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Supporting Information

Mesoporous silica coated CeO_2 nanozymes with combined lipid-lowering and antioxidant activity induce long-term improvement of the metabolic profile in obese Zucker rats

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Table of Contents.

Supporting Figures

Figure S1. TEM images, size distribution and BET analysis of the CeO_2NPs cores and CeO_2@mSiO_2 nanocomposites.

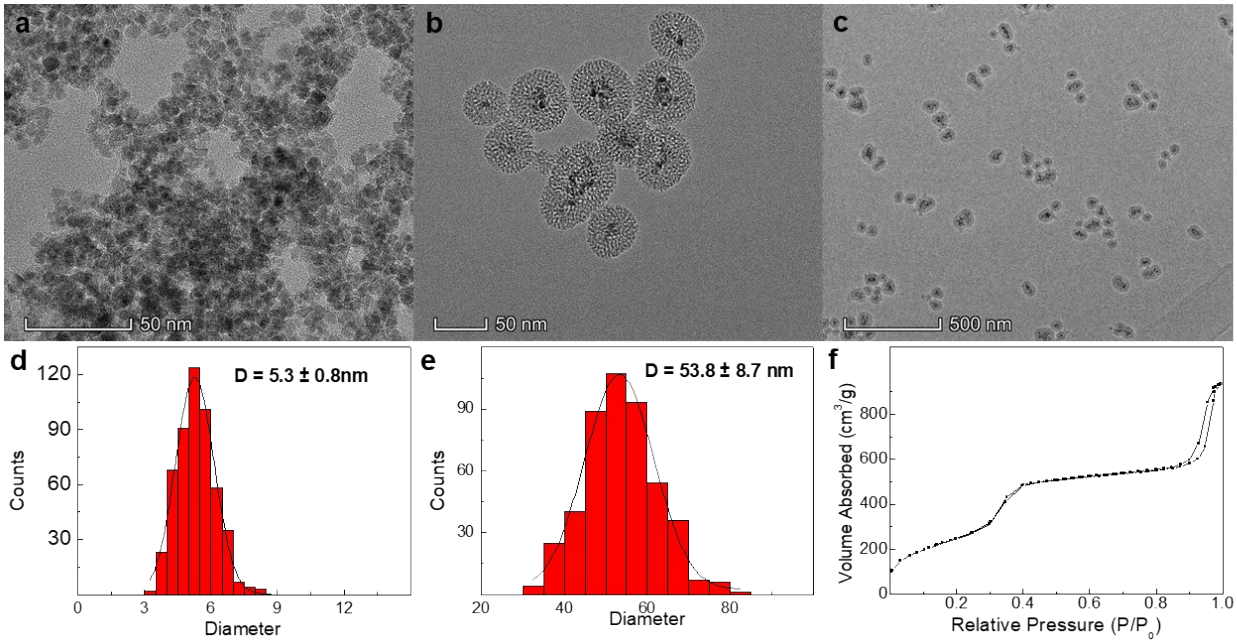


Figure S1. (a-c) Additional TEM images of the CeO_2NPs (a) and CeO_2@mSiO_2 at different magnifications **(b, c)**. Images are also taken from different synthesis, and at different time points of storage, showing the reproducibility and stability of the process. **(d-e)** The CeO_2NPs and CeO_2@mSiO_2 nanocomposites size of typical synthesis, calculated by image analysis based on transmission electron microscopy (TEM) images and counting more than 500 particles. **f)** CeO_2@mSiO_2 isotherms exhibiting the characteristic IV behavior of a well-developed mesoporous structure. The Brunauer–Emmett–Teller (BET) surface area was calculated as 905 m^2/g and 1.4 cm3/g and a narrow pore size distribution of 4.0 nm was determined using the Barrett–Joiner–Halenda (BJH) method.

Figure S2. Additional characterization: XRD, UV-VIS spectra and ζ-Potential.

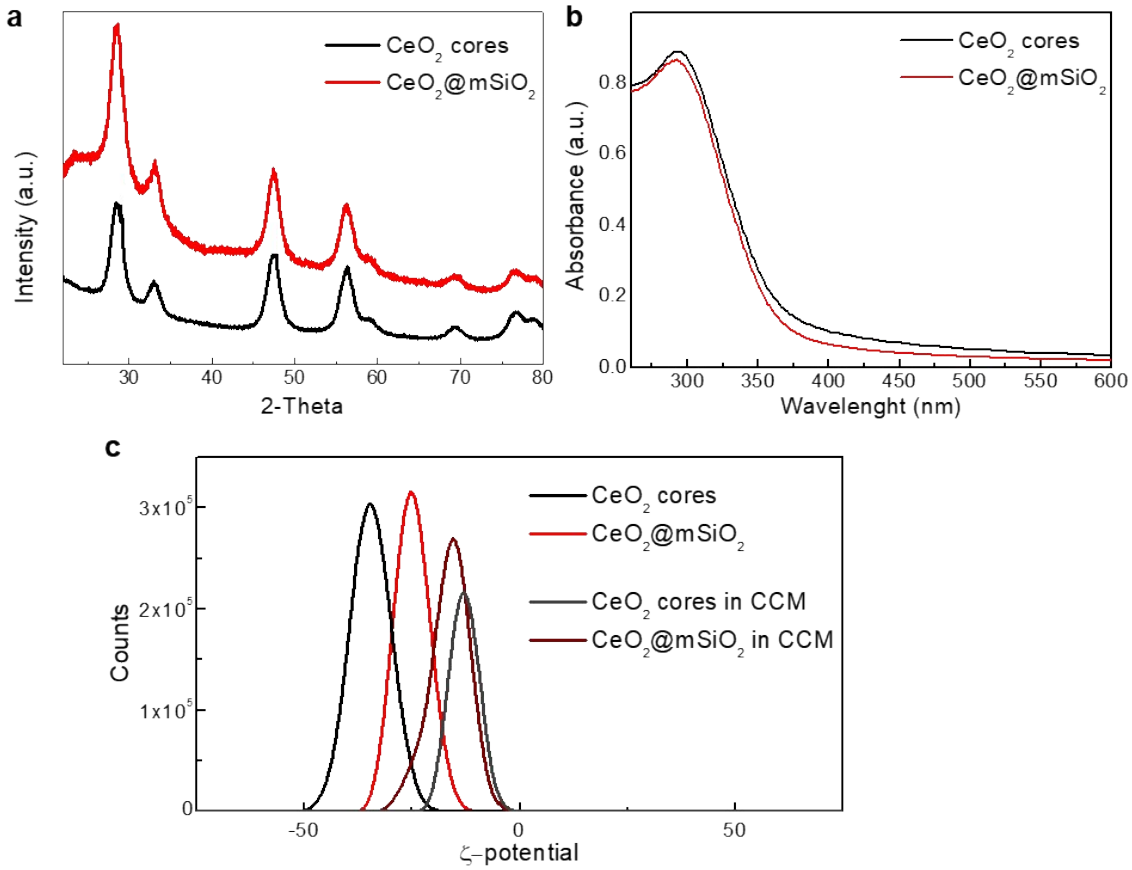


Figure S2. (a) XRD spectra of the CeO_2NP cores (black line) and the CeO_2@$mSiO_2$ core-shell (red line) showing the maintainance of the crystalline structure of the CeO_2 cores inside the shell. **(b)** UV-VIS spectra of the CeO_2NP cores and the CeO_2@$mSiO_2$ core-shell, showing the successful coating of all CeO_2NPs without inducing aggregation or degradation of the NPs. The spectra of the CeO_2@$mSiO_2$ was recorded without further dilution, while the spectra of the CeO_2NPs was recorded taking into account the dilution factor of the CeO_2 cores employed in the synthesis. A small blue shift and varying intensity can be observed in the spectra, attributed to the modification of the refractive index of the environment surrounding the CeO_2 cores after $mSiO_2$ encapsulation. Furthermore, for both nanomaterials, ICP-MS indicated a full conversion of Ce to CeO_2NPs, hence the final CeO_2 concentration was determined as 1.2 mg/mL ($3.5x10^{15}$ CeO_2NPs/mL) in the case of CeO_2@$mSiO_2$ and 1.72 mg/mL ($3.5x10^{15}$ CeO_2NPs/mL) in the case of CeO_2NPs. The values of NP/mL are calculated taking the mean diameter of the CeO_2 cores as 5 nm. **c)** ζ-potential of the CeO_2NP cores (black line, -35.5 mV) and CeO_2@$mSiO_2$ (red line, -24.9 mV) after synthesis. After incubation 24 hours in cell culture medium (DMEM + 10%FBS) and purification, CeO_2 cores ζ-potential was -12.8 mV (grey line) and CeO_2@$mSiO_2$ was -16.3 mV (dark red line). Both nanomaterials reached similar values as the proteins in the cell culture medium (c.a. -10 mV) which is consistent with the formation of a stable (hard) protein corona.

Figure S3. CeO_2@$mSiO_2$ and CeO_2NPs cell internalization.

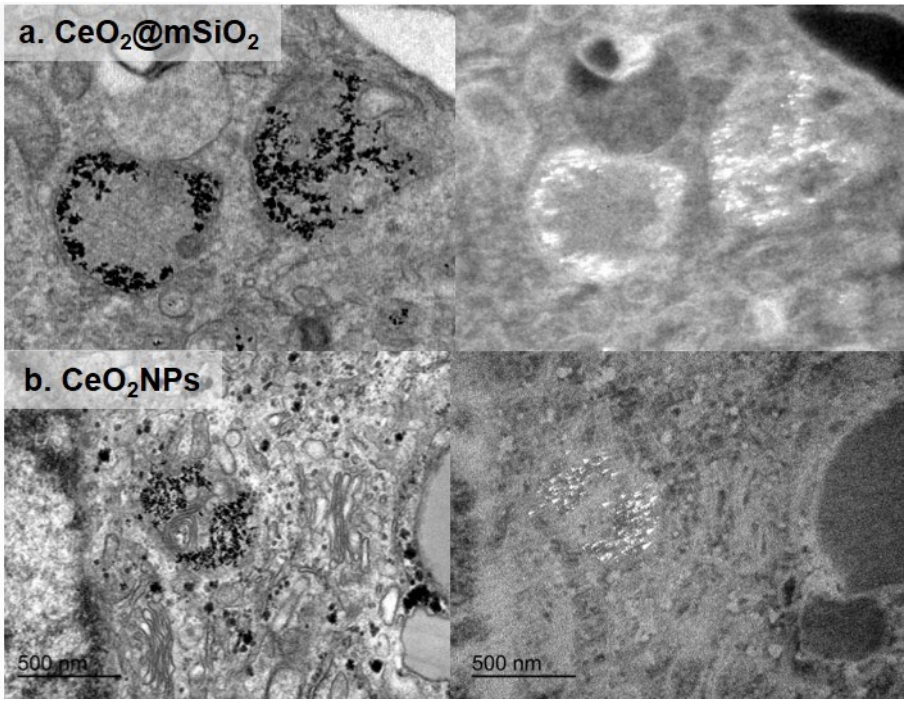
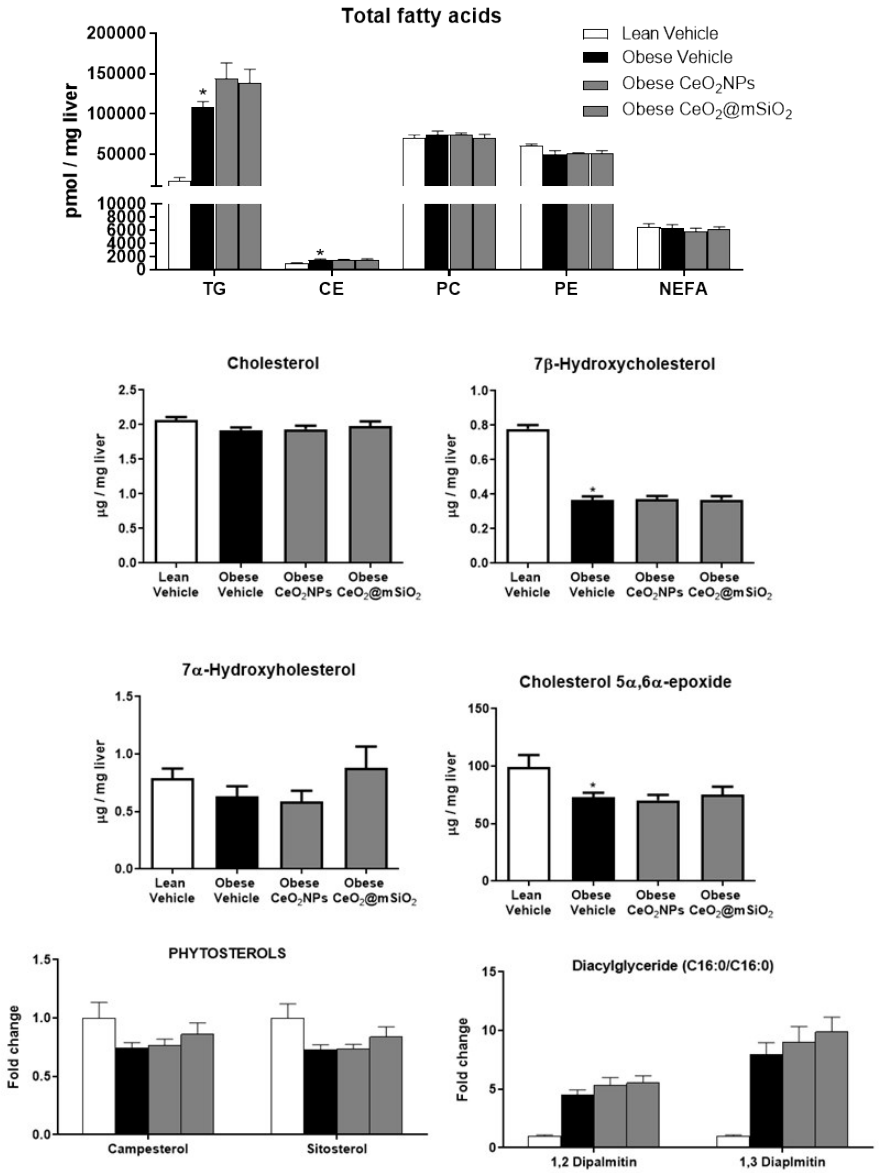


Figure S3. Bright and dark-field additional TEM images of **(a)** CeO_2@$mSiO_2$ and **(b)** CeO_2NPs uptake by HepG2 cells. The crystallinity of the CeO_2 makes them easy to distinguish from the amorphous cellular structures under dark-field.

Figure S4. Effect of nanomaterials on fatty liver accumulation.



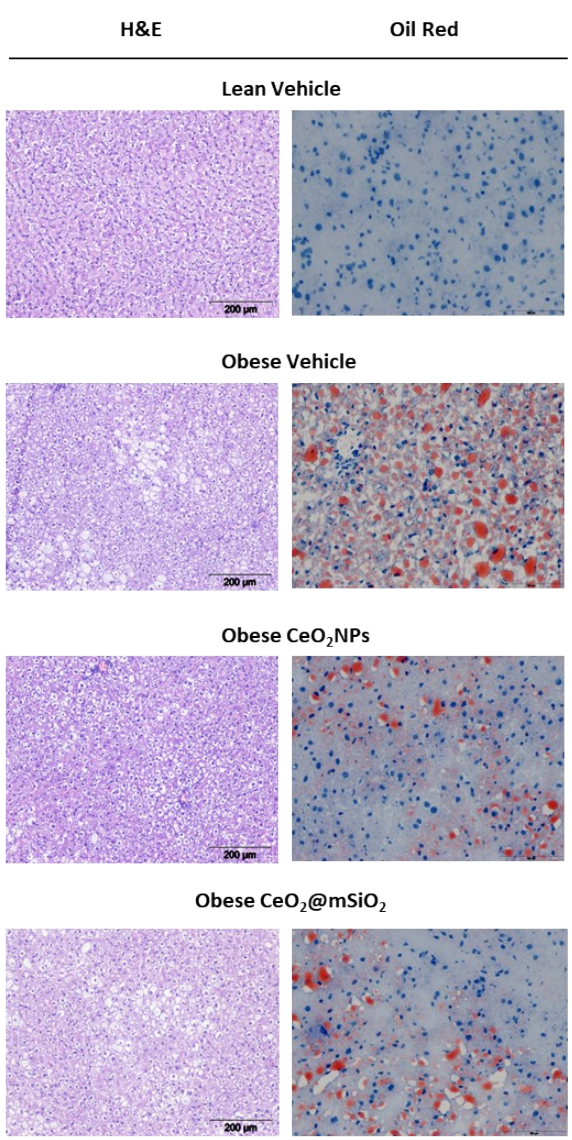


Figure S4. (a) Effect of nanomaterials on lipids measured by gas chromatography-mass spectrometry. **(b)** Haematoxylin-eosin (H&E) and Oil-Red staining of representative liver sections from lean rats receiving vehicle and obese rats receiving vehicle or treated with CeO_2NPs or CeO_2@mSiO_2.

Supporting Tables.

Table S1. Effects of CeO_2NPs and CeO_2@mSiO_2 on body weight, liver-body weight ratio and serum biochemical parameters, lipid profile and adipokines in obese Zucker rats.

	Lean rats	Obese rats		
	Vehicle (n=10)	Vehicle (n=10)	CeO_2NPs (n=10)	CeO_2@mSiO_2 (n=10)
Body and liver weight				
Body weight (g)	344 ± 6	466 ± 14*	441 ± 13*	469 ± 16*
Liver weight (g)	14.7 ± 0.5	22.7 ± 1.1*	21.2 ± 1.0*	23.0 ± 1.4*
Liver-body weight ratio (%)	4.30 ± 0.13	4.88 ± 0.13	4.81 ± 0.16	4.91 ± 0.24
Glucose and insulin resistance				
Glucose (mg/dL)	122.4 ± 5.3	114.9 ± 7.6	112.3 ± 6.5	118.4 ± 4.4
Insulin (pg/mL)	822 ± 108	2677 ± 252*	2740 ± 360*	2687 ± 181*
HOMA-IR	75 ± 13	223 ± 30*	219 ± 31*	213 ± 14*
Serum lipids				
Triglycerides (mg/dL)	135.8 ± 9.4	462.8 ± 51.9*	358.2 ± 31.3*#	285.1 ± 31.2*#
Total cholesterol (mg/dL)	119.3 ± 3.4	244.6 ± 6.0*	236.2 ± 8.6*	235.7 ± 13.7*
LDL-cholesterol (mg/dL)	19.8 ± 0.7	30.3 ± 4.5*	20.5 ± 0.9#	17.6 ± 1.4#
HDL-cholesterol (mg/dL)	83.0 ± 3.3	175.0 ± 3.1*	170.5 ± 7.3*	174.2 ± 8.7*
Serum adipokines				
IL-1β (pg/mL)	7.2 ± 0.7	52.1 ± 10.7*	47.0 ± 6.0*	52.2 ± 12.5*
MCP-1 (pg/mL)	328 ± 16	462 ± 33*	408 ± 22	396 ± 46
TNF-α (pg/mL)	1.59 ± 0.17	2.31 ± 0.32	1.81 ± 0.34	1.46 ± 0.25
Leptin (pg/mL)	2493 ± 267	7091 ± 446*	8358 ± 497*	7272 ± 659*
Renal and liver function				
Creatinine (mg/dL)	0.35 ± 0.02	0.48 ± 0.02*	0.44 ± 0.01*	0.44 ± 0.03*
Sodium (mmol/L)	143.4 ± 0.5	145.9 ± 0.6*	144.2 ± 0.5#	143.6 ± 0.5#
Potassium (mmol/L)	4.6 ± 0.2	4.7 ± 0.1	4.9 ± 0.1	4.7 ± 0.2
AST (U/L)	67.8 ± 3.8	96.9 ± 8.1*	117.5 ± 10.1*	104.0 ± 7.7*
ALT (U/L)	64.8 ± 2.6	97.9 ± 6.9*	97.9 ± 9.0*	101.8 ± 5.8*
Total proteins (g/L)	63.1 ± 0.6	74.8 ± 0.7*	73.7 ± 0.8*	73.8 ± 1.1*
Albumin (g/L)	36.0 ± 0.4	40.9 ± 0.4*	40.3 ± 0.3*	40.7 ± 0.6*

Data expressed as mean ± SEM. *p <0.05 compared with lean Zucker rats (Lean Vehicle). #p <0.05 compared with obese Zucker rats receiving vehicle (Obese Vehicle). One-way ANOVA with the Newman-Keuls post hoc test. HOMA-IR calculated by applying the following formula: glucose (mmol/L) x insulin (mIU/L) / 22.5.

Table S2. Total fatty acid serum levels in lean Zucker rats receiving vehicle and obese Zucker rats receiving vehicle and treated with CeO_2NPs and CeO_2@mSiO_2.

Fatty acids (nmol/mL)	Lean Zucker rats Vehicle (n=10)	Obese Zucker rats Vehicle (n=10)	Obese Zucker rats CeO_2NPs (n=10)	Obese Zucker rats CeO_2@mSiO_2 (n=8)
C12:0	22.01 ± 8.36	34.75 ± 10.64	18.46 ± 3.31	27.99 ± 10.70
C14:0	100.7 ± 12.80	339.0 ± 31.06*	306.5 ± 25.55*	259.1 ± 30.95*
C14:1	6.31 ± 1.19	34.86 ± 3.73*	37.18 ± 3.88*	25.50 ± 2.95*†
C15:0	31.50 ± 1.56	38.61 ± 4.98	32.70 ± 2.77	27.78 ± 2.45
C16:0	2737 ± 133.6	6989 ± 441.1*	6176 ± 385.2*	5342 ± 311.9*†
C16:1	340.5 ± 35.35	1802 ± 143.0*	1651 ± 103.6*	1291 ± 104.8*†
C17:0	39.35 ± 3.36	60.97 ± 10.87	46.64 ± 4.90	42.32 ± 6.24
C18:0	1089 ± 57.39	3631 ± 258.1*	3075 ± 100.3*†	2989 ± 171.8*†
C18:1n9c	1035 ± 72.31	3251 ± 230.9*	2770 ± 212.8*	2279 ± 189.2*†
C18:1n9t	532.5 ± 33.16	1208 ± 128.1*	929.1 ± 68.33*†	827.8 ± 68.59*†
C18:2n6c	2663 ± 115.7	2970 ± 206.1	2807 ± 136.0	2409 ± 189.7
C18:2n6t	244.1 ± 16.50	684.6 ± 42.48*	582.5 ± 47.34*	483.1 ± 41.56*†
C18:3n6	31.27 ± 2.14	99.67 ± 8.86*	136.1 ± 18.78*†	84.52 ± 8.98*
C18:3n3	127.1 ± 8.23	284.5 ± 20.76*	243.7 ± 21.59*	199.4 ± 18.37*†
C20:0	13.60 ± 0.70	22.72 ± 1.79*	20.72 ± 1.71*	18.60 ± 1.26*
C20:1n9	51.94 ± 21.03	44.82 ± 4.93	56.13 ± 11.87	32.59 ± 4.91
C20:2	37.67 ± 3.16	54.98 ± 4.55	44.21 ± 6.17	40.87 ± 4.94
C20:3n6	76.26 ± 6.20	590.9 ± 44.43*	474.8 ± 31.61*†	446.6 ± 29.37*†
C20:4n6	3612 ± 173.1	7470 ± 252.2*	6602 ± 175.7*	6901 ± 525.3*
C20:5n3	59.44 ± 4.38	230.0 ± 21.58*	246.0 ± 29.27*	174.8 ± 19.06*
C21:0	3.48 ± 0.16	4.01 ± 0.32	3.64 ± 0.24	3.42 ± 0.20
C22:0	24.91 ± 0.96	47.78 ± 2.66*	41.66 ± 1.59*	43.87 ± 3.13*
C22:6n3	536.5 ± 36.95	1366 ± 63.65*	1091 ± 73.29*†	1071 ± 69.64*†
C23:0	19.36 ± 0.98	31.66 ± 2.06*	25.96 ± 1.01*†	26.62 ± 1.97*†
C24:0	56.12 ± 3.10	88.64 ± 6.06*	75.46 ± 3.21*	78.27 ± 5.58*
C24:1n9	63.46 ± 4.77	121.7 ± 7.63*	94.28 ± 6.74*	113.6 ± 13.54*
Unsaturated/Sat FA	2.279 ± 0.060	1.819 ± 0.056*	1.806 ±0.123*	1.858 ± 0.045*
n6/n3	9.315 ± 0.343	6.325 ± 0.183*	6.671 ± 0.380*	7.189 ± 0.329*
C18:0/C16:0	0.400 ± 0.017	0.522 ± 0.019*	0.499 ± 0.025*	0.564 ± 0.024*
C16:1/C16:0	0.122 ± 0.009	0.256 ± 0.008*	0.268 ±0.011*	0.240 ± 0.009*
C16:0/C18:2n6c	1.030 ± 0.031	2.378 ± 0.091*	2.198 ± 0.081*	2.253 ± 0.088*
C18:1n9c/C18:0	0.9591 ± 0.062	0.9043 ± 0.049	0.9127 ± 0.062	0.7711 ± 0.064
C18:3n3/C18:2n6c	0.047 ± 0.002	0.093 ± 0.003*	0.089 ± 0.003*	0.083 ± 0.003*†
C18:3n6/C18:2n6c	0.012 ± 0.001	0.035 ± 0.003*	0.044 ± 0.005*	0.035 ± 0.002*
C20:4n6/C20:3n6	49.08 ± 2.858	12.33 ± 0.715*	13.95 ± 0.704*	16.00 ± 1.775*
C20:4n6/C18:3n6	119.4 ± 8.354	78.56 ± 6.397*	49.11 ± 8.143*†	87.75 ± 9.962*
C20:4n6/C18:2n6c	1.376 ± 0.079	2.619 ± 0.181*	2.353 ± 0.098*	3.025 ± 0.379*
C20:5n3/C18:3n3	0.479 ± 0.038	0.802 ± 0.044*	0.868 ± 0.135*	0.906 ± 0.094*
C20:2n6/C18:2n6c	0.014 ± 0.001	0.018 ± 0.001	0.012 ± 0.002†	0.017 ± 0.001
Peroxidability Index (%)	167.4 ± 5.196	154.5 ± 5.392	151.9 ± 4.352	166.0 ± 7.244
Saturated FA	4137 ± 199.4	11251 ± 701.2*	9156 ± 732.1*†	8858 ± 495.9*†
Unsaturated FA	9364 ± 361.0	20206 ± 922.7*	15955 ± 1128*†	17082 ± 471.9*†
Total FA	13501 ± 536.4	31457 ± 1567*	25111 ± 1727*†	25244 ± 1270*†

Mean ± SEM. *p<0.05 compared with control group (lean Zucker rats Vehicle); †p<0.05 compared with vehicle group (obese Zucker rats Vehicle). One-way ANOVA with the Newman-Keuls post hoc test.

Table S3. Differentially expressed genes in the liver of obese Zucker rats treated with vehicle compared to lean vehicle group.

Genes	Fold regulation	P value
Up-regulated		
Slc2a4	12.18	0.013
Cd36	8.42	0.035
Elovl6	6.14	0.000
G6pd	3.92	0.039
Apoa1	3.75	0.003
Pdk4	3.73	0.034
Fasn	3.47	0.017
Srebf1	3.40	0.046
Acly	2.74	0.037
Dgat2	2.68	0.005
Scd1	2.55	0.029
Pklr	2.38	0.013
Fas	2.36	0.040
Akt1	2.10	0.000
Mtor	2.10	0.000
Stat3	1.89	0.016
Pck2	1.74	0.048
Ndufb6	1.58	0.021
Down-regulated		
Nox4	-26.89	0.000
Acsm3	-2.26	0.040
Gk	-1.47	0.014

Fold regulation. Obese Zucker rats treated with vehicle compared with lean rats treated with vehicle (unpaired Student's t-test).

Table S4. Differentially expressed genes in the liver of obese Zucker rats treated with CeO_2NPs compared with obese vehicle group.

Genes	Fold regulation	P value
Slc2a4	-5.84	0.028
Tnf	-3.52	0.039
Abcg1	-1.94	0.032
Stat3	-1.80	0.021
Pik3ca	-1.74	0.015
Akt1	-1.68	0.002
Mtor	-1.56	0.033

Fold regulation. Obese Zucker rats treated with CeO2NPs compared with obese rats treated with vehicle (unpaired Student's t-test).

Table S5. Differentially expressed genes in the liver of obese Zucker rats treated with CeO_2@mSiO_2 compared to obese vehicle group.

Genes	Fold regulation	P value
Slc2a4	-6.84	0.021
Mtor	-1.93	0.006
Apoa1	-1.70	0.032
Stat3	-1.70	0.030
Mapk1	-1.67	0.043
Abca1	-1.65	0.036
Akt1	-1.61	0.000
Abcg1	-1.60	0.048
Insr	-1.56	0.005
Lpl	-1.52	0.016
Ndufb6	-1.52	0.015
Pik3r1	-1.47	0.023
Gsk3b	-1.36	0.033

Fold regulation. Obese Zucker rats treated with CeO_2@mSiO_2 compared with obese rats treated with vehicle (unpaired Student's t-test).

Table S6. Messenger expression of genes involved in adipokine signalling, carbohydrate metabolism, insulin signalling, lipid metabolism and transport, oxidative phosphorylation, inflammatory response and apoptosis in the liver of obese Zucker rats receiving vehicle and treated with CeO_2NPs and CeO_2@$mSiO_2$.

Genes	Obese rats Vehicle (n=4)	Obese rats CeO_2NPs (n=4)	Obese rats CeO_2@$mSiO_2$ (n=4)
Adipokine signaling, inflammation and apoptosis			
Akt1	2.10*	1.25$^{\#}$	1.31*$^{\#}$
Fas	2.36*	1.65	1.44
Mapk1	1.34	-1.04	-1.25$^{\#}$
Mtor	2.10*	1.35$^{\#}$	1.09$^{\#}$
Nox4	-26.89*	-27.61*	-32.22*
Pik3ca	1.41	-1.24$^{\#}$	-1.01
Stat3	1.89*	1.05$^{\#}$	1.11$^{\#}$
Tnf	2.22	-1.59$^{\#}$	-1.23
Xbp1	-1.07	-1.21	-1.58*
Carbohydrate metabolism			
Acly	2.74*	2.60*	2.69*
G6pd	3.92*	5.73*	4.65*
Gsk3b	1.58	1.32	1.16$^{\#\dagger}$
Mlxipl	-1.02	-1.13	-1.50*
Pck2	1.74*	1.26	1.00
Pdk4	3.73*	2.94	1.90*
Pklr	2.38*	1.74*	1.68*
Rbp4	1.09	1.19	-1.35†
Insulin signaling			
Igf1	-1.40	-1.36	-1.94*†
Igfbp1	-1.87	-1.49*	-2.39*†
Insr	1.24	1.02	-1.26$^{\#}$
Irs1	-1.09	-1.38	-1.61*
Pik3r1	1.30	1.43	-1.13$^{\#}$
Scl2a4	12.18*	2.09$^{\#}$	1.78$^{\#}$
Lipid metabolism and transport			
Abca1	1.13	-1.27	-1.46*$^{\#}$
Abcg1	1.06	-1.83$^{\#}$	-1.51$^{\#}$
Acaca	1.75	2.25*	1.87*
Acadl	1.46	1.44*	1.48*
Acsl5	2.21	3.12*	1.80*†
Acsm3	- 2.26*	-1.42	-3.39*†
Apoa1	3.75*	3.17*	2.20*$^{\#}$
Cd36	8.42*	9.40*	7.31*
Cyp2e1	-1.42	-1.37	-2.07†
Dgat2	2.68*	2.36*	1.75*
Elovl5	1.60	1.47*	1.29
Elovl6	6.14*	4.68*	6.02*
Fabp5	2.71	3.18*	2.28
Fasn	3.47*	4.24*	2.95*
Foxa2	2.36	2.00*	1.21†
Gk	-1.47*	-1.82*	-1.51*
Hmgcr	-1.02	1.19	-1.34*†
Hsd17b13	1.35	1.38*	1.14
Lpl	1.73	1.34	1.14$^{\#}$
Nr1h3	1.65	1.16	-1.15†

Nr1h4	1.16	1.24	-1.31*†
Ppa1	1.19	1.41*	1.16
Scd1	2.55*	2.68*	2.98*
Slc27a5	1.03	1.12	-1.47†
Srebf1	3.40*	2.25	1.93
Oxidative phosphorylation			
Atp5c1	1.24	1.71*	1.06
Ndufb6	1.58*	1.22	1.04#

Fold regulation compared with control group (lean Zucker rats). *p <0.05 compared with control; #p <0.05 compared with obese Zucker rats treated with vehicle. †p <0.05 compared with obese Zucker rats treated with CeO_2NPs. Biological cut-off was set to a fold regulation of ± 1 (unpaired Student's t-test).

Table S7. Total fatty acid hepatic levels in lean Zucker rats receiving vehicle and obese Zucker rats receiving vehicle or treated with CeO_2NPs or CeO_2@mSiO_2.

	Lean Zucker rats	Obese Zucker rats		
Fatty acids (pmol/mg liver)	**Vehicle (n=10)**	**Vehicle (n=10)**	**CeO_2NPs (n=10)**	**CeO_2@mSiO_2 (n=8)**
C12:0	40.80 ± 3.586	229.7 ± 30.02*	250.0 ± 34.31*	222.9 ± 18.01*
C14:0	645.9 ± 22.66	6803 ± 1019*	7195 ± 1199*	7099 ± 973*
C14:1	54.10 ± 5.034	930.0 ± 150.3*	1092 ± 223.2*	1016 ± 158.8*
C15:0	193.5 ± 13.76	374.8 ± 42.33*	304.8 ± 22.25*	380.2 ± 32.92*
C16:0	27977 ± 436.0	151405 ± 25810*	150768 ± 23230*	149321 ± 19049*
C16:1	2565 ± 148.5	34454 ± 5376*	34684 ± 5647*	34764 ± 4578*
C17:0	389.2 ± 32.09	496.5 ± 53.97	389.8 ± 19.55	489.0 ± 21.69
C17:1	99.40 ± 5.883	586.9 ± 95.29*	422.6 ± 33.33*	559.3 ± 64.14*
C18:0	16143 ± 397.9	24863 ± 1123*	23883 ± 1023*	25461 ± 878.9*
C18:1n9c	5147 ± 237.4	65128 ± 12262*	56446 ± 8658*	59950 ± 8104*
C18:1n9t	5077 ± 255.1	15275 ± 2226*	13371 ± 1548*	12217 ± 1207*
C18:2n6c	13861 ± 579.2	14918 ± 1118	16729 ± 1683	16681 ± 1605
C18:2n6t	1342 ± 63.79	15703 ± 3066*	13448 ± 2071*	14380 ± 2012*
C18:3n6	178.0 ± 10.53	608.9 ± 59.04*	769.5 ± 122.5*	781.2 ± 129.4*
C18:3n3	597.4 ± 26.77	5968 ± 1145*	5172 ± 792.9*	5442 ± 747.1*
C20:0	75.20 ± 3.392	92.67 ± 5.231*	96.70 ± 7.364*	94.11 ± 3.011*
C20:1n9	112.5 ± 4.949	252.2 ± 25.95*	244.6 ± 27.68*	264.9 ± 24.31*
C20:2	366.0 ± 25.35	214.4 ± 7.941*	224.1 ± 7.078*	230.0 ± 11.84*
C20:3n6	899.0 ± 97.24	2035 ± 93.43*	2346 ± 127.1*	2429 ± 201.3*
C20:4n6	19738 ± 962.2	18293 ± 909.4	18064 ± 681.6	19338 ± 547.4
C20:5n3	245.6 ± 40.71	555.2 ± 37.51*	687.1 ± 69.45*	675.0 ± 75.61*
C21:0	8.300 ± 0.2603	8.100 ± 0.4583	8.300 ± 0.6333	8.300 ± 0.3350
C22:0	137.1 ± 7.182	151.1 ± 6.894	141.1 ± 3.433	151.6 ± 7.022
C22:6n3	6343 ± 219.5	5969 ± 283.6	5713 ± 321.8	6198 ± 322.2
C23:0	110.0 ± 4.323	91.56 ± 3.481*	84.44 ± 1.864*	97.60 ± 6.797
C24:0	334.1 ± 19.74	292.8 ± 8.593	300.2 ± 8.701	327.5 ± 16.85
C24:1n9	194.2 ± 12.66	203.6 ± 10.93	177.0 ± 6.962	199.3 ± 10.71
Total FA	129956 ± 2479	387684 ± 50942*	373128 ± 46184*	381830 ± 37490*
Saturated FA	46250 ± 673.9	184770 ± 27941*	183402 ± 25243*	183571 ± 20431*
Unsaturated FA	82408 ± 2274	202914 ± 23131*	189726 ± 21283*	198259 ± 17297*

Mean ± SEM. *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001 compared with control group (Lean Zucker rats Vehicle); †p<0.05, ††p<0.01 compared with vehicle group (Obese Zucker rats Vehicle). One-way ANOVA with the Newman-Keuls post hoc test.

Table S8. Differentially expressed genes in the adipose tissue of obese Zucker rats treated with vehicle compared to lean vehicle group.

Genes	Fold regulation	P value
Up-regulated		
Il6	9.49	0.019
Ramp3	9.08	0.006
Cnr1	8.31	0.000
Gcgr	6.69	0.004
Drd1	5.77	0.028
Nmur1	3.49	0.026
Tnf	3.45	0.004
Cd68	3.35	0.026
Lep	2.78	0.001
Ins2	2.37	0.013
Il1b	2.22	0.014
Il1r1	1.61	0.042
Down-regulated		
Calca	-1.66	0.027
Adipor2	-1.56	0.024
Pparg	-1.52	0.007
Thrb	-1.43	0.037

Fold regulation. Obese Zucker rats treated with vehicle compared with lean rats treated with vehicle (unpaired Student's t-test).

Table S9. Differentially expressed genes in the adipose tissue of obese Zucker rats treated with CeO_2NPs compared with obese vehicle group.

Genes	Fold regulation	P value
Ins2	-2.25	0.012
Htr2c	-1.90	0.028
Nr3c1	-1.33	0.044

Fold regulation. Obese Zucker rats treated with CeO_2NPs compared with obese rats treated with vehicle (unpaired Student's t-test).

Table S10. Differentially expressed genes in the adipose tissue of obese Zucker rats treated with CeO_2@$mSiO_2$ compared to obese vehicle group.

Genes	Fold regulation	P value
Drd1	-3.72	0.044
Agrp	-2.27	0.023
Ins2	-2.26	0.025
Adra2b	-1.80	0.030
Nr3c1	-1.50	0.015

Fold regulation. Obese Zucker rats treated with CeO_2@$mSiO_2$ compared with obese rats treated with vehicle (unpaired Student's t-test).

Table S11. Adipose tissue messenger expression of obesity-related genes in obese Zucker rats.

Genes	Obese rats Vehicle (n=4)	Obese rats CeO_2NPs (n=4)	Obese rats CeO_2@mSiO_2 (n=4)
Energy expenditure			
Adipoq	-1.59	-1.25	-2.13*
Adipor2	-1.56*	-1.19	-1.86
C3	5.45	1.39	-1.23
Pparg	-1.52*	-1.51*	-1.49*
Ppargc1a	1.36	-2.12	-2.48*
Thrb	-1.43*	-1.67*	-1.79*
Macrophage infiltation and characterization			
Cd68	3.35*	2.42	2.81*
Il10	1.21	1.67*	1.43
Nos2	1.30	1.29*	1.45*
Orexigenic			
Adra2b	-1.04	-1.12	-1.86*#
Agrp	1.80	1.65	-1.26#†
Cnr1	8.31*	4.73	6.92*
Galr1	3.38	4.33*	3.03*
Npy1r	-1.56	-1.59*	-1.91*
Nr3c1	1.12	-1.19*#	-1.35*#
Anorectic			
Atrn	1.48	1.59*	-1.07†
Calca	-1.66*	-1.83	-2.61*
Calcr	-1.01	-1.13	-1.57†
Cck	11.53	11.63*	19.95*
Drd1	5.77*	3.68*	1.55#†
Gcgr	6.69*	4.35	5.34*
Hrh1	1.19	-1.25	1.06†
Htr2c	3.24*	1.71#	4.66*†
Il1b	2.22*	1.48	2.06*
Il1r1	1.61*	1.43	1.63*
Il6	9.49*	8.94*	11.88*
Ins2	2.37*	1.05#	1.05#
Insr	-1.32	-1.43*	-1.77*
Lep	2.78*	2.37*	2.22*
Nmb	-1.47	-1.25	-2.08*
Nmu	3.18	1.99*	1.58
Nmur1	3.49*	1.78	2.95*
Ramp3	9.08*	6.26*	8.37*
Tnf	3.45*	2.99*	3.26*

Fold regulation compared with control group (lean Zucker rats). *p <0.05 compared with control; #p <0.05 compared with obese Zucker rats treated with vehicle. †p <0.05 compared with obese Zucker rats treated with CeO_2NPs. Biological cut-off was set to a fold regulation of ± 1.

Supporting Methods.

Nanomaterials Characterization.

TEM images were acquired with a JEOL 1010 Electron Microscope operating at an accelerating voltage of 80 kV. Samples for TEM were prepared by drop casting on carbon coated cooper TEM grids (Ted-pella, Inc). The grids were left to dry at room temperature. Observations were made on different parts of the grid and with different magnifications and more than 500 particles were computer-analysed and measured for the size distribution.

HRTEM, HAADF-STEM and elemental mapping by EDX were acquired with a JEOL JEM-2100. Samples were centrifuged and dispersed in water previous to their deposition (10 µL) on an ultrathin formvar-coated 200-mesh copper grid (Ted-pella, Inc.)

Nitrogen sorption isotherms were measured with a ASAP2010 analyser (Micromeritcs, USA). Before measurements, the samples were dried in a vacuum oven at room temperature for 24 h, and outgassed in the instrument at 60 °C for 24 h. The specific surface areas were calculated by the Brunauer-Emmett-Teller (BET) method in a linear relative pressure range between 0.05 and 0.25. The pore size distributions were derived from the desorption branches of the isotherms by the NLDFT method kernel file developed for silica exhibiting a cylindrical pore geometry. The total pore volumes were derived by the nitrogen sorption amount at the relative pressure values where the capillary condensation of the primary mesopores finished, in order to exclude the contribution from the textual porosity of the nanoparticles.

UV-visible spectrophotometry. UV-visible spectra were acquired with a Shimadzu UV-2400 Spectrophotometer. One mL of the NP solution was placed in a cuvette, and spectral analysis was performed in the 190 nm to 800 nm range.

ζ-Potential and DLS measurements were made with a Malvern ZetaSizer Nano ZS Instrument operating with a light source wavelength of 532 nm and a fixed scattering angle of 173° for DLS measure. The software was arranged with the specific parameters of refractive index and absorption coefficient of the material and the viscosity of the solvent according the manufacturer instructions.