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Supplemental Materials and Methods 1

Embedding of tissue with paraffin

Fresh tissue samples were placed in 10% formalin for 24 *h* and dehydrated with a graded series of alcohol and xylene (75% alcohol, 2 *h* → 85% alcohol, 1 *h* → 95% alcohol I, 30 *min* → 95% alcohol II, 30 *min* → 100% alcohol I, 10 *min* → 100% alcohol II, 10 *min* → xylene I, 30 *min* → xylene II, 30 *min* → paraffin I, 2 *h* → paraffin wax II, 2 *h*). Then, the embedded tissues were sliced to a thickness of 5 μm using a microtome.

Supplemental Materials and Methods 2

Hematoxylin & Eosin (*HE*) staining

Tissues slices were dewaxed by heating to 62°*C* in an oven for 2 *h* and then rehydrated in a graded series of xylene/alcohol/*PBS* (xylene I, 10 *min* → xylene II, 10 *min* → 100% alcohol I, 5 *min* → 100% alcohol II, 5 *min* → 95% alcohol I, 5 *min* → 95% alcohol II, 5 *min* → 85% alcohol, 5 *min* → 75% alcohol, 5 *min* → *PBS* I, 5 *min*). Afterward, the tissues slices were stained with hematoxylin for 10 min. Color separation was performed by rinsing the tissue slices with 1% hydrochloric acid and alcohol (300 *mL* of 75% alcohol, 2 *mL* of concentrated *HCl*) for 30 *s* followed by running tap water for 5 *min*. Next, the tissues were stained with eosin dye solution for about 50 *s* and then rinsed with 95% alcohol. The slices were then subjected to a graded series of alcohol and xylene for dehydration and transparency (75% alcohol, 5 *min* → 85% alcohol, 5 *min* → 95% alcohol, 3 *min* → 100% alcohol, 3 *min* →

xylene I, 10 *min* → xylene II, 10 *min*). Afterward, the slices were mounted onto glass slides with neutral gum and observed under a microscope.

Supplemental Materials and Methods 3

TUNEL analysis

The tissue slices were dewaxed by heating to 62°*C* in an oven for 2 *h* and then rehydrated in a graded series of xylene/alcohol/*PBS* (xylene I, 10 *min* → xylene II, 10 *min*→ 100% alcohol I, 5 *min*→ 100% alcohol II, *min* → 95% alcohol I, 5 *min* → 95% alcohol II, 5 *min* → 85% alcohol, 5 *min* → 75% alcohol, 5 *min* → PBS I, 5 *min* → PBS II, 5 *min*). The slides were immersed in 3% H_2O_2 to block endogenous peroxidase activity, incubated for 20 *min* at room temperature, and then washed three times with *PBS* for 5 *min* each time. Following the addition of proteinase K at 37°*C* for 30 *min*, the slides were washed twice with *PBS* for 5 *min* each time.

The *TUNEL* reaction mixture consisted of 50 μL of *TdT* enzyme and 450 μL of *dUTP*.

Experimental group: 100 μL of the *TUNEL* reaction mixture.

Positive control group: 100 μL DNase I solution at room temperature for 10 *min*, then 100 μL of the *TUNEL* reaction mixture.

Negative control group: 50 μL of *dUTP* solution.

The sections were incubated at 37°*C* for *1* h in the dark. At the end of the reaction, the samples were washed three times with PBS for 5 *min* each time. Next, 50 μL of converter-POD working solution were added and the samples were incubated at 37°*C*

in the dark for 60 *min*, then washed with *PBS* three times for 5 *min* each time. Color was developed by dropwise addition of 50 μL of *DAB* color developing solution and reacted for 10 *min* at room temperature, then washed three times with *PBS* for 5 *min* each time. The nuclei were counterstained with hematoxylin. Finally, the samples were mounted on glass slides with neutral gum and observed under a microscope.

Supplemental Materials and Methods 4

The *mRNA* extraction

Before the experiment, all relevant instruments were treated with *DEPC* water to remove RNase and then autoclaved. The tissue fragments were placed in 1.5 *mL* Eppendorf tube and mixed with 1 *mL* of *Trizol* reagent, then placed on ice for 5 *min* to fully lyse the cells. Afterward, the tissues were disrupted by shaking with magnetic beads at 300 *rpm* for 5 *min*. Following centrifugation at 12,000 *rpm* at 4°*C* for 5 *min*, the supernatant was transferred to a new Eppendorf tube, then mixed with 200 μL of chloroform, shaken vigorously for 15 *s*, and placed on ice for 10 *min*. Afterward, the samples were centrifuged at 12,000 *rpm* and 4°*C* for 15 *min*. The homogenate in the tube was divided into three layers with the *RNA* dissolved in the colorless upper layer, which was transfer to a new eppendorf tube. Following the addition of an equal volume of isopropanol, the sample was mixed well and then incubated at room temperature for 10 *min*. Following centrifugation at 12,000 *rpm* at 4°*C* for 10 *min*, the supernatant was removed. Then, the *RNA* pellet was washed with 1 mL of 75% ethanol and centrifuged at 12,000 *rpm* and 4°*C* for 5 *min*. After the ethanol was

removed, the tube was incubated at 55°*C* for 10 *min*. Next, the *RNA* was suspended in 20–50 μL of RNase-free *DEPC* water. The concentration of the *RNA* was measured at 260 *nm* and purity at 280 *nm*, expressed as *A260/A280*. Finally, the samples were stored at -80°*C* until use.

Supplemental Materials and Methods 5

Reverse Transcription

RNA (2 μg), N6 primer (1 μL), and DEPC water to a final volume of 15 μL were mixed well in a 70°*C* water bath for 5 *min*, and then cooled on ice for 2 *min*. According to the measured *mRNA* concentration, the volume of *RNA* to be added was calculated. Each 10 μL reaction volume consisted of dNTPs (1 μL), 5 × buffer (5 μL), Rasin (1.25 μL), *DEPC* water (1.75 μL), and MLV (1 μL). The reaction was conducted in a 37°*C* water bath for 60 *min*.

Supplemental Materials and Methods 6

Real-time fluorescent quantitative *PCR*

The Gene IDs of the target genes of the required species were retrieved from the GeneBank database and the primers were obtained from PrimerBank (Supplemental Table 1). Each 10 μL reaction system consisted of *SYBR* Green I (dye (5 μL), forward primer (0.5 μL), reverse primer (0.5 μL), *cDNA* (1 μL), and *DEPC* water (3 μL). After the above reaction system was fully mixed and centrifuged, the *PCR* reaction was carried out according to the following reaction conditions: pre-denaturation at 95°*C*

for 30 s followed by 40 cycles of amplification at 95°*C* for 5 s and 60°*C* for 32 *s*. Dissolution curve program: 95°*C* for 15 *s*, 60°*C* for 15 *s*, and 95°*C* for 15 *s* for 1 cycle.

The purity of the amplified products was determined by reference to the melting curve. According to dynamic analysis, the relative expression of target gene *mRNA* was calculated with the following formula: $2^{-\Delta\Delta Ct} = 2^{-\Delta Ct \text{ Object group} - \Delta Ct \text{ control group}}$

Supplemental Materials and Methods 7

Immunohistochemical analysis

The slices were dewaxed by heating to 60°*C* in an oven for 2 *h* and then deparaffinized with a graded series of xylene/ethanol/water (xylene, 10 *min* → xylene, 10 *min* → xylene, 10 *min* → absolute ethanol, 10 *min* → 95% ethanol, 5 *min* → 85% ethanol, 5 *min* → 75% ethanol, 5 *min* → ddH_2O, 5 *min*). Endogenous peroxidase was inactivated by immersing the slices in 3% H_2O_2 for 30 *min*. Antigen retrieval was performed with acid retrieval solution (21.9 *g* of trisodium citrate, 3.6 *g* of citric acid, and ddH_2O to a final volume of 3,000 *mL*). Next, blocking was performed with 1% BSA at 37°*C* for 30 *min*. Then, the slices were incubated overnight with primary antibodies (dilution, 1:500–10,000) at 4°*C* followed by incubation with horseradish peroxidase-conjugated secondary antibodies at 37°*C* for 30 *min*. Color was developed with the use of DAB solution for 3–10 *min*. The nuclei were stained with hematoxylin for 10 min (differentiation 1–2 times). The slices were dehydrated with a graded series of ethanol/xylene/phenolic acid (75% ethanol, 5 *min* → 85% ethanol, 5 *min* →

95% ethanol, 10 *min* → absolute ethanol, 10 *min* → phenolic acid, 5 *min* → xylene, 10 *min* → xylene, 10 *min*). Afterward, the slices were sealed in resin and stored for later use.

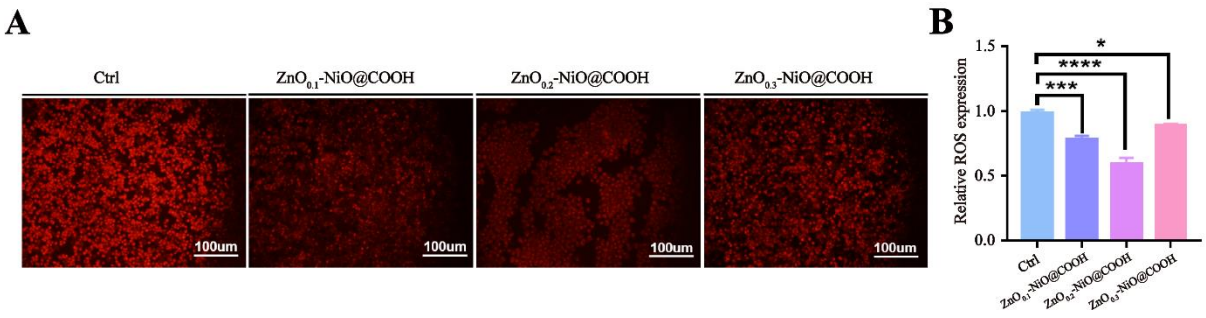
Supplemental Table1

Gene		Primer sequence (5′-3′)
TNFα	Forward	AACTCCAGGCGGTGCCTATG
TNFα	Reverse	TCCAGCTGCTCCTCCACTTG
IL-1β	Forward	AGCTTCAGGCAGGCAGTATC
IL-1β	Reverse	TCATCTCGGAGCCTGTAGTG
IL-6	Forward	AAGTCCGGAGAGGAGACTTC
IL-6	Reverse	TGGATGGTCTTGGTCCTTAG
IL-10	Forward	CCTGGCTCAGCACTGCTATG
IL-10	Reverse	TCACCTGGCTGAAGGCAGTC
β-actin	Forward	CATGTACGTTGCTATCCAGGC
β-actin	Reverse	CTCCTTAATGTCACGCACGAT

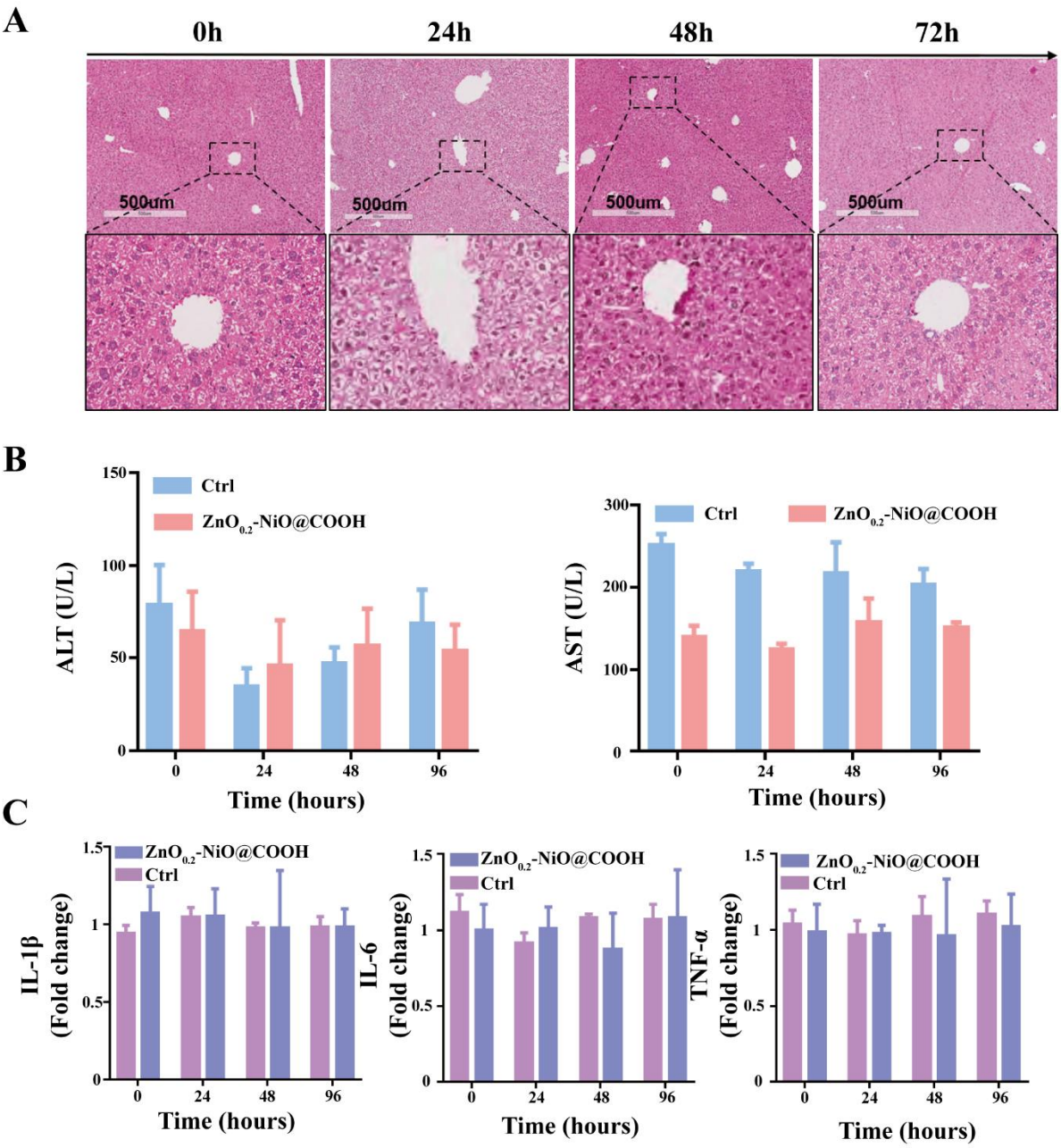
Supplemental Table 2. Reagent details

	Reagent name	CAS	company
1	eBioscience^{TM}Amexin V-FITC Apop Kit 300 Tests	LOT 215819000	InvitrogenZ
2	FastStart Universal SYBR® Green	LOT 50837000	Roche

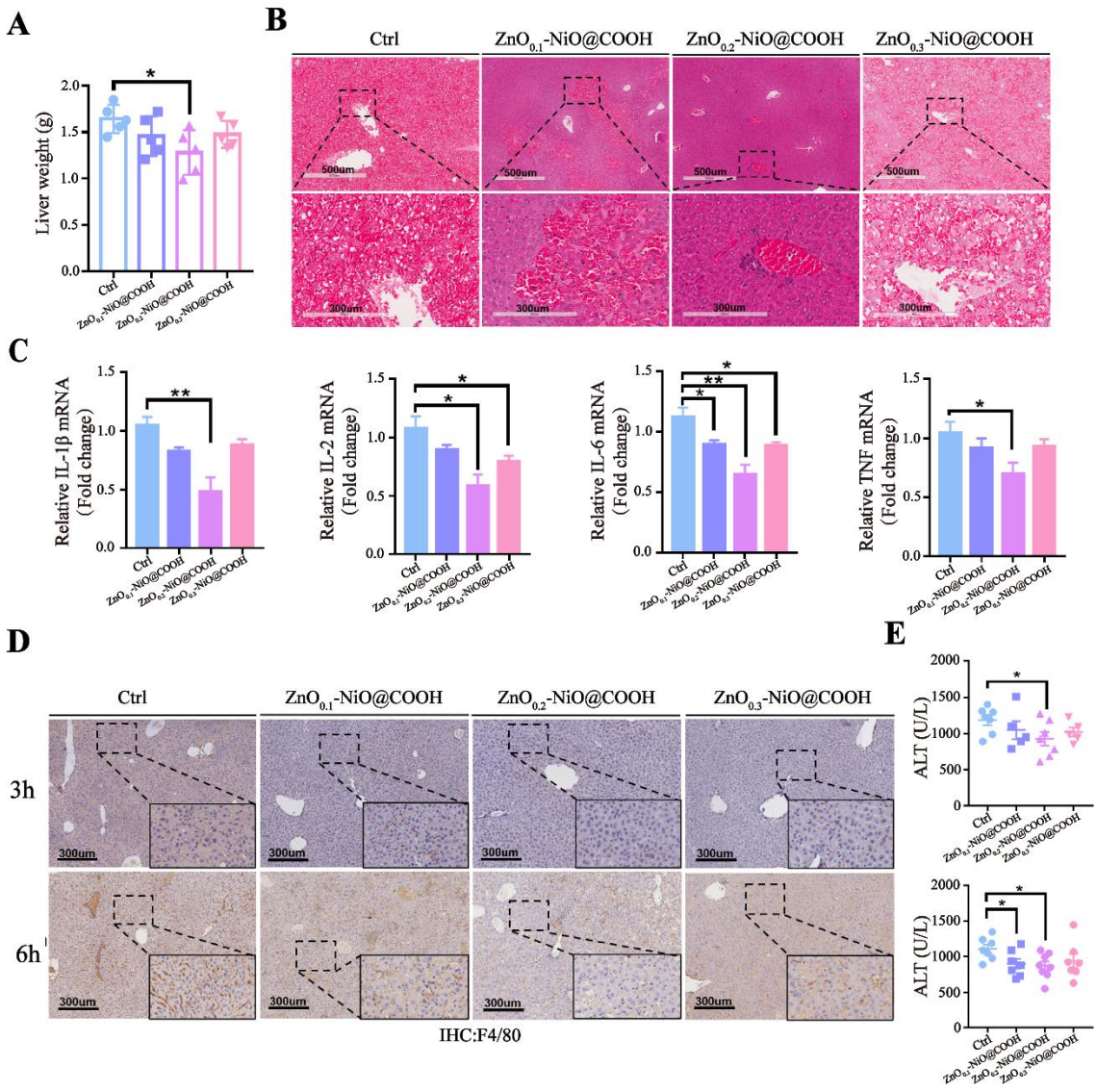
	Master(ROX)		
3	Random Primer d(N)e		BOGUANG
4	4*dNTP Mixture		BOGUANG
5	M-MLV Reverse Transcriptase	0000321392	PROMEGA
6	M-MLV RT 5*Buffer	0000318756	PROMEGA
7	Recombinant RNsasin® Ribonuclease Inhibitor	0000329876	PROMEGA
8	D- (+)-Galactosamive hydrochloride	G0500-5G	SIGMA
9	Lipopolysaccharides from Escherichia colio o111:B4	L4130	SIGMA
10	RayBio® Mouse IL-6 ELISA Kit		RayBio
11	RayBio® Mouse TNF-alpha ELISA Kit		RayBio
12	Reactive Oxygen Species Assay Kit	50101ES01	BIOLAI
13	Goat Anti-Rat IgG(H+L),HRP	ABS20031	absin
14	Caspase 3	19677-1-AP	PROTEINTECH
15	Caspase 9	9505S	CST
16	CD11b	ab133357	abcam
17	F4/80	ab16911	abcam



Supplyment Figure 1. Verification of particles uptake of *ROS*. A, Fluorescent probe to detect *ROS* in cells (*n=2*). B, Statistics of *ROS* fluorescence intensity (*n=3*, $^{*}p < 0.05$, $^{***}p < 0.001$, $^{****}p < 0.0001$).



Supplyment Figure 2. Animal safety verification of *$ZnO_{0.2}$–NiO@COOH*. A, H*E staining* to observe liver tissue damage at 0, 24, 48, and 72 *h* (*n=5*). B, Detection of *ALT* and *AST* to assess liver function (*n=5*, *p > 0.05*). C, Liver tissue expression levels of inflammatory factors (*n=3*, *p > 0.05*).



Supplyment Figure 3A-E. Verify the effect of particles on acute liver injury. A, Construct an *ALI* model and weigh the livers of four groups of mice after death (*n=5*, $^{*}p < 0.05$). B, *HE staining* of liver tissue. C and D, Detection of inflammatory factors in liver tissue by *PCR* and immunohistochemical staining (*n*=3, $^{*}p < 0.05$, $^{**}p < 0.01$). E, Detection of *ALT* and *AST* (*n=5-8*, $^{*}p < 0.05$).