

Electronic supplementary information

Table S1. Reagents, materials and laboratory animal information

| Materials | Catalog No. | Company |
|-------------------------------------|---------------|---|
| COST (Mw ≤ 1,000 Da) | 160926C | Shangdong AK Biotech Co., Ltd. (Qingdao, Shandong, China) |
| Orlistat | 2016120860088 | Zhongshan Wanhan Pharmaceutical Co., Ltd. (Guangzhou, Guangdong, China) |
| BCA Protein Concentration Assay Kit | P0011 | Beyotime Biotechnology Co., Ltd. (Shanghai, China) |
| LEICA Paraplast High Melt Paraffin | 39601095 | Leica Biosystems melbourne Pty., Ltd. (Melbourne, Australia) |
| LEICA Paraplast Low Melt Paraffin | 39603002 | Leica Biosystems melbourne Pty., Ltd. (Melbourne, Australia) |
| Paraformaldehyde | 885233 | Shanghai Macklin Biochemical Co., Ltd. (Shanghai, China) |
| Hematoxylin-Eosin dye | DH0006 | Beijing leagene Biotechnology Co., Ltd. (Beijing, China) |
| Bovine Serum Albumin | 9048-46-8 | Sigma-Aldrich (USA) |
| Gibco-Fetal Bovine Serum (FBS) | 10270-106 | Thermo Fisher Scientific (USA) |
| Gibco-DMEM basic | C11995500bt | Thermo Fisher Scientific (USA) |

Table S2. The primer sequences of rats

| Gene | Forward primer | Reverse primer |
|---------------|---------------------------|------------------------------|
| GAPDH | GTCCATGCCATCACTGCCACTC | CGCCTGCTTCACCACCTTCTTG |
| SREBP-1c | TTCTGCCTTGTGCGGTATGTTGAG | TCTGCTCCTGAGTGGACCATGAT C |
| FAS | GTGTGGTAGGCTTGGTGAACCTGTC | GTGAGATGTGCTGCTGAGGTTGG |
| ACC α | TGGTGAGGATGGCGGCTCTG | GGTGGTGTGAAGGCGTTGTCC |
| PPAR γ | GAGGACATCCAAGACAACCTGCTG | GTGCTCTGTGACAATCTGCCTGA G |
| PPAR α | CTGAGGAAGCCATTCTGCGACATC | GCGTCTGACTCGGTCTTCTTGATG |
| GRP78 | GGTGGTGAACCTTCGATGT | ATTCTTCAGGGGTCAGGCG |
| GRP94 | ATGAAGGCACAAGCATAACCAGACG | TCTGTGGTGTCTTCAGGCTCCTC |
| ATF4 | GACCGAGATGAGCTTCCTGAACAG | GTGTCTGAGGCACTGACCAACC |
| CHOP | GCCAGCAGAGGTCACAAGCAC | CTTGAGCCGCTCGTTCTCTTCAG |

| | | |
|-------|--------------------|----------------------|
| XBP1S | CTGAGTCCGCAGCAGGTG | GCTCTCTGTCTCAGAGGGGA |
|-------|--------------------|----------------------|

Table S3. The primer sequences of cells

| Gene | Forward primer | Reverse primer |
|---------------|--------------------------|--------------------------|
| SREBP1 | GCTGTTGGTGCTCGTCTCCTTG | GCTTGCGATGCCTCCAGAAGTAC |
| FAS | GTGGTGGGCTTGGTGAAGTGTG | AGGTGCTGCTGAGGTTGGAGAG |
| ACC α | TACCTTCTTCTACTGGCGGCTGAG | GCCTTCACTGTTCTTCCACTTCC |
| PPAR γ | TGAATCCAGAGTCCGCTGACCTC | ATCGCCCTCGCCTTTGCTTTG |
| PPAR α | AGGCTATACGGACCACCCAGTTG | CAGCACAGTCGAGGCAGGTTAATC |
| GRP78 | CCGAGGAGGAGGACAAGAAGGAG | ACACGCCGACGCAGGAGTAG |
| GRP94 | GCAACGCTTCGGTCAGGGTATC | GGTTCTTCTTCGGGCTTCTTCC |
| ATF4 | ATTCAGGCTTCTCACGGCATTGAG | CACCAACACCTCGCTGCTCAG |
| CHOP | TGAACGGCTCAAGCAGGAAA | GGATTGAGGGTCACATCATTGGCA |

Table S4 Effects of COST on food intake and body weight in rats (n=10)

| group | food intake (g/d) | initial weight (g) | final weight (g) | Weight gain (g) |
|----------|-------------------|----------------------|----------------------|--------------------|
| SD | 24.74 \pm 0.62 | 415.03 \pm 24.95** | 504.04 \pm 29.91** | 89.01 \pm 7.61* |
| HF | 23.76 \pm 0.62 | 567.82 \pm 13.20 | 708.54 \pm 18.16 | 123.05 \pm 10.20 |
| Orlistat | 25.30 \pm 0.58 | 557.87 \pm 21.07 | 638.73 \pm 24.77* | 80.86 \pm 7.02** |
| COST-H | 23.84 \pm 0.46 | 566.57 \pm 11.61 | 630.66 \pm 14.90** | 64.09 \pm 5.98** |
| COST-M | 24.15 \pm 0.55 | 574.22 \pm 8.15 | 627.22 \pm 11.86** | 53.00 \pm 7.92** |
| COST-L | 24.21 \pm 0.43 | 576.71 \pm 7.59 | 667.56 \pm 17.79 | 90.84 \pm 11.70* |

* P< 0.05 and ** p < 0.01 vs. the HF group.

Table S5. Effect of COST on adipose tissue weight in rats (n=10)

| group | Perirenal fat (g) | Epididymal fat (g) | subcutaneous fat (g) | Body fat (g) | Lipid/body ratio (%) |
|----------|-------------------|--------------------|----------------------|--------------------|----------------------|
| SD | 7.52 \pm 1.03** | 6.29 \pm 0.73** | 5.62 \pm 0.81** | 19.43 \pm 1.86** | 3.90 \pm 0.45** |
| HF | 22.41 \pm 2.98 | 16.10 \pm 2.83 | 14.77 \pm 1.52 | 53.28 \pm 6.50 | 7.72 \pm 0.72 |
| Orlistat | 16.06 \pm 0.85* | 10.41 \pm 1.55* | 10.66 \pm 1.60* | 37.13 \pm 3.56** | 5.93 \pm 0.53* |
| COST-H | 15.64 \pm 2.54* | 10.30 \pm 1.46* | 11.38 \pm 1.46* | 37.31 \pm 3.83** | 6.23 \pm 0.55* |
| COST-M | 17.08 \pm 0.99* | 11.06 \pm 1.13* | 13.56 \pm 1.37 | 41.70 \pm 2.17* | 6.75 \pm 0.26 |
| COST-L | 19.12 \pm 2.64 | 12.36 \pm 1.61 | 14.30 \pm 2.19 | 45.78 \pm 4.38 | 7.03 \pm 0.57 |

*P< 0.05 and ** p < 0.01 vs. the HF group

Table S6. Effect of COST on serum lipid levels in rats (n=10)

| group | TC (mmol/L) | TG (mmol/L) | HDL-C (mmol/L) | LDL-C (mmol/L) |
|----------|-------------|-------------|----------------|----------------|
| SD | 1.81±0.16** | 0.87±0.11** | 0.25±0.02** | 1.56±0.14** |
| HF | 3.19±0.27 | 2.10±0.53 | 0.16±0.01 | 2.34±0.12 |
| Orlistat | 1.67±0.35** | 1.01±0.09** | 0.20±0.02 | 1.42±0.13** |
| COST-H | 2.01±0.05** | 1.05±0.18** | 0.23±0.03* | 1.75±0.23* |
| COST-M | 2.07±0.35** | 1.03±0.07** | 0.21±0.02 | 1.93±0.28 |
| COST-L | 2.26±0.24* | 1.22±0.21* | 0.15±0.02 | 2.32±0.21 |

*P < 0.05 and ** p < 0.01 vs. the HF group

Table S7. Effects of COST on liver weight and liver index in rats (n=10)

| group | Liver weight (g) | Organ index (%) |
|----------|------------------|-----------------|
| SD | 10.00±0.31** | 1.82±0.05** |
| HF | 14.02±0.64 | 2.04±0.03 |
| Orlistat | 11.92±0.15** | 1.87±0.03** |
| COST-H | 11.44±0.37** | 1.90±0.03* |
| COST-M | 11.92±0.36** | 1.87±0.02** |
| COST-L | 12.31±0.69* | 1.92±0.06* |

*P < 0.05 and ** p < 0.01 vs. the HF group

Table S8. Effect of COST on liver lipid levels in rats (n=10)

| group | TC (mmol/gprot) | TG (mmol/gprot) | FFA (gprot/L) |
|----------|-----------------|-----------------|---------------|
| SD | 1.56±0.18* | 0.57±0.10** | 0.48±0.04** |
| HF | 2.85±0.68 | 1.40±0.14 | 0.97±0.08 |
| Orlistat | 1.64±0.23* | 0.64±0.07** | 0.48±0.03** |
| COST-H | 1.75±0.28* | 0.50±0.05** | 0.58±0.06** |
| COST-M | 1.93±0.36 | 0.69±0.11** | 0.69±0.10** |
| COST-L | 2.32±0.27 | 0.86±0.04** | 0.89±0.04 |

*P < 0.05 and ** p < 0.01 vs. the HF group