Supporting Information

Edible and high biocompatible nanodots from natural plants for treatment of stress gastric ulcers

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Supplementary Tables

Table S1. The inhibition rate of medicines and semi-carbonized nanodots (SCNDs) against gastric ulcer.

Group	Charred herbs (source of SCNDs)	Crude herbs	Inhibition rate of crude herbs	Inhibition rate of SCNDs
Normal	—	—	—	—
OME	—	—	—	36.2%
Ranitidine	—	—	—	81.2%
SCNDs-1	charred Atractylodes Macrocephala	Atractylodes Macrocephala	14.23%	95.6%
SCNDs-2	Licorice charcoal	Licorice	23.2%	78.9%
SCNDs-3	Rhubarb charcoal	Rhubarb	13%	55.9%
SCNDs-4	charred Arteisia frigida	Arteisia frigida	0	58.9%
SCNDs-5	Nodus Nelumbinis Rhizomatis Charcoal	Nodus Nelumbinis Rhizomatis	0	89.5%
SCNDs-6	Sophora flavescens charcoal	Sophora flavescens	0	60.0%
SCNDs-7	Charred Portunus trituberculatus shells	Portunus trituberculatus shells	6.3%	47.6%

Note: Different groups of rats were administrated orally by the listed medicines and SCNDs. Omeprazole (OME) and Ranitidine are the commonly used first-line drugs. Each kind of SCNDs is extracted from the corresponding charred herb prepared by fire processing of crude herb. Both inhibition rates of SCNDs and crude herbs against gastric ulcer of rats are listed.

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31 **Table S2**. Effects of SCNDs-1 on gastric mucosa in rats with stress ulcer.

Group	Proportion of the ulcer area （%）	inhibition rate（%）	Ulcer index	Protective index
Normal	0	100	0	1
Model	19.05±4.29$^{###}$	0	33.86±4.93$^{###}$	0
Control	3.579±0.7012***	81.21	10.50±2.57***	0.69
L	3.697±1.150***	80.59	10.63±3.29***	0.69
M	0.8399±0.1617***	95.59	3.125±0.99***	0.91
H	0.8537±0.2780***	95.52	3.571±1.097***	0.89

32 Note: Data are expressed as mean ± SD with n=6 ($\bar{x}\pm s$, n=6). $^{***}P < 0.001$ vs model group. $^{###}P$

33 < 0.001 vs normal group.

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Table S3. Metabolites with significant difference.

Compounds	Index	VIP	Fold Change (FC)	Log_2 FC	Type
L-Homocitrulline	MEDN047	1.84	0.45	-1.15	down
N-Phenylacetylglycine	MEDN061	1.38	0.36	-1.48	down
Dulcitol	MEDN120	1.49	0.44	-1.18	down
D-Sorbitol	MEDN213	1.65	0.43	-1.23	down
D-Glucose	MEDN220	1.77	0.36	-1.49	down
D-Arabinose	MEDN228	1.90	0.35	-1.52	down
D-Glucoronic Acid	MEDN237	1.34	0.41	-1.28	down
2-Hydroxyisocaproic Acid	MEDN284	1.05	0.46	-1.13	down
3-Hydroxypropanoic Acid	MEDN293	1.85	0.30	-1.74	down
Hippuric Acid	MEDN317	1.81	0.08	-3.74	down
L-3-Phenyllactic Acid	MEDN324	1.62	0.30	-1.75	down
Phenyllactate (Pla)	MEDN338	1.54	0.42	-1.25	down
13-HOTrE [13S-hydroxy-9Z,11E,15Z-octadecatrienoic acid]	MEDN375	1.37	0.48	-1.05	down
Oxoadipic Acid	MEDN470	2.11	3.02	1.60	up
Formononetin	MEDN625	1.26	0.24	-2.05	down
Isopropyl myristate	MEDN673	1.68	3.61	1.85	up
N-(2-Methylbenzoyl)glycine	MEDN720	1.39	0.34	-1.57	down
(±)17-HDHA [(±)17-hydroxy-4Z,7Z,10Z,13Z,15E,19Z-docosahexaenoic acid]	MEDN754	1.38	0.28	-1.85	down
14(S)-HDHA [14S-hydroxy-4Z,7Z,10Z,12E,16Z,19Z-docosahexaenoic acid]	MEDN769	1.51	0.43	-1.20	down
Xylose	MEDN813	1.87	0.48	-1.06	down
Asp-Phe	MEDP037	1.88	0.49	-1.04	down

N-Isovaleroylglycine	MEDP072	1.37	0.48	-1.07	down
Phenylacetyl-L-Glutamine	MEDP077	1.13	0.31	-1.69	down
Trimethylamine N-Oxide	MEDP084	1.64	0.27	-1.89	down
4-Pyridoxic Acid	MEDP118	1.37	0.31	-1.70	down
Lactose	MEDP229	1.63	0.24	-2.08	down
2,6-Diaminooimelic Acid	MEDP285	1.66	0.44	-1.19	down
Dl-2-Aminooctanoic Acid	MEDP307	1.43	0.49	-1.04	down
2-(Dimethylamino)Guanosine	MEDP380	2.03	0.48	-1.07	down
δ-Valerolactam	MEDP541	1.11	0.19	-2.36	down
18-Hydroxycorticosterone	MEDP550	1.33	0.39	-1.35	down
(E)-2-Octen-1-ol	MEDP701	1.27	0.42	-1.26	down
Octanal	MEDP794	1.09	0.41	-1.27	down
1-Aminopropan-2-ol	MEDP831	1.59	0.28	-1.84	down

Supplementary Figures

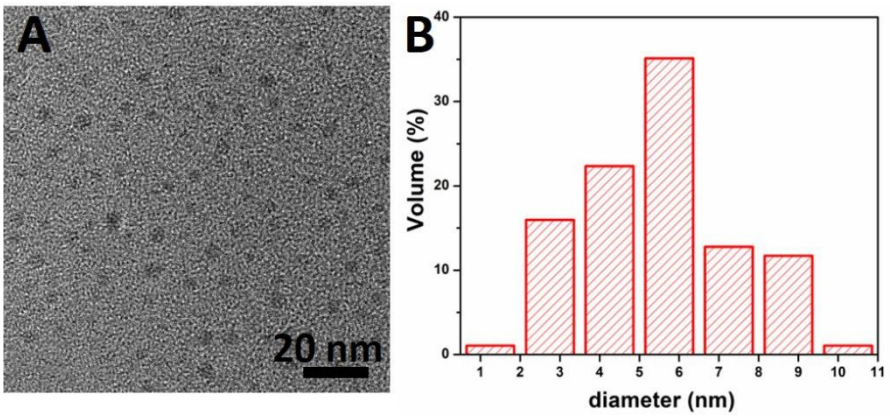
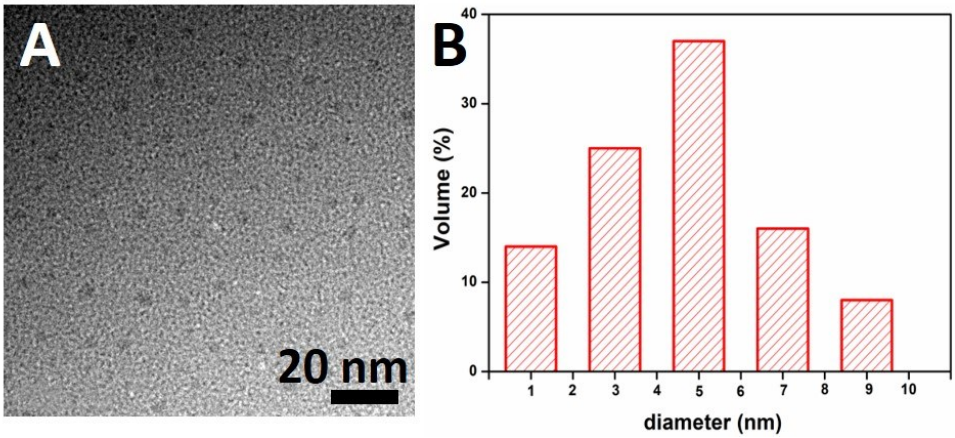


Fig S1. **Morphological characterization of SCNDs-1**. (A) TEM image and (B) particle size distribution.



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43 **Fig S2**. **Morphological characterization of SCNDs-2**. (A) TEM image and (B) particle size
44 distribution.

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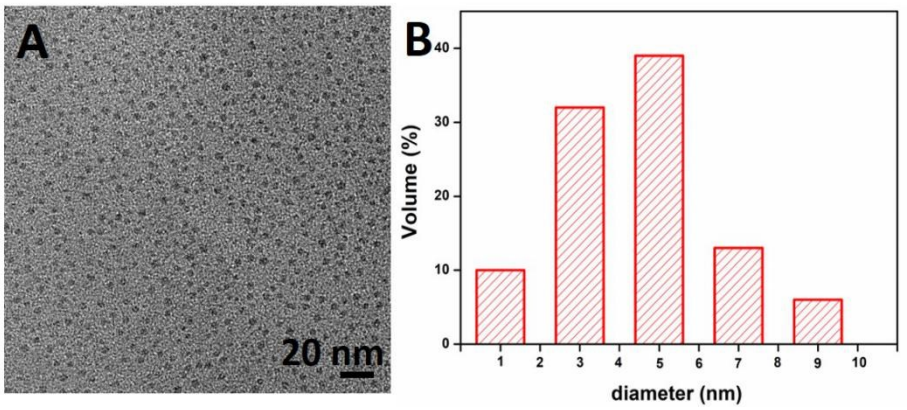

Fig S3. **Morphological characterization of SCNDs-3**. (A) TEM image and (B) particle size distribution.

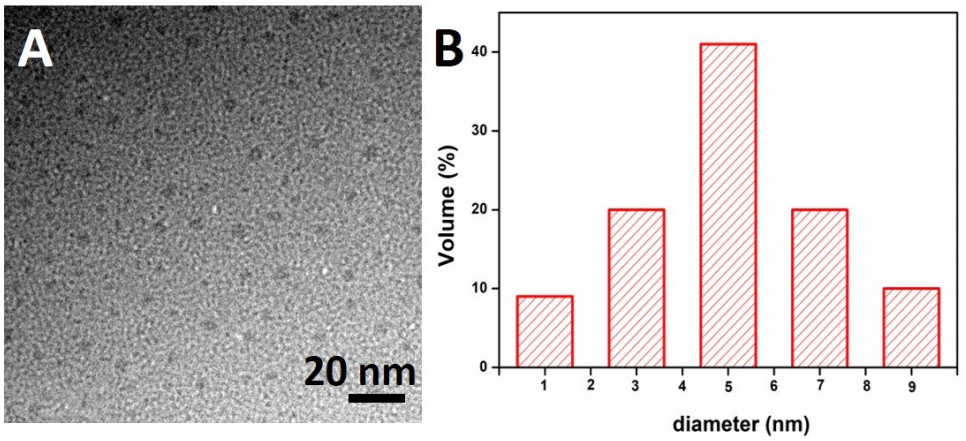

Fig S4. **Morphological characterization of SCNDs-4**. (A) TEM image and (B) particle size distribution.

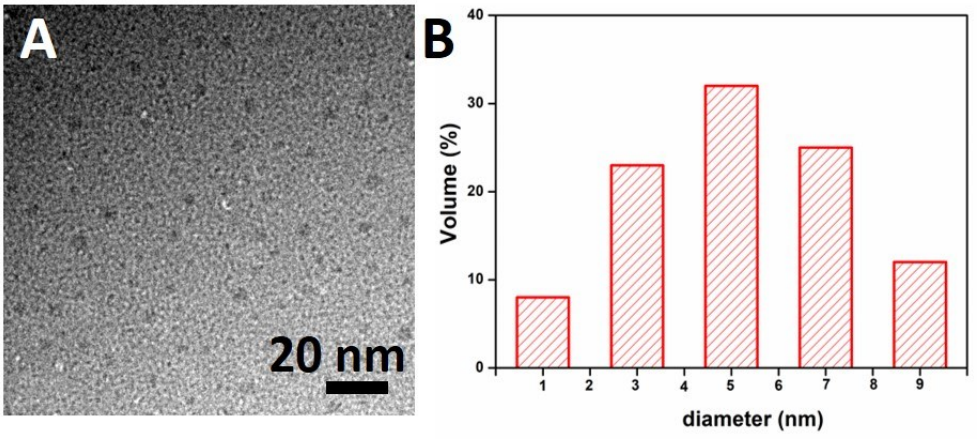

Fig S5. **Morphological characterization of SCNDs-5**. (A) TEM image and (B) particle size distribution.

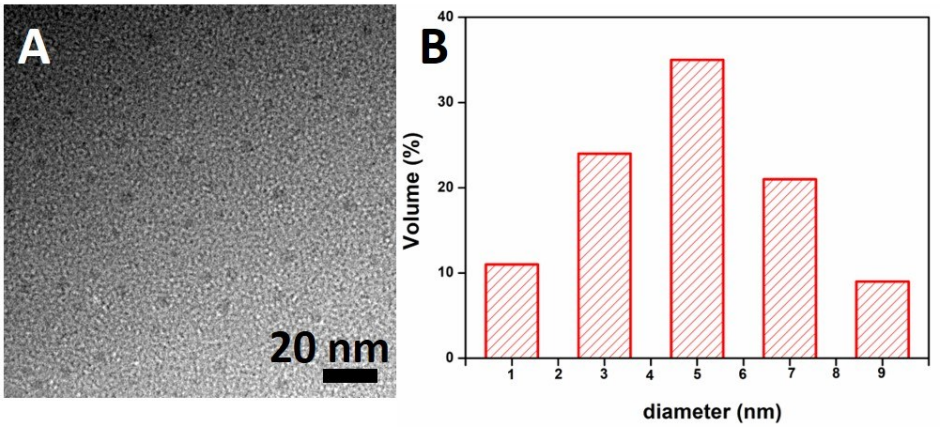

Fig S6. **Morphological characterization of SCNDs-6**. (A) TEM image and (B) particle size distribution.

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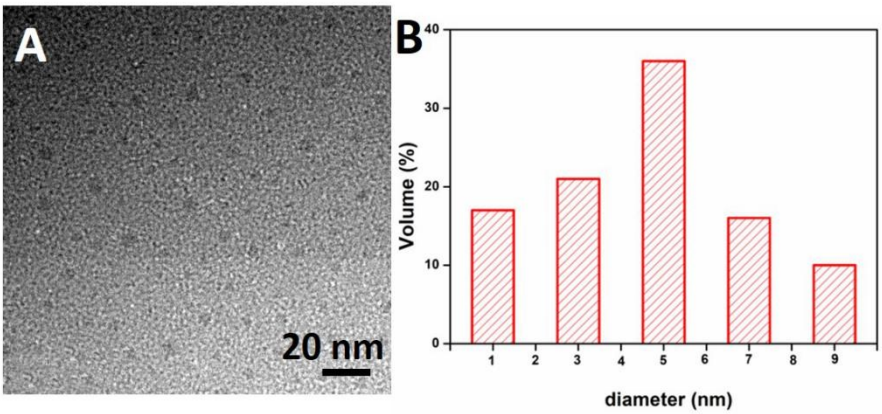

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68 **Fig S7**. **Morphological characterization of SCNDs-7**. (A) TEM image and (B) particle size
69 distribution.

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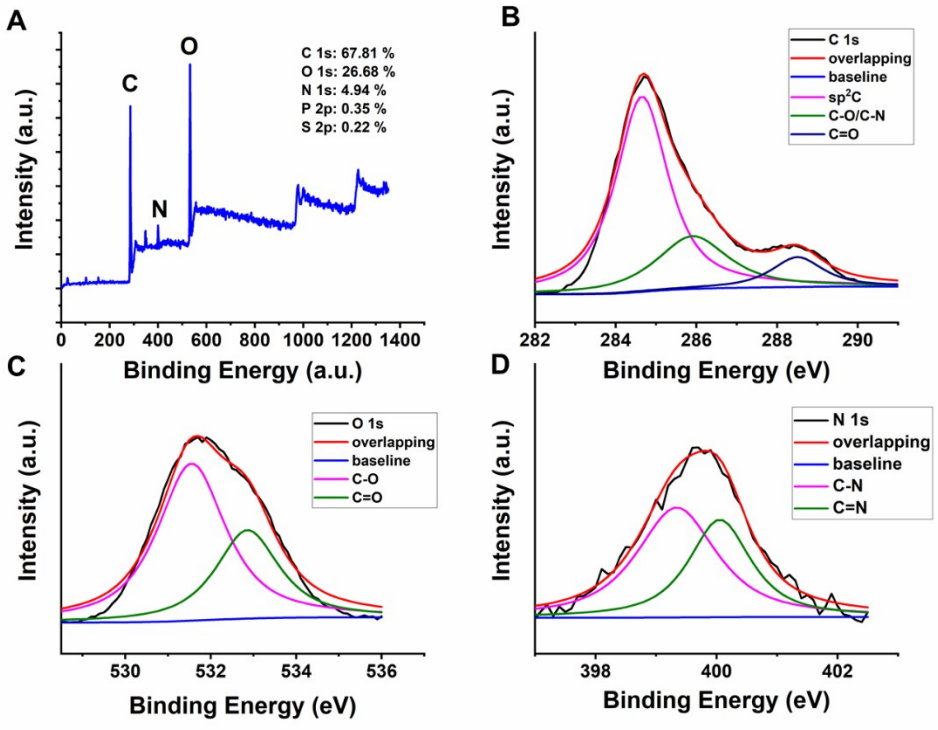

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73 **Fig S8**. **XPS spectra of SCNDs-1.** (A) The full-scan spectrum; (B) High-resolution C 1s; (C)
74 High-resolution O 1s and (D) High-resolution N 1s.

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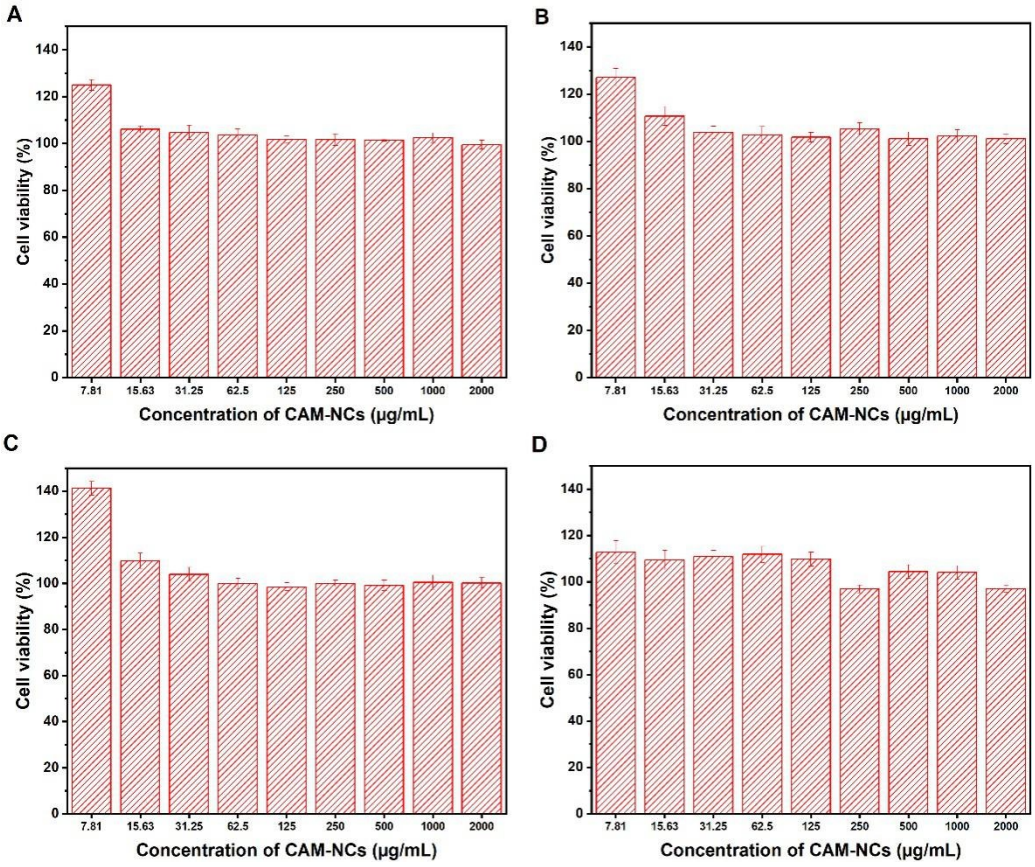

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79 **Fig S9.** Effects of different concentrations of SCNDs-1 on the viability of RAW264.7 cells. The
80 incubation time was (A) 12 h; (B) 24 h; (C) 36 h and (D) 48 h.

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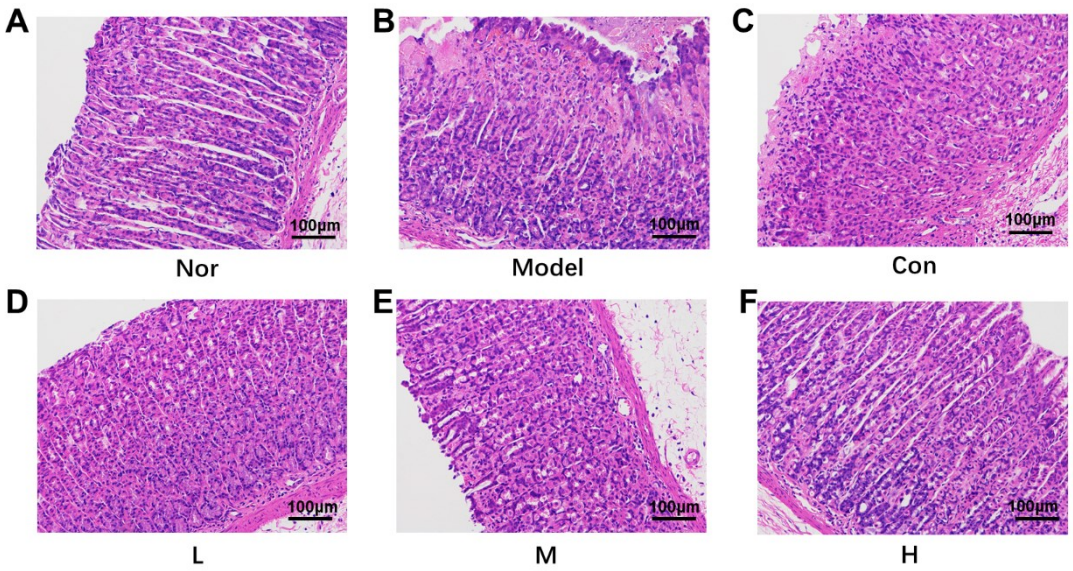


Fig S10. Histopathological examination of the gastric mucosa in rats. (A) Normal group; (B) Model group; (C) Ranitidine control group (Control); SCNDs-1 groups at dose of (D) low (L), (E) medium (M), and (F) high (H).

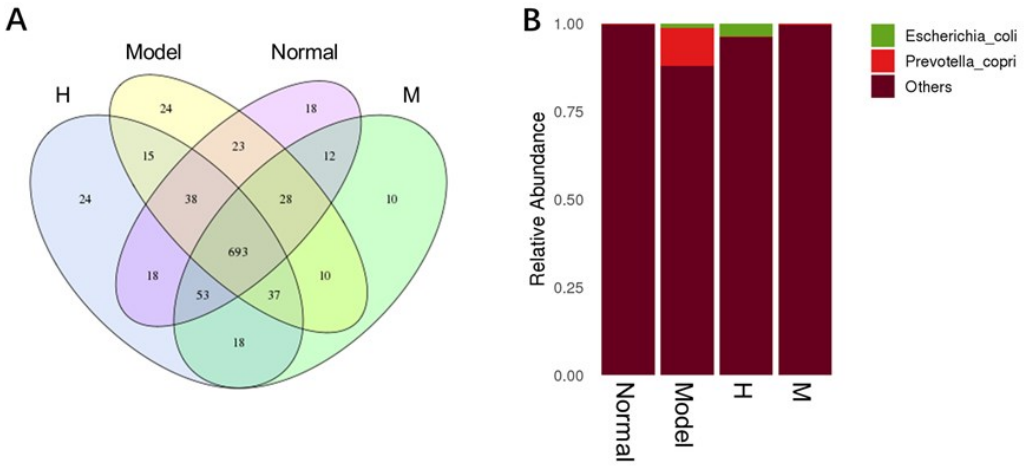
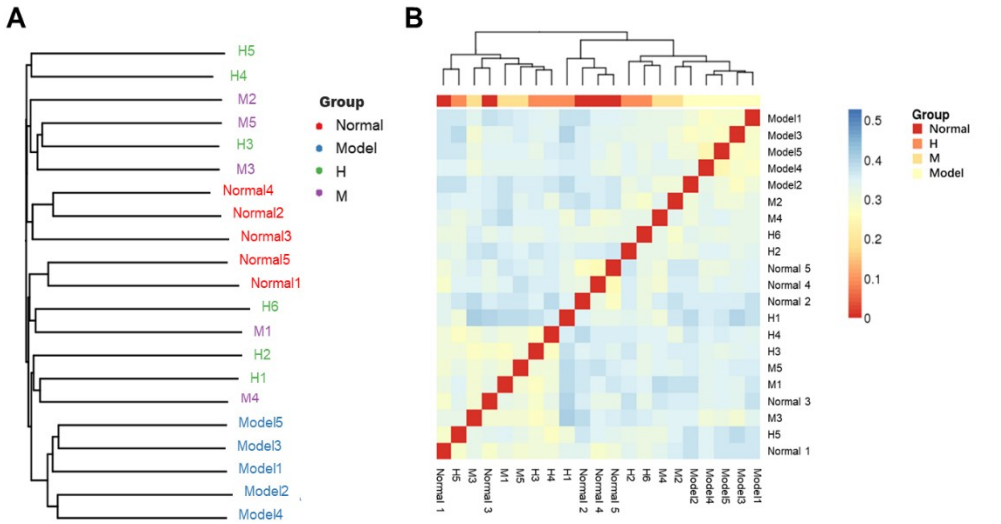


Fig S11. (A) OUT Venn and (B) Species abundance at Species level of intestinal microflora of rats. Rats were divided into Normal group, Model group, SCNDs-1 groups at doses of medium (M), and high (H). The abundance of the species less than 0.5% are expressed as Others.



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95 **Fig S12**. (A) system cluster tree and (B) beta diversity heat map of the intestinal microflora analysis

96 of rats

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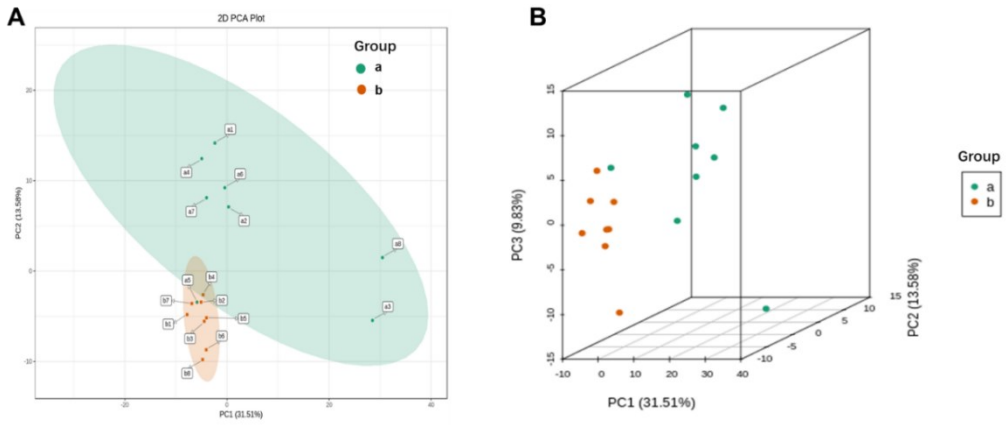

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100 **Fig S13**. Principal component analysis (PCA) of detected blood serum metabolites in different
101 groups. (A) PCA chart; (B) PCA of 3D analysis (a. Model group; b. SCNDs-1 group).

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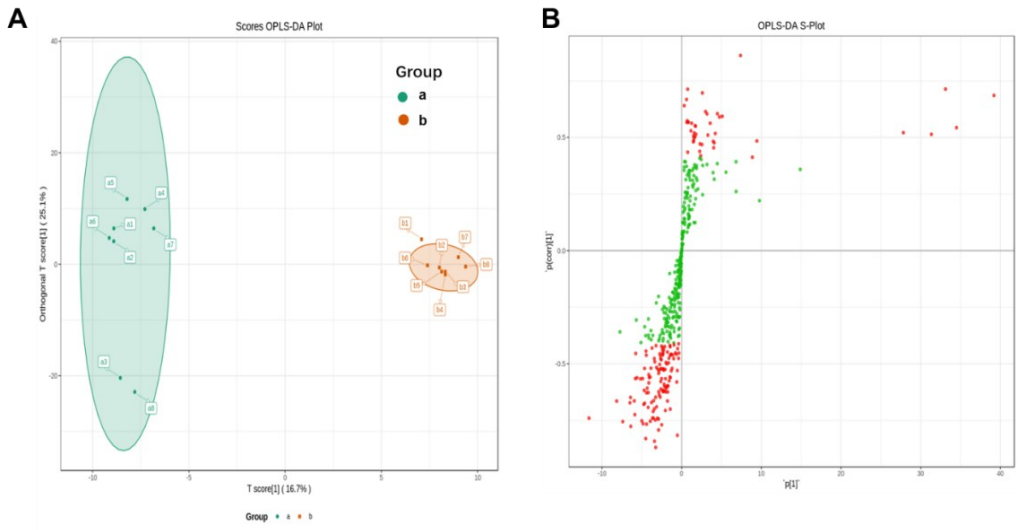
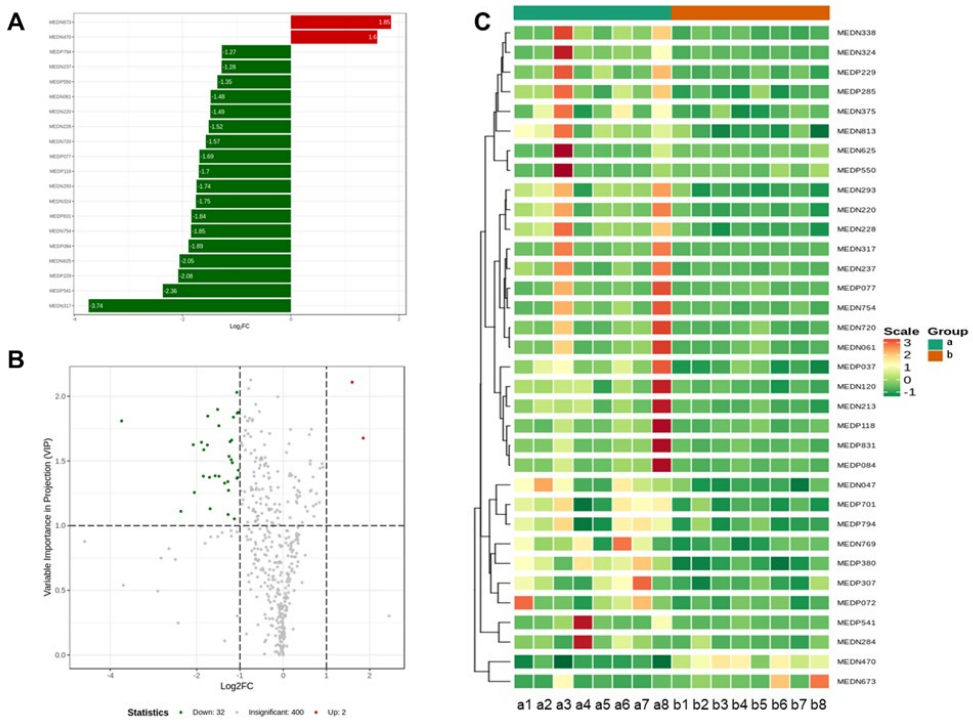


Fig S14. OPLS-DA analysis of detected blood serum metabolites in different groups. (A) OPLS-DA score chart (a. model group; b. SCNDs-1 group); (B) OPLS-DA Scatter plot (S-plot), the red point indicates that the VIP value of these metabolites is greater than or equal to 1, and the green point indicates that the VIP value of these metabolites is less than 1.



110

111 **Fig S15**. Screening of differential metabolites. A. Histogram of the difference multiple; B. volcano
112 map of the difference metabolite. Green indicates down regulation, red indicates up regulation, and
113 black indicates no statistical difference. C. Clustering thermograph of differential metabolites.

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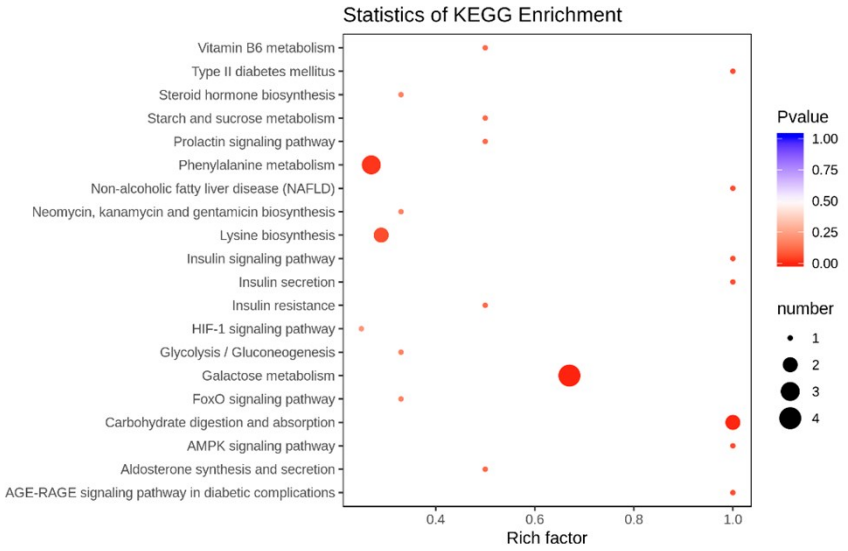

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116 **Fig S16**. Enrichment map of differential metabolite from KEGG. The color of the point corresponds
117 to the P value. The red indicates the enrichment is more significant. The size of the point represents
118 the number of different metabolites enriched.

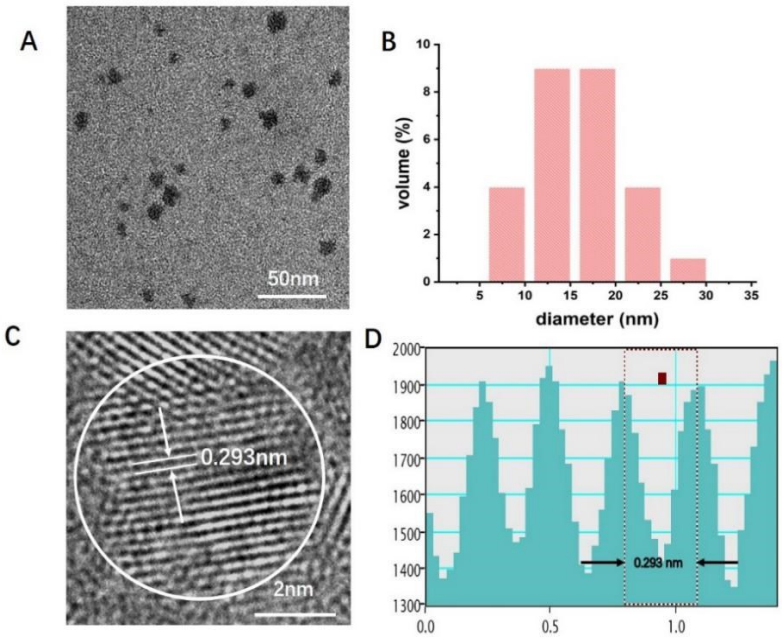

Fig S17. The morphological characteristics of SCNDs-1 prepared under the condition of 250℃. (A) TEM image, (B) Size distribution, (C) HRTEM image and (D) lattice spacing of SCNDs in HRTEM.

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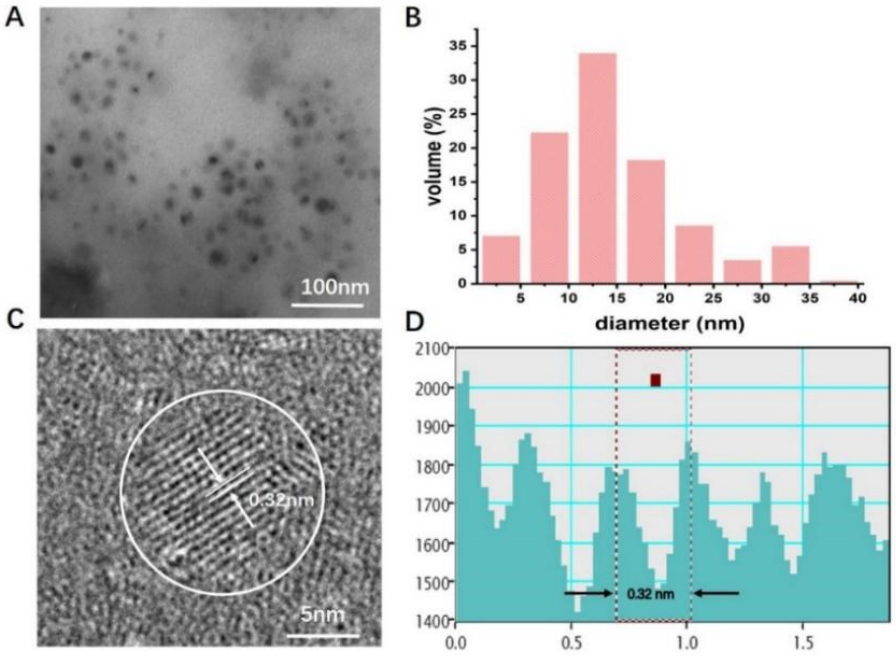

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128 **Fig S18.** The morphological characteristics of SCNDs-1 prepared under the condition of 300℃. (A)
129 TEM image, (B) Size distribution, (C) HRTEM image and (D) lattice spacing of SCNDs in
130 HRTEM.

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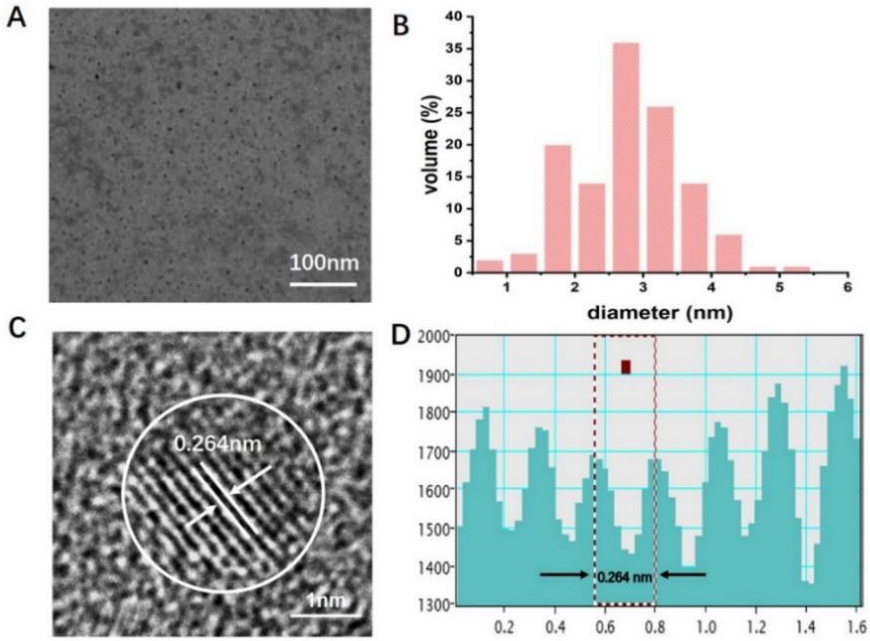

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135 **Fig S19.** The morphological characteristics of SCNDs-1 prepared under the condition of 400℃. (A)
136 TEM image, (B) Size distribution, (C) HRTEM image and (D) lattice spacing of SCNDs in
137 HRTEM.

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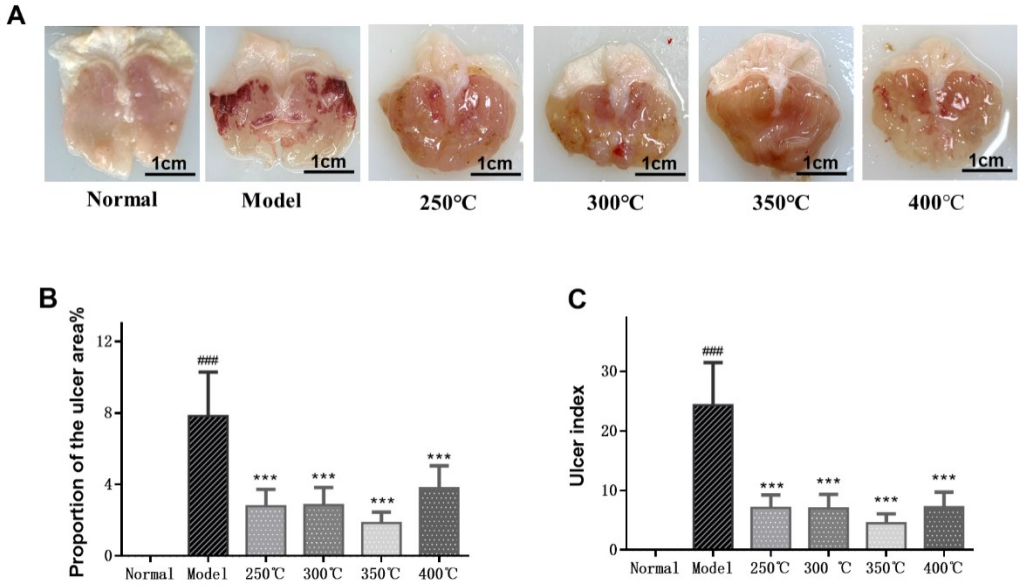

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142 **Fig S20**. The effect of SCNDs-1 prepared under different conditions on gastric ulcer model. (A)
143 Representative macroscopic photographs of stomachs; (B) Proportion of the ulcer area; (C) Ulcer
144 index. Data are expressed as mean ± SD with n=6 ($\bar{x}\pm s$, n=6). $^{***}P < 0.001$ vs model group. $^{###}P <$
145 0.001 vs normal group.

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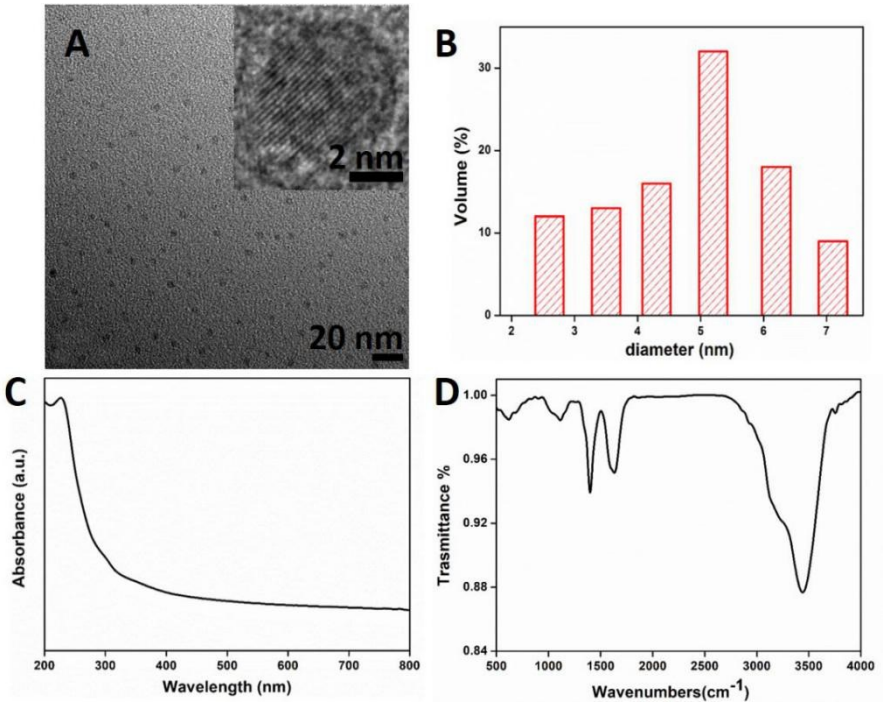

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150 **Fig S21**. TEM image and size distribution of graphitic CDs.

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