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Reporting Summary

Nature Portfolio wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Portfolio policies, see our Editorial Policies and the Editorial Policy Checklist.

Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed	
☐	☒	The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒	A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒	The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☒	☐	A description of all covariates tested
☒	☐	A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒	A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒	For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐	For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐	For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☐	☒	Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection

1H NMR spectra were acquired using a Bruker Avance III HD 400MHz spectrometer.
FTIR spectra of OPDEA-PCL, Art, and OAMs were recorded using a Thermo Scientific Nicolet™ iS50 FTIR spectrometer.
Hydrodynamic diameter and zeta potential of micelles were measured utilizing a Malvern Zetasizer Nano ZS90.
RP-HPLC chromatography was conducted using an Agilent 1260 Infinity II system equipped with a ZORBAX SB-C18 column (5 μm, 4.6 × 250 mm) and a variable wavelength detector.
LC-MS/MS data for Art concentrations in plasma were collected using a Shimadzu Nexera X2 LC-30AD ultra-high performance liquid chromatography system coupled to an AB SCIEX 5500 QTRAP hybrid triple quadrupole-linear ion trap mass spectrometer with an electrospray ionization (ESI) source.
Transmission electron microscopy (TEM) images of micelles and mitochondrial morphology were obtained using a JEM-1400flash transmission electron microscope.
In vivo fluorescence imaging of Cy5-labelled micelles was performed using a PerkinElmer IVIS Spectrum system.
Ex vivo fluorescence imaging of tissues (brain and major organs) was conducted using the PerkinElmer IVIS Spectrum system.
Flow cytometry data for endocytosis, exocytosis, apoptosis, lipid ROS, and JC1 assay were collected using a Beckman Coulter CytoFLEX flow cytometer or Dakewe Biotech flow cytometer.
Confocal laser scanning microscope (CLSM) images of cells were acquired using a Leica CLSM.
Trans-endothelial transport assay fluorescence was detected using a Molecular Devices SpectraMax M5 reader.
Absorbance values for CCK-8, LDH, and ELISA assays were measured using a Thermo Fisher Scientific microplate reader.
TUNEL staining, tissue ROS, mitochondrial iron/ROS, IHC, H&E staining, and immunofluorescence (cell/tissue) images were captured using an Olympus optical or fluorescence microscope .
qRT-PCR data were collected using a Bio-Rad CFX96 Touch™ Real-Time PCR Detection System with 2× Universal Blue SYBR Green Master Mix.

Western blotting and Co-IP assay signals were captured using a Bio-Rad ChemiDoc™ Imaging System with enhanced chemiluminescence (ECL).
TEER values for bEnd.3 cell monolayers were measured using a Millicell ERS-2 epithelial voltmeter/ohmmeter.
Biochemical indices (Fe^{2+}, MDA, 4-HNE, GSH) were detected usingusing a Thermo Fisher Scientific microplate reader.
Mitochondrial iron and ROS images were acquired using an Olympus fluorescence microscope.

Data analysis

1H NMR spectra were analyzed with MestReNova 14.0 software.
FTIR spectra were analyzed with OMNIC 9.2.0.41 software.
Hydrodynamic diameter and zeta potential data were analyzed with Zetasizer Software 8.01.4906.
RP-HPLC data were processed with OpenLab CDS ChemStation Edition (version C.01.07 SR3) software.
Fluorescence signals (in vivo/ex vivo) were quantified as mean fluorescence intensity (MFI) within the region of interest (ROI) using Living Image v4.7.3 software.
LC-MS/MS data processing and quantitative analysis were performed using Analyst® version 1.6.3 software (AB SCIEX).
Flow cytometry data were analyzed with FlowJo v10.8.1 software.
CLSM images were analyzed with ImageJ software to quantify Pearson's correlation coefficients and integrated fluorescence intensities.
Trans-endothelial transport assay data were analyzed with SoftMax Pro software.
Cell viability (CCK-8) and LDH release rates were calculated based on absorbance values.
TUNEL-positive cell ratio, IHC staining intensity, immunofluorescence MFI, and mitochondrial morphology parameters were quantified using ImageJ software.
ELISA concentrations of NSE and S100β were calculated based on standard curves using ELISACalc software.
qRT-PCR results were normalized to GAPDH (internal reference) for relative gene expression analysis.
Western blotting and Co-IP band intensities were quantified using ImageJ software.
Differential gene expression analysis was performed using DESeq2 software (DEGs defined as FDR < 0.05 and |fold change| ≥ 2).
GO functional enrichment and KEGG pathway analyses were conducted using the GO (http://geneontology.org) and KEGG (https://www.kegg.jp/kegg/) databases.
Heatmaps, Venn diagrams, volcano plots, and enrichment plots were generated using the OmicStudio platform (https://www.omicstudio.cn/tool).
Gene set enrichment analysis (GSEA) was performed using GSEA v4.1.0 software with the Molecular Signatures Database (MSigDB), with significance defined as |NES| > 1, NOM p-value < 0.05, and FDR q-value < 0.25.
Protein-protein interaction (PPI) networks were constructed and analyzed using the STRING database (https://string-db.org).

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our policy

The raw sequence data reported in this paper have been deposited in the Genome Sequence Archive (Genomics, Proteomics & Bioinformatics 2025) in National Genomics Data Center (Nucleic Acids Res 2025), China National Center for Bioinformation / Beijing Institute of Genomics, Chinese Academy of Sciences (GSA: CRA034992) that are publicly accessible at https://ngdc.cncb.ac.cn/gsa/browse/CRA034992. All other data supporting this study are available in the main article, Supplementary Information or Source Data file. Source data file is provided with this paper. Source data are provided with this paper.

Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	n/a
Reporting on race, ethnicity, or other socially relevant groupings	n/a
Population characteristics	n/a
Recruitment	n/a
Ethics oversight	n/a

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	No statistical methods were used to predetermine the sample size. Sample size was chosen based on previous lab experience to detect meaningful differences between treatments. Sample size followed common standard of n=3 or more biological replicates.
Data exclusions	There were no data exclusions except those resulting from technical errors making data interpretation impossible.
Replication	All experiments were successfully replicated with at least three biological replicates.
Randomization	In all animal experiments, we randomized the animals to ensure that each animal has an equal opportunity to be assigned to either the experimental or control group. The order of analysis for specific experiments was also randomized, including in vivo fluorescence imaging of Cy5-labelled micelles, ex vivo fluorescence imaging of tissues, flow cytometry analysis (endocytosis, exocytosis, apoptosis, lipid ROS, JC1 assay), confocal laser scanning microscope (CLSM) imaging, trans-endothelial transport assay fluorescence quantification, TUNEL staining, tissue ROS/mitochondrial iron/ROS detection, IHC, H&E staining, immunofluorescence imaging, qRT-PCR, Western blotting, Co-IP assay, and biochemical indices detection (Fe^{2+}, MDA, 4-HNE, GSH).
Blinding	Neurological assessments were performed and independently verified by two blinded investigators. No blinding was performed in other experiments in order to make comparisons between specific treatments.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☐	☒ Antibodies
☐	☒ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☐	☒ Animals and other organisms
☒	☐ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☐	☒ Flow cytometry
☒	☐ MRI-based neuroimaging

Antibodies

Antibodies used	GAPDH (For western blot, Cell Signaling Technology, Cat# 2118, Clone: 14C10, Lot# 10) Iba1 (For immunofluorescence, Cell Signaling Technology, Cat# 17198, Clone: E4O4W, Lot# 3) CD31 (For immunofluorescence, R&D Systems, Cat# AF3628, Polyclonal, Lot# YZUO122052) NeuN (For immunofluorescence, Cell Signaling Technology, Cat# 24307, Clone: D4G4O, Lot# 23) HMOX1 (For western blot, Cell Signaling Technology, Cat# 43966, Clone: E3F4S, Lot# 14) β-actin (For immunofluorescence, Cell Signaling Technology, Cat# 4970, Clone: 13E5, Lot# 7) NCOA4 (For IP, Abcam, Cat# ab314553, Clone: EPR28511-12) NCOA4 (For western blot, Thermofisher, Cat# H00008031-M04, Clone: 1B7) FTH1 (For western blot, Zenbio, Cat# R23306, Polyclonal, Lot# N19MA05) LC3 (For western blot, Proteintech, Cat# 14600-1-AP, Polyclonal, Lot# 00119545) GPX4 (For western blot, Proteintech, Cat# 67763-1-IG, Clone: 3F5G5, Lot# 10026631) ACSL4 (For western blot, Proteintech, Cat# 22401-1-AP, Polyclonal, Lot# 10018706) iNOS (For immunofluorescence, Abcam, Cat# Ab178945, Clone: EPR16635, Lot# GR3248775-14) Arg1 (For immunofluorescence, Proteintech, Cat# 16001-1-AP, Polyclonal, Lot# 00069077) BAX (For western blot, Zenbio, Cat# R22708, Polyclonal, Lot# N02JL09) Bcl-2 (For western blot, Zenbio, Cat# 381702, Polyclonal, Lot# N01JL01) Cleaved caspase-3 (For western blot and Immunohistochemistry, Cell Signaling Technology, Cat# 9661S, Clone: Asp175,Lot# 7) HRP-conjugated anti-rabbit IgG (Cell Signaling Technology, Cat# 7074, Polyclonal, Lot# 27) HRP-conjugated anti-mouse IgG (Cell Signaling Technology, Cat# 7076, Polyclonal, Lot# 33) Donkey anti-goat IgG (H+L) conjugated to Alexa Fluor 488 (Invitrogen, A-11055, Lot#2285156) Donkey anti-rabbit IgG (H+L) conjugated to Alexa Fluor 488 (Invitrogen, A-21206, Lot#2376850)
Validation	All primary antibodies were validated for the species (mouse) and specific applications as follows: GAPDH (Cell Signaling Technology, Cat# 2118, WB): Validated via the manufacturer's official website, which confirms Clone 14C10 is suitable for western blot (WB) in mouse samples; consistent with our experimental results (target band ~37 kDa, used as loading

control).
Iba1 (Cell Signaling Technology, Cat# 17198, IF): Validated by the manufacturer (Clone E4O4W) for immunofluorescence (IF) in mouse microglial cells; our experiments showed specific staining of microglial morphology (consistent with expected cellular localization).
CD31 (R&D Systems, Cat# AF3628, IF): Validated via R&D Systems' product documentation for IF in mouse endothelial cells; our experiments showed specific staining of brain vascular structures (target localization in endothelial cell membranes).
NeuN (Cell Signaling Technology, Cat# 24307, IF): Validated by the manufacturer (Clone D4G4O) for IF in mouse neuronal nuclei; our experiments showed specific nuclear staining of hippocampal neurons.
HMOX1 (Cell Signaling Technology, Cat# 43966, WB): Validated via the manufacturer's website for WB in mouse samples; our experiments detected the target band (~35 kDa) in brain tissue lysates.
β-actin (Cell Signaling Technology, Cat# 4970, IF): Validated by the manufacturer (Clone 13E5) for IF in mouse cells; our experiments showed uniform cytoplasmic staining (used as loading control for IF).
NCOA4 (Abcam, Cat# ab314553, IP): Validated via Sigma's product specification for WB in mouse samples; our experiments detected the target band (~72 kDa) in cell lysates.
NCOA4 (Thermofisher, Cat# H00008031-M04, WB): Validated via Affinity's product documentation for WB in mouse samples; results were consistent with those obtained using the Sigma NCOA4 antibody.
FTH1 (Zenbio, Cat# R23306, WB): Validated via Zenbio's product instructions for WB in mouse samples; our experiments detected the target band (~20 kDa) in brain tissue lysates.
LC3 (Proteintech, Cat# 14600-1-AP, WB): Validated via Proteintech's official website for WB in mouse samples; our experiments detected both LC3-I (~16 kDa) and LC3-II (~14 kDa) bands (consistent with autophagy-related expression).
GPX4 (Proteintech, Cat# 67763-1-IG, WB): Validated via Proteintech's product documentation for WB in mouse samples; our experiments detected the target band (~22 kDa) in cell/tissue lysates.
ACSL4 (Proteintech, Cat# 22401-1-AP, WB): Validated via Proteintech's official website for WB in mouse samples; our experiments detected the target band (~70 kDa) in cell lysates.
iNOS (Abcam, Cat# Ab178945, IF): Validated via Abcam's product specification (Clone EPR16635) for IF in mouse immune cells; our experiments showed specific staining in activated BV2 microglial cells.
Arg1 (Proteintech, Cat# 16001-1-AP, IF): Validated via Proteintech's official website for IF in mouse cells; our experiments showed specific staining in M2-polarized BV2 microglial cells.
BAX (Zenbio, Cat# R22708, WB): Validated via Zenbio's product instructions for WB in mouse samples; our experiments detected the target band (~21 kDa) in cell lysates.
Bcl-2 (Zenbio, Cat# 381702, WB): Validated via Zenbio's product specification for WB in mouse samples; our experiments detected the target band (~26 kDa) in cell lysates.
Cleaved caspase-3 (Cell Signaling Technology, Cat# 9661S, WB/IHC): Validated by the manufacturer (Clone Asp175) for WB (target band ~17/19 kDa) and immunohistochemistry (IHC) in mouse samples; our experiments showed specific staining in apoptotic cells (WB/IHC).
Secondary antibodies (HRP-conjugated anti-rabbit/mouse IgG) were validated via the manufacturer's (Cell Signaling Technology) product documentation for HRP-based detection in WB/IHC.
Secondary antibodies (Donkey anti-goat IgG (H+L) conjugated to Alexa Fluor 488 and Donkey anti-rabbit IgG (H+L) conjugated to Alexa Fluor 488) were validated via the manufacturer's (Invitrogen) product documentation for immunofluorescence.

Eukaryotic cell lines

Policy information about cell lines and Sex and Gender in Research

Cell line source(s)	HT22 (murine hippocampal cell line): Obtained from Wenye Biotechnology (Shanghai, China); derived from mouse vertebrate models. bEnd.3 (mouse brain microvascular endothelial cell line): Obtained from Procell (Wuhan, China); derived from mouse vertebrate models. BV2 (mouse microglial cell line): Obtained from Procell (Wuhan, China); derived from mouse vertebrate models. Primary astrocytes (PRI-MOU-00169): Obtained from Zhong Qiao Xin Zhou Biotechnology (Shanghai, China); derived from male mouse vertebrate models. Primary pericytes (PRI-MOU-00204): Obtained from Zhong Qiao Xin Zhou Biotechnology (Shanghai, China); derived from male mouse vertebrate models. Primary oligodendrocytes (PRI-MOU-00199): Obtained from Zhong Qiao Xin Zhou Biotechnology (Shanghai, China); derived from male mouse vertebrate models.
Authentication	All cell lines were acquired from commercial suppliers (Wenye Biotechnology, Procell, Zhong Qiao Xin Zhou Biotechnology) that provide pre-authenticated cell lines. No additional authentication procedures were performed in our laboratory.
Mycoplasma contamination	All cell lines (HT22, bEnd.3, BV2, primary astrocytes, primary pericytes, primary oligodendrocytes) were tested for mycoplasma contamination using a commercial qPCR-based detection kit (Beyotime, Cat# C0303S) prior to experimental use, and all results were negative.
Commonly misidentified lines (See ICLAC register)	None of the cell lines used in this study (HT22, bEnd.3, BV2, primary astrocytes, primary pericytes, primary oligodendrocytes) are listed as commonly misidentified cell lines in the ICLAC register.

Animals and other research organisms

Policy information about studies involving animals; ARRIVE guidelines recommended for reporting animal research, and Sex and Gender in Research

Laboratory animals	Rats: Rattus norvegicus (species: rat), strain: Sprague-Dawley (SD), sex: male, age: 8–12 weeks, body weight: 200–250 g. Purchased from Vital River Laboratory (Zhejiang, China) and acclimatised for 1 week before experiments.

	Mice: Mus musculus (species: mouse), strain: C57BL/6, sex: male, age: 10–12 weeks, body weight: 20–25 g. Purchased from Vital River Laboratory (Zhejiang, China) and acclimatised for 1 week before experiments.
Wild animals	The study did not involve wild animals.
Reporting on sex	Findings apply only to male individuals. Sex was considered in the study design (male mice were specifically selected to focus on the target biological effect in this sex). No sex-based analysis was performed, as the study was designed to investigate outcomes in male subjects exclusively.
Field-collected samples	The study did not involve samples collected from the field.
Ethics oversight	All animal experiments were approved by the Ethics Committee of the Second Affiliated Hospital, Zhejiang University School of Medicine (No. 2022-162) and conducted in accordance with NIH guidelines.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Plants

Seed stocks	n/a
Novel plant genotypes	n/a
Authentication	n/a

Flow Cytometry

Plots

Confirm that:

☒ The axis labels state the marker and fluorochrome used (e.g. CD4-FITC).

☒ The axis scales are clearly visible. Include numbers along axes only for bottom left plot of group (a 'group' is an analysis of identical markers).

☒ All plots are contour plots with outliers or pseudocolor plots.

☒ A numerical value for number of cells or percentage (with statistics) is provided.

Methodology

Sample preparation	Cell lines: bEnd.3 (mouse brain microvascular endothelial cells), HT22 (mouse hippocampal cells), BV2 (mouse microglial cells). Cells were cultured to 80% confluency, harvested via 0.25% trypsin-EDTA digestion (37°C, 2-5 min), terminated with complete medium, washed twice with cold PBS (200×g, 5 min), and resuspended in staining buffer (PBS + 2% FBS) at 0.5-1×10^6 cells/mL. Primary cells: Isolated from the brain (hippocampus/cortex) of male C57BL/6 mice. Tissues were minced into ≤1mm pieces, digested with 0.1% collagenase (37°C, 30 min), filtered through a 70 μm cell strainer, centrifuged (200×g, 5 min) to remove debris, and resuspended in staining buffer.Endocytosis/exocytosis: Cells were incubated with Cy5-labeled micelles at 37°C for specified time points, then washed 3 times with cold PBS to remove unbound probes. Apoptosis detection: Stained with Annexin V-FITC/PI kit (37°C, 15 min) in dark conditions per manufacturer's protocol. Lipid ROS detection: Loaded with C11-BODIPY dye (37°C, 30 min) in dark conditions. Mitochondrial membrane potential (JC1): Stained with JC1 kit (37°C, 20 min), with FCCP-treated cells as positive control. All samples were verified for viability ≥90% via trypan blue staining before analysis.
Instrument	Data were collected using either a Beckman Coulter CytoFLEX flow cytometer or a Dakewe Biotech flow cytometer.
Software	Data acquisition was performed using the instrument-native software (Beckman Coulter CytoFLEX Software / Dakewe Flow Cytometry Acquisition Software). All post-acquisition analysis was conducted using FlowJo v10.8.1 software.
Cell population abundance	No cell sorting was performed in this study. All analyses focused on the percentage of target cell populations within the total viable cell gate: Endocytosis/exocytosis: Cy5-positive cells (representing micelle-internalized cells); Apoptosis: Annexin V^+/PI^- (early apoptotic) and Annexin V^+/PI^+ (late apoptotic) cells; Lipid ROS/JC1: Fluorescence-positive cells (representing ROS accumulation or mitochondrial membrane potential change). The purity of viable cell populations after gating was ≥95%.
Gating strategy	Gating was performed sequentially following standard protocols: Debris exclusion: FSC-A vs SSC-A plot to gate out cell debris and aggregates;

Single cell gating: FSC-A vs FSC-H plot to select single cells (exclude doublets);
Viable cell gating: DAPI staining to exclude dead cells (viable cells = $DAPI^-$);
Specific population gating:
Negative control (unstained cells) was used to set background fluorescence threshold (threshold = mean + 2×SD of negative control);
For multi-parameter assays, single-stained controls were used to adjust fluorescence compensation;
JC1 assay: Gates for JC1 aggregates (red fluorescence) and monomers (green fluorescence) were defined using untreated cells (normal potential) and FCCP-treated cells (depolarized potential).

☒ Tick this box to confirm that a figure exemplifying the gating strategy is provided in the Supplementary Information.