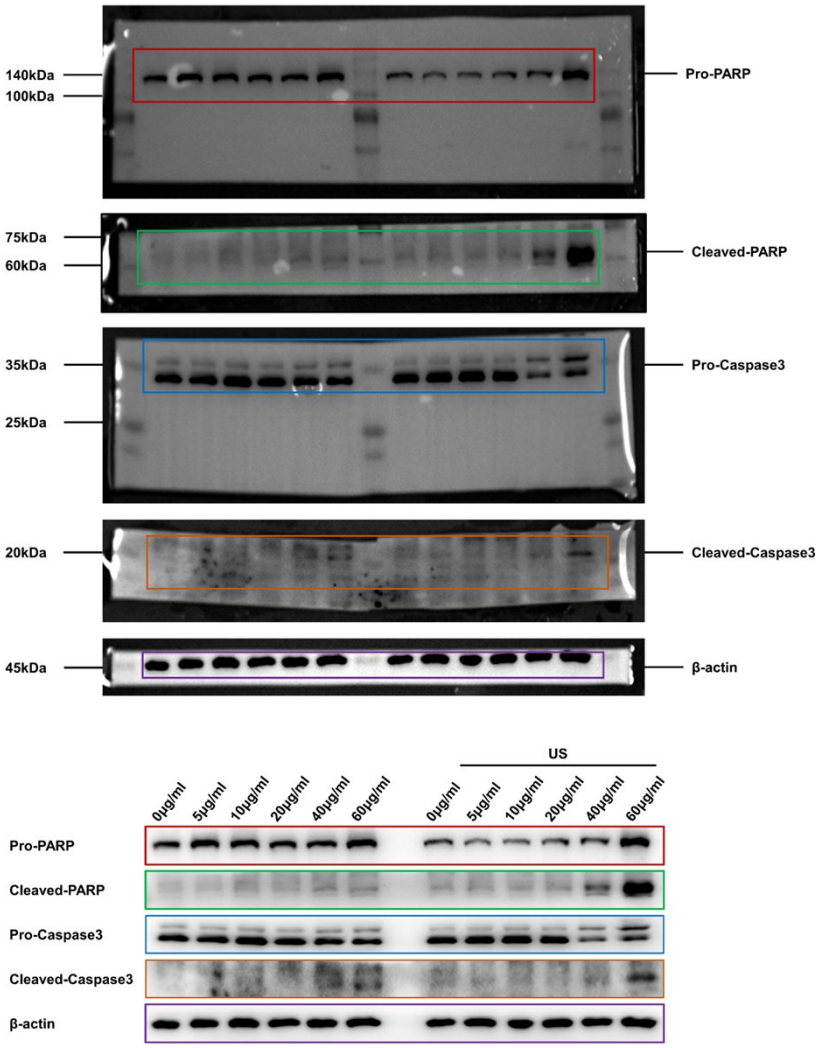

Fig. S24. (Related to Fig.5c) The expressions of cleaved PARP, cleaved caspase-3, and β-actin in MDA-MB-231 cells incubated with PMQDs are examined by western blot analysis.