Multi-Omics Strategy Reveals *Cordyceps Sinensis* Ameliorates Sepsis-Associated Acute Kidney Injury (S-AKI) via Reprogramming Mitochondrial Energy Metabolism and Macrophage Polarization

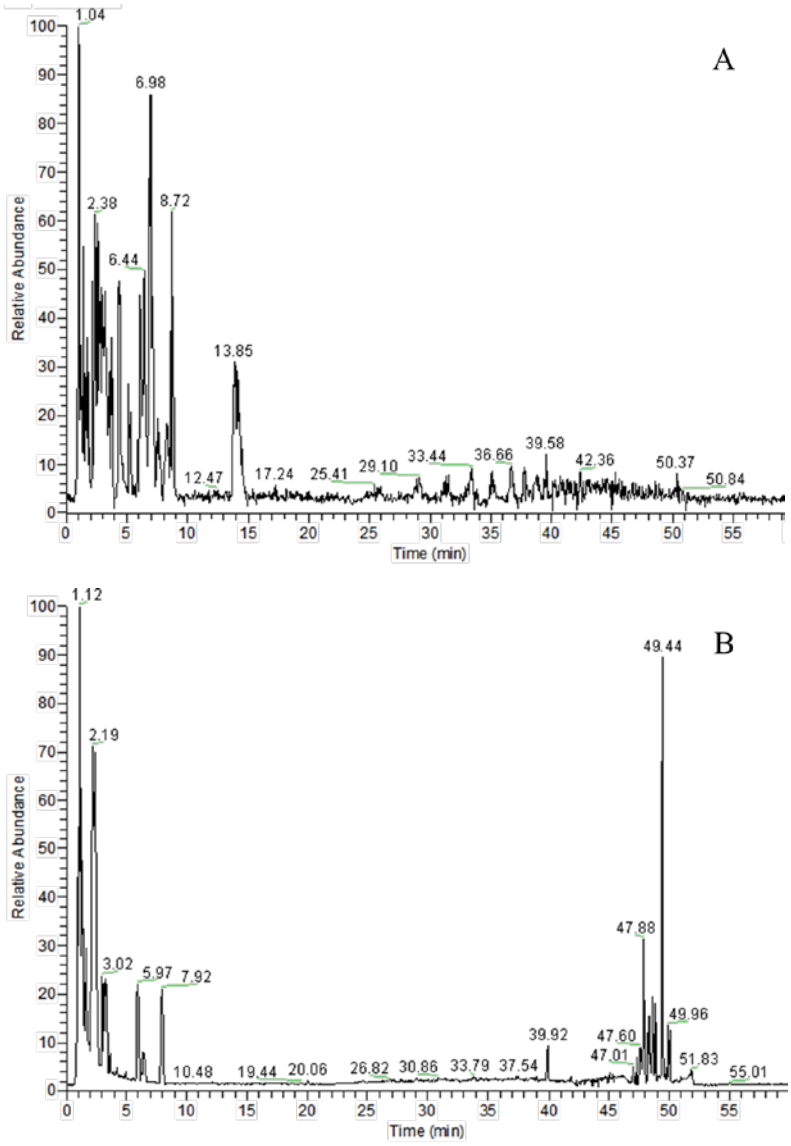

Fig. S1. Total ion chromatogram of *Cordyceps Sinensis* by UHPLC-LTQ-Orbitrap-MS in positive mode (A) and negative mode (B).

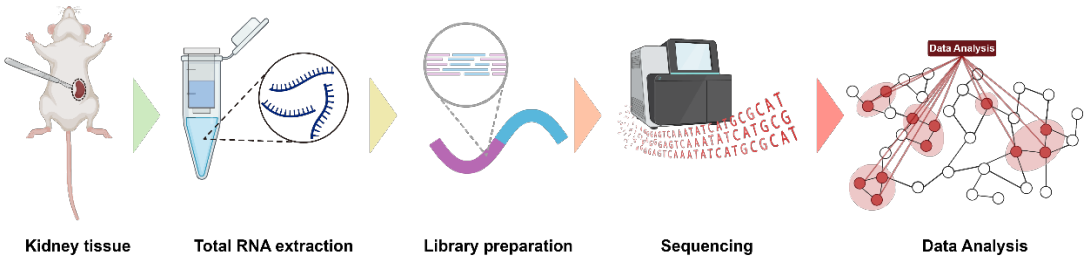

Fig. S2. Overall workflow for transcriptome analysis.

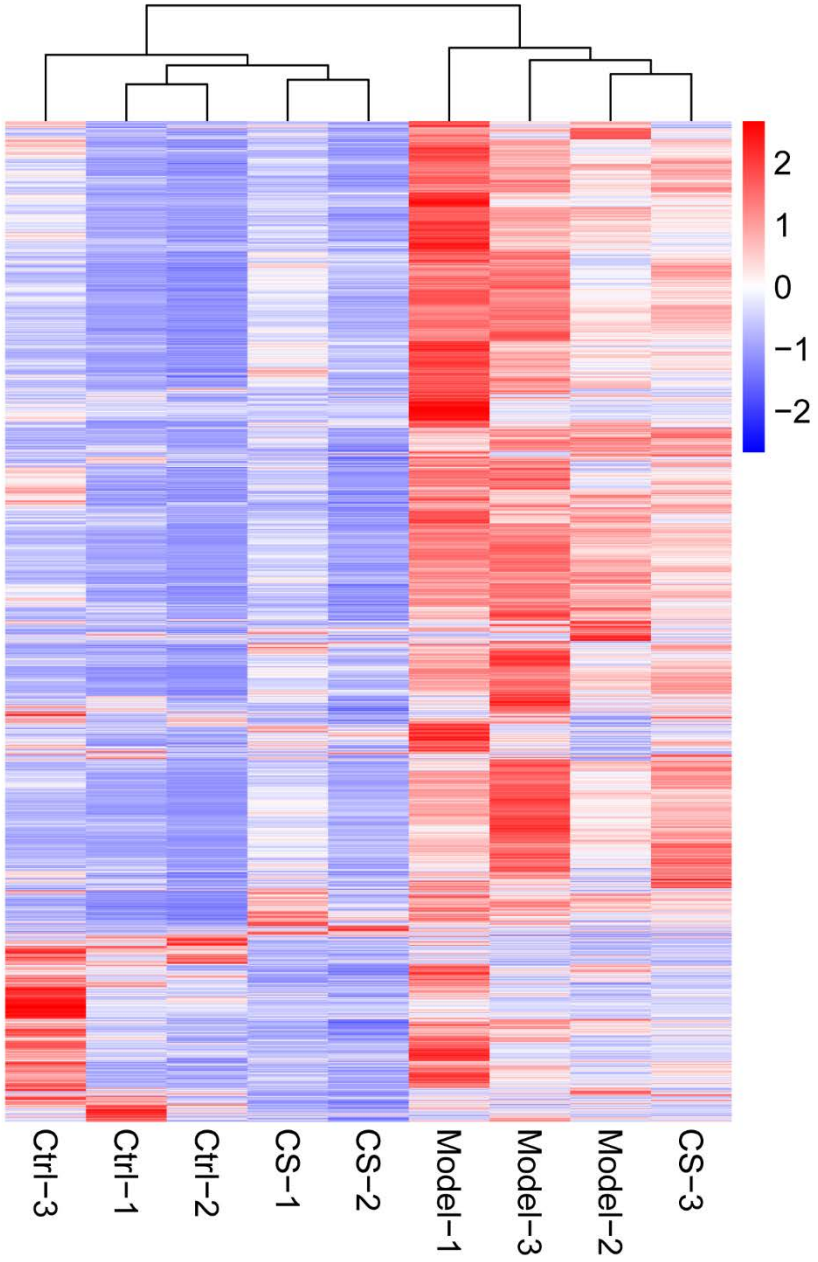

Fig. S2. Heatmap showing the abundance of genes across the three groups by transcriptome.

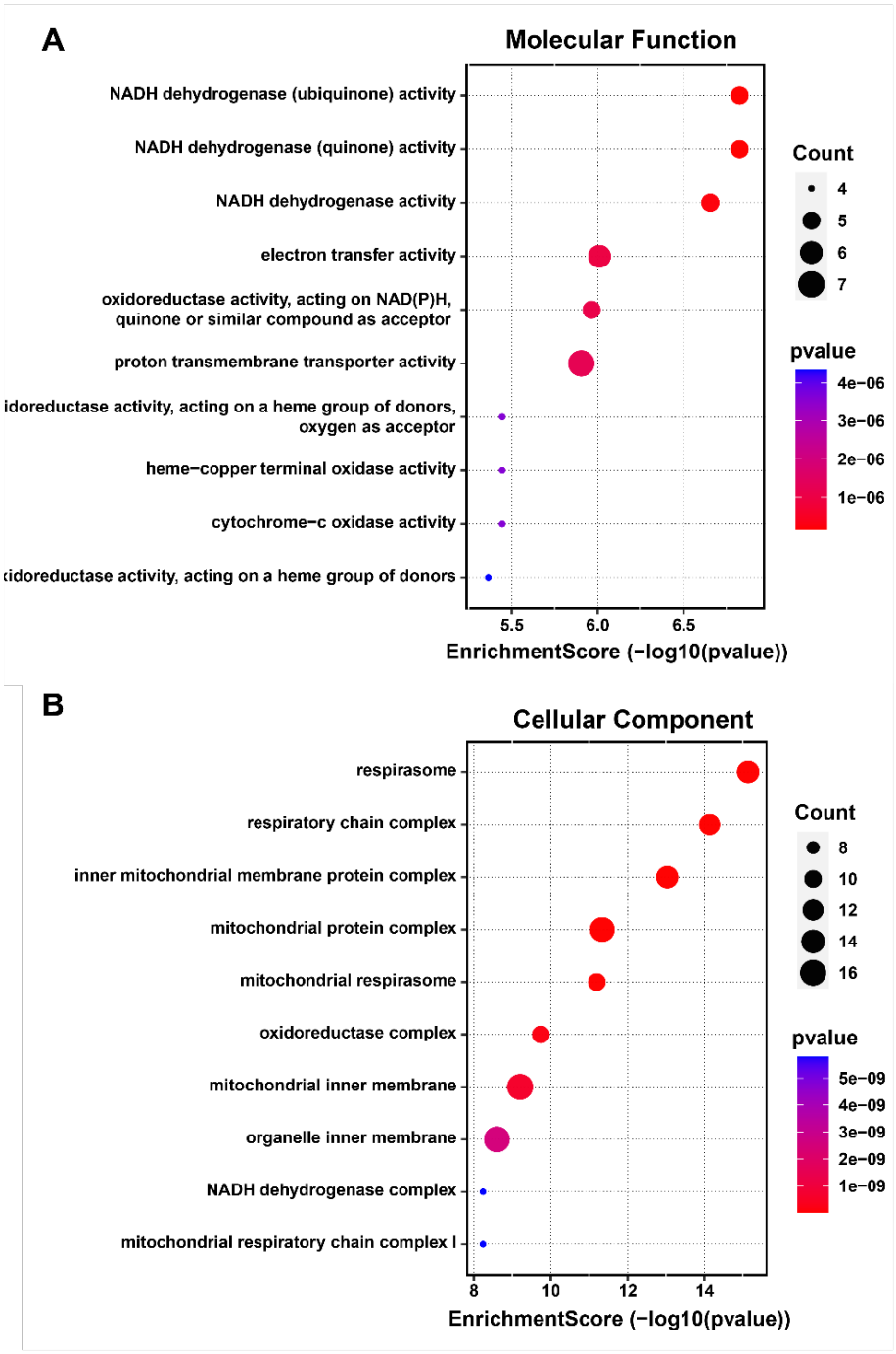

Fig. S3. GO enrichment analysis of the DEGs in “Model vs. Ctrl” and “CS vs. Model” in terms of molecular function (A) and cellular component (B).

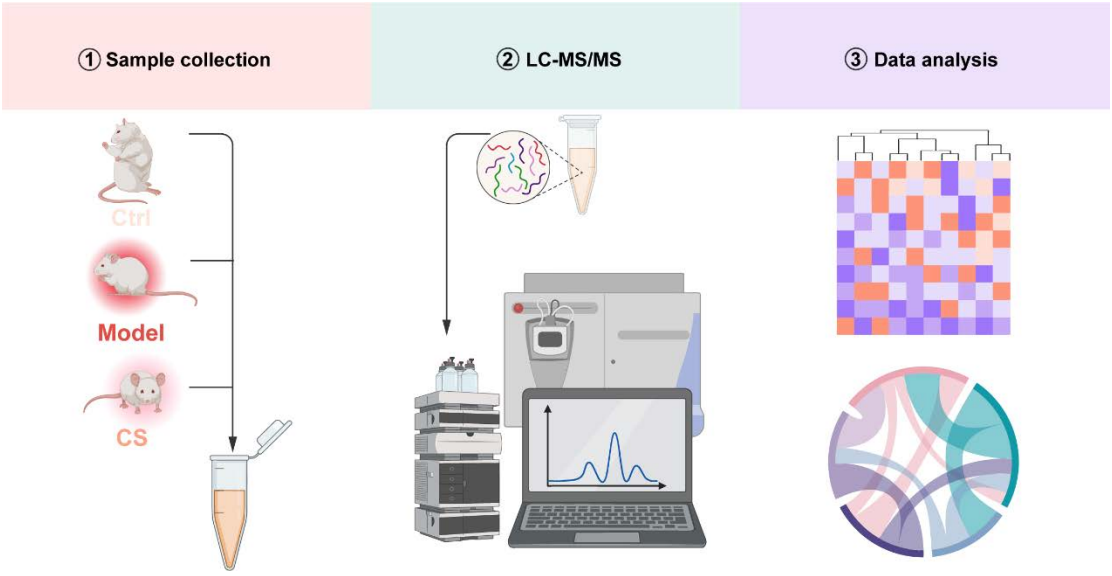

Fig. S4. Overall workflow for proteomic analysis.

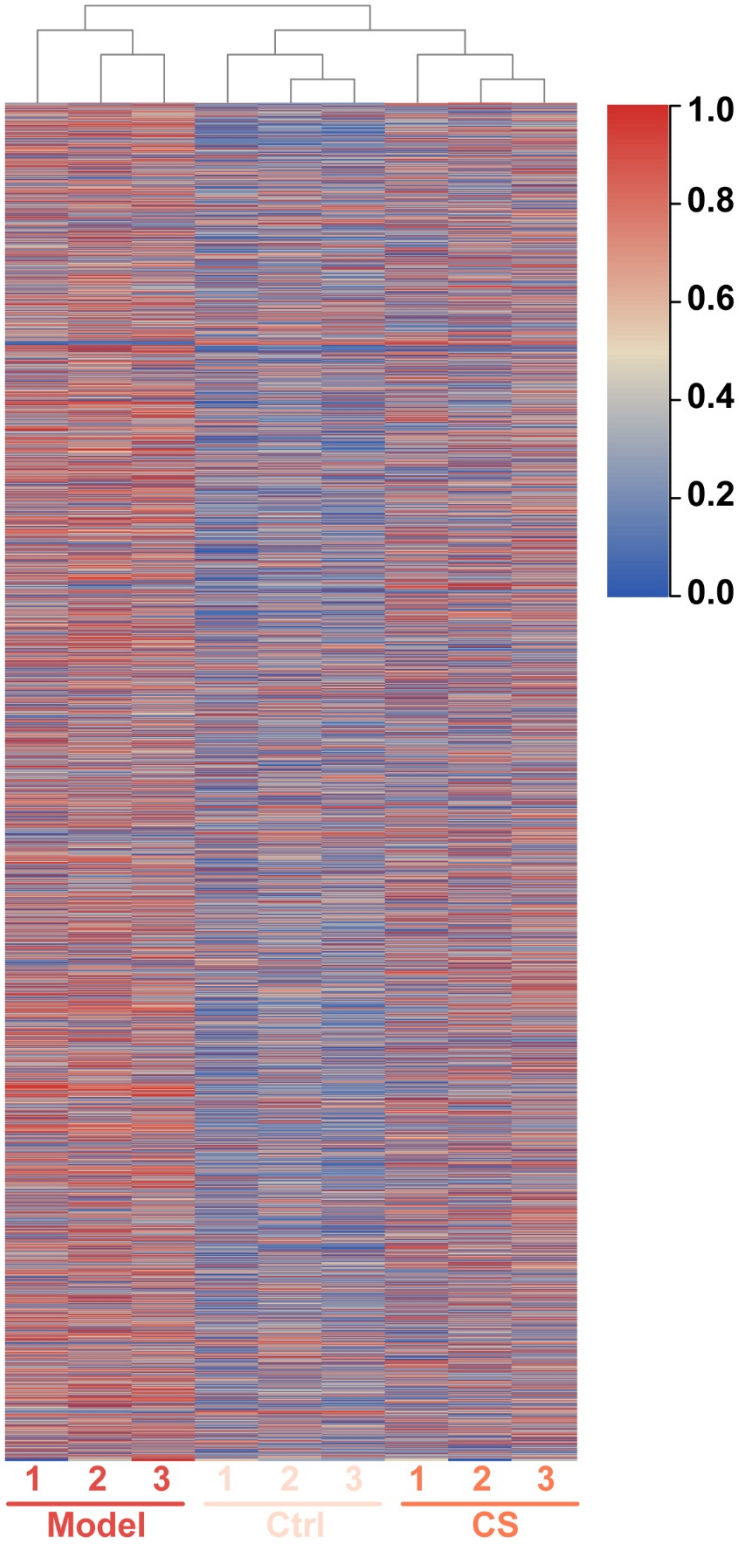

Fig. S5. Heatmap showing the abundance of proteins across the three groups.

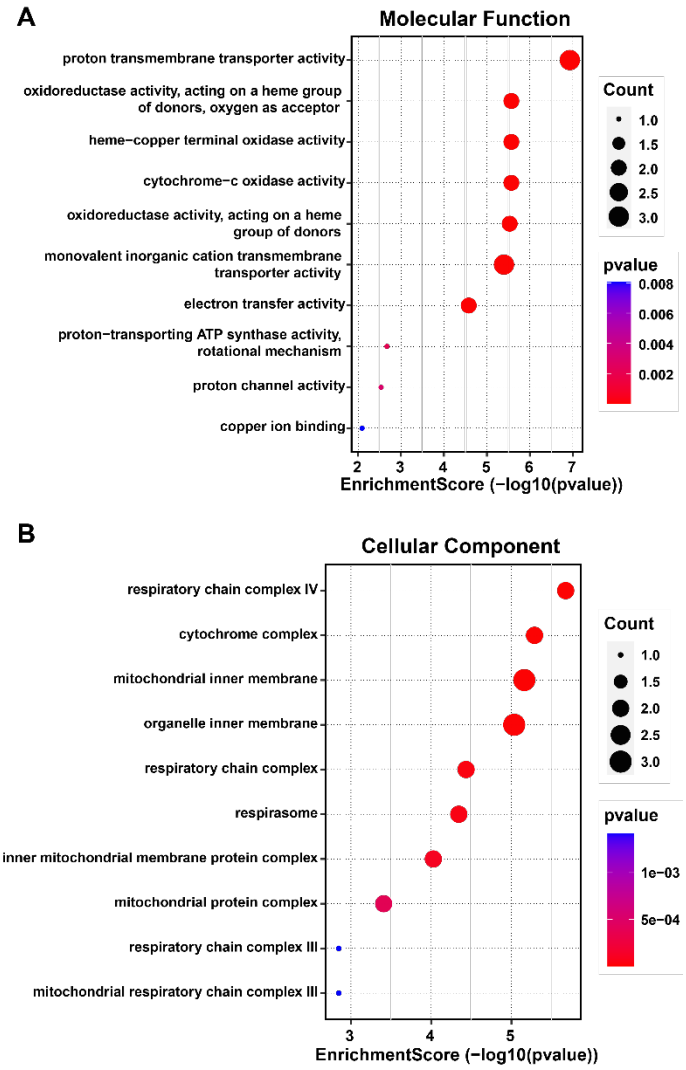

Fig. S6. GO enrichment analysis of the upregulated proteins in "CS vs. Model" in terms of molecular function (A) and cellular component (B).

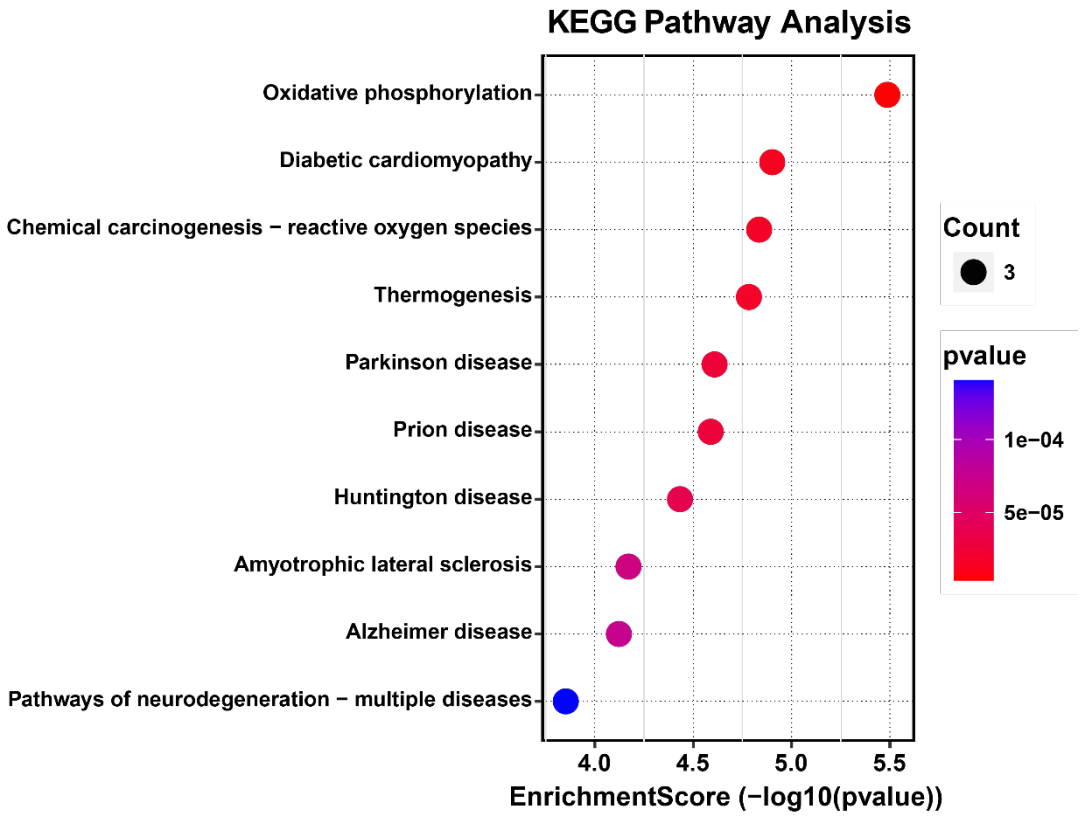

Fig. S7. The KEGG enrichment result of the upregulated proteins in “CS vs. Model”.

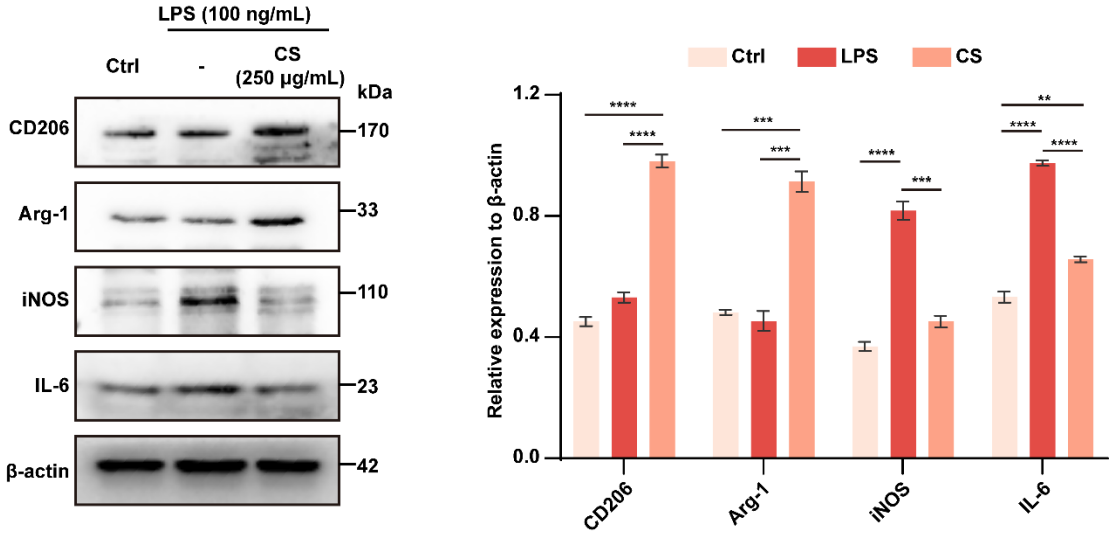

Fig. S8. CS modulated LPS-induced macrophage polarization *in vitro*. Representative blots of M2 markers (CD206 and Arg1) and M1 markers (iNOS and IL-6) in RAW264.7 cells (n=3). Protein expression was normalized to β-actin expression and represented as mean ± SEM. **p < 0.01, ***p < 0.001; ****p < 0.0001.

Table S1. Identification of chemical constituents of *Cordyceps Sinensis* by UHPLC-LTQ-Orbitrap-MS.

No.	t_R (min)	Molecular formula	Error (ppm)	$[M+H]^+/[M+Na]^+$		$[M-H]^-/[M-Cl]^-$		MS/MS	Compound
				Measured (m/z)	Theoretical (m/z)	Measured (m/z)	Theoretical (m/z)		
Nucleosides									
1	1.44	$C_9H_{14}N_3O_8P$	-3.726	324.0579	324.0591				CMP
2	1.49	$C_{10}H_{15}N_5O_{10}P_2$	-2.537			426.0200	426.0210		ADP
3	1.65	$C_9H_{13}N_2O_9P$	-1.216			323.0271	323.0275	280.0232,211.0015,96.9699	UMP
4	2.03	$C_9H_{13}N_3O_5$	-4.044	244.0918	244.0928				Cytidine
5	2.41	$C_{10}H_{14}N_2O_6$	-4.449	259.0913	259.0925				3'-O-Methyluridine
6	2.69	$C_9H_{12}N_2O_5$	0.494			227.0664	227.0662		2'-Deoxyuridine/3'-Deoxyuridine
7	3.67	$C_9H_{12}N_2O_6$	2.540			243.0618	243.0612	200.05676,152.03581,140.03572,110.02509，82.03002	Uridine
8	4.70	$C_{10}H_{15}N_2O_8P$	-0.805			321.0480	321.0482	195.0065,176.9962	TMP
9	5.58	$C_9H_{12}N_2O_5$	-1.444			227.0659	227.0662		2'-Deoxyuridine/3'-Deoxyuridine
10	6.61	$C_{10}H_{14}N_2O_5$	-4.147	243.0965	243.0975				Thymidine
11	7.20	$C_{10}H_{13}N_5O_4$	-4.067	268.1029	268.1040			136.0615	2'-Deoxyguanosine
12	7.83	$C_{10}H_{12}N_4O_5$	-1.071			267.0721	267.0724		Inosine
13	9.50	$C_{10}H_{13}N_5O_5$	-0.372			282.0832	282.0833	150.04227,133.01598	Guanosine
14	9.70	$C_{10}H_{13}N_5O_4$	-0.340			266.0883	266.0884	150.04224，133.01569	Adenosine
15	17.34	$C_{11}H_{15}N_5O_4$	-4.610	282.1184	282.1197			150.0772	N6-Methyladenosine/2'-O-Methyladenosine
16	24.40	$C_{11}H_{15}N_5O_4$	-4.397	282.1184	282.1197			150.0772	N6-Methyladenosine/2'-O-Methyladenosine
17	30.47	$C_{12}H_{17}N_5O_5$	-3.144			310.1136	310.1146		N-(2-Hydroxyethyl)adenosine
Amino acids									

18	0.91	$C_6H_{14}N_2O_2$	2.590			145.0975	145.0972		L-Lysine
19	0.94	$C_6H_9N_3O_2$	3.226			154.0616	154.0611	137.03586，136.05186，118.04103，110.07235，93.04583	Histidine
20	0.95	$C_5H_9NO_4$	4.696			146.0455	146.0448	128.03557,135.02998,120.61879,118.01016	glutamic acid
21	1.00	$C_6H_{14}N_4O_2$	-4.867	175.1181	175.1190				Arginine
22	1.03	$C_5H_9NO_3$	-4.617	132.0649	132.0655				hydroxyproline/5-aminolevulinic acid
23	1.03	$C_5H_9NO_3$	-4.617	132.0649	132.0655				hydroxyproline/5-aminolevulinic acid
24	1.16	$C_5H_9NO_2$	-4.524	116.0701	116.0706			70.0647	Proline
25	1.54	$C_5H_{11}NO_2$	-4.024	118.0858	118.0863				Valine
26	1.84	$C_8H_{16}N_2O_3$	-3.167	189.1228	189.1234			130.0860,84.0804	N-α-acetyl-L-lysine
27	2.88	$C_7H_{11}NO_5$	1.176			188.0556	188.0553		N-acetyl-dl-glutamic acid crystalline
28	3.19	$C_6H_{13}NO_2$	-4.657	132.1013	132.1019			86.0961	isoleucine
29	3.47	$C_9H_{11}NO_3$	-4.063	182.0804	182.0812			165.05438，147.04385，136.07550，123.04386	Tyrosine
30	7.92	$C_9H_{11}NO_2$	-4.005	166.0856	166.0863				Phenylalanine
31	40.02	$C_8H_{15}NO_3$	1.396			172.0971	172.0968	130.0875	N-Acetyl-D-allo-isoleucine
32	41.87	$C_{14}H_{16}N_2O_4$	-2.557			275.1019	275.1026	257.0932,231.1140,215.0828,203.00828,188.1082,170.0975	cyclo (Pro-Leu)
Purine alkaloids									
33	7.23	$C_5H_5N_5$	-2.732	136.0614	136.0618			119.0488,108.0885,91.0538	Adenine
34	8.54	$C_{10}H_{13}N_5O_3$	-3.276	252.1083	252.1091				Cordycepin
35	8.93	$C_5H_4N_4O_2$	-4.260	153.0401	153.0407				Xanthine
36	9.00	$C_5H_5N_5O$	-3.725	152.0561	152.0567			135.0298,110.0345	Guanine
37	11.31	$C_5H_4N_4O$	-4.067	137.0452	137.0458				Hypoxanthine

Pyrimidine alkaloids									
38	1.14	$C_5H_6N_2O_2$	-3.495	127.0498	127.0502				Thymine
39	2.03	$C_4H_5N_3O$	-4.626	112.0500	112.0505				Cytosine
40	2.03	$C_9H_{13}N_3O_5$	-4.044	244.0918	244.0928				Cytarabine
41	3.95	$C_4H_4N_2O_2$	-3.751	113.0341	113.0346			95.0852,85.0643,71.0487,67.0538	Uracil
Organic acid									
42	1.02	$C_6H_{12}O_7$	1.645			195.0503	195.0499		Gluconic acid
43	1.13	$C_7H_{12}O_6$	3.535			191.0557	191.0550		D-(-)-Quinic acid
44	1.25	$C_4H_6O_5$	4.287			133.0137	133.0131	115.0039,71.0140	DL-Malic acid
45	1.54	$C_8H_9NO_2$	-3.913	152.0700	152.0706				N-methylanthranilic acid
46	2.07	$C_6H_8O_7$	-4.140	193.0335	193.0340				Citric Acid
47	3.47	$C_9H_8O_3$	-4.427	165.0539	165.0546			147.0438,123.0438,119.0490	p-Hydroxy-cinnamic acid
48	34.15	$C_8H_8O_3$	2.115			151.0393	151.0390		(2-hydroxyphenyl)acetic acid
49	45.07	$C_9H_{16}O_4$	0.612			187.0966	187.0965		Azelaic Acid
Nucleotides									
50	2.75	$C_{10}H_{14}N_5O_8P$	-4.355	364.0637	364.0653			308.12131，152.05656	5'-Guanylic acid
51	3.98	$C_{10}H_{14}N_5O_7P$	-2.169			346.0540	346.0547	328.04501，195.00687，176.99590	5'-Adenylic Acid
Sugar alcohols									
52	0.95	$C_6H_{14}O_6$	2.957			181.0712	181.0707	163.0615,113.0245,101.0246,89.0245,71.0140,59.0140	Dulcitol
53	1.03	$C_6H_{14}O_6$	-4.668	183.0855	183.0863			165.1019,155.0812,105.0332	D-Mannitol
Others									
54	1.03	$C_7H_{15}NO_3$	-4.194	162.1118	162.1125				Carnitine
55	7.20	$C_9H_{17}NO_8$	0.922	268.1029	268.1027			136.0615	(5S,6R,7S,8R)-5-amino-(2Z,4Z)-1,2,3-trihydroxybuta-2,4-dienyloxy-pentane-6,7,8,9-tetraol

56	20.67	$C_9H_{17}NO_5$	-3.585	220.1172	220.1179				Vitamin B5
57	29.25	$C_7H_6O_2$	4.826			121.0290	121.0284	112.9859,101.0243,93.0301,61.9883	p-Hydroxybenzaldehyde
58	46.53	$C_{10}H_{12}O_3$	-0.339			179.0702	179.0703		2 ', 4' - dihydroxy-3 ', 5' - dimethylacetophenone

Note: 12 compounds (D-mannitol, cordycepin, tyrosine, uridine, arginine, histidine, inosine, adenosine, guanosine, 5'-guanylic acid, 5 '-adenosine, L-lysine) were determined by comparison with the standard substances. The other compounds were determined by comparison with the molecular weight of known compounds, MS, MS^2 fragment information and literature.