Supplementary Materials and Methods

Measurement of cell viability

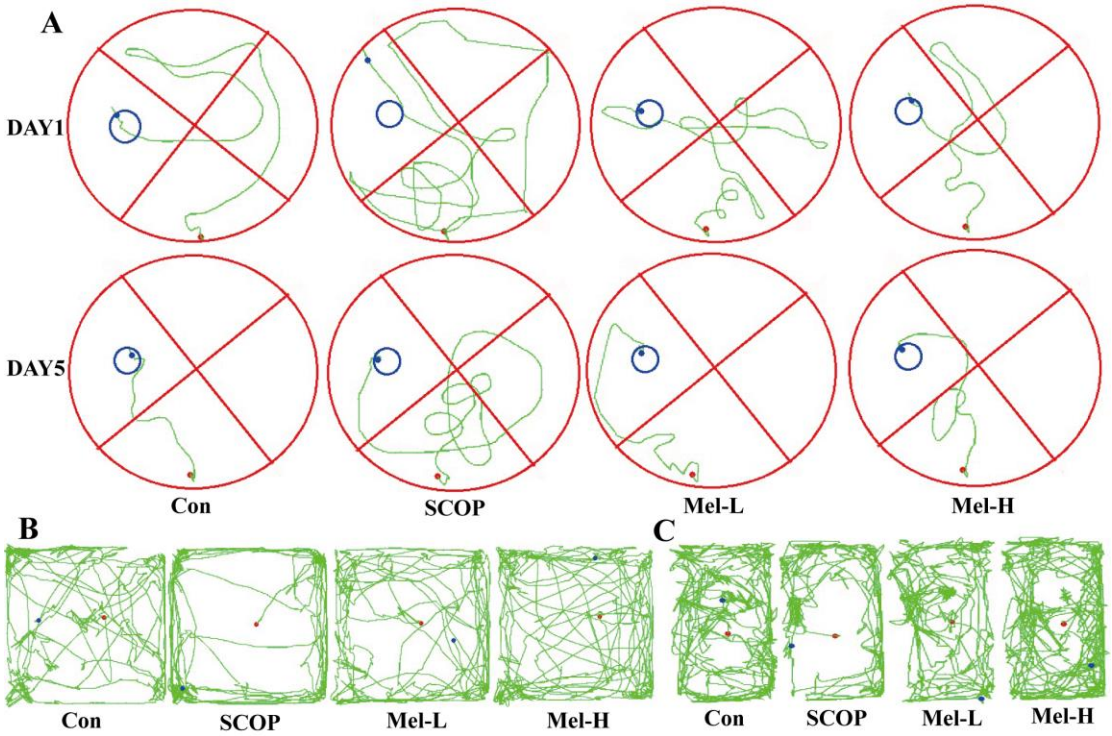
The 10 % MTT solution replaced the medium with different treatments for 4 h. Then, removed the MTT solution, added the DMSO. After the formazan crystals were completely dissolved, the absorbance was measured at 570 nm by Universal Microplate Spectrophotometer (Bio-Rad, Hercules, CA, USA). The rate of cell viability was calculated (OD value of treatment groups / OD value of control group × 100 %).

Real-time quantitative PCR

Total RNA was isolated from HT22 cells using RNAiso Plus, chloroform, isopropanol in turn and the concentration of RNA was measured by NanoDrop 2000/2000c (Thermo Fisher Scientific, Rockford, IL, USA). The mRNA was converted into cDNA using Prime Script RT Master Mix through a reverse transcription reaction process. PCR reaction was executed with Applied Biosystems 7500 Real-Time PCR System (Thermo Fisher Scientific, Rockford, IL, USA) by using TB Green Premix Ex Taq. The primer sequences were as follows: *Sirt1* forward, 5’-TGGTTCCAGTACTGCAGACA-3’, reverse, 5’-GTATACCTCAGCACCGTGGA-3’; *Sirt2* forward, 5’-GAGCCGGACCGATTCAGAC-3’, reverse, 5’-GGAGCGGAAGTCAGGGATAC-3’; *Sirt3* forward, 5’-GATTCGGATGGCGCTTGAC-3’, reverse, 5’-TCTCCCACCTGTAACACTCCC-3’; *Sirt4* forward, 5’-AGACCCATCCAGCACATTGA-3’, reverse, 5’-TCCACGTTCTGAGTCACCAA-3’; *Sirt5* forward, 5’-CATTCTGGAGGAGGTGGACA-3’, reverse, 5’-GGGTCCGGGAAAATGAAACC-3’; *Sirt6* forward, 5’-GGGGCTGTCAGTCTTTGTTG-3’, reverse, 5’-GCTCCGTTAACATGAGGCAG-3’; *Sirt7* forward, 5’-AGAAATATCCCCGCCTCTGG-3’, reverse, 5’-GAAAGTCTTCAGGGCAGCAG-3’; *ACTB* forward,

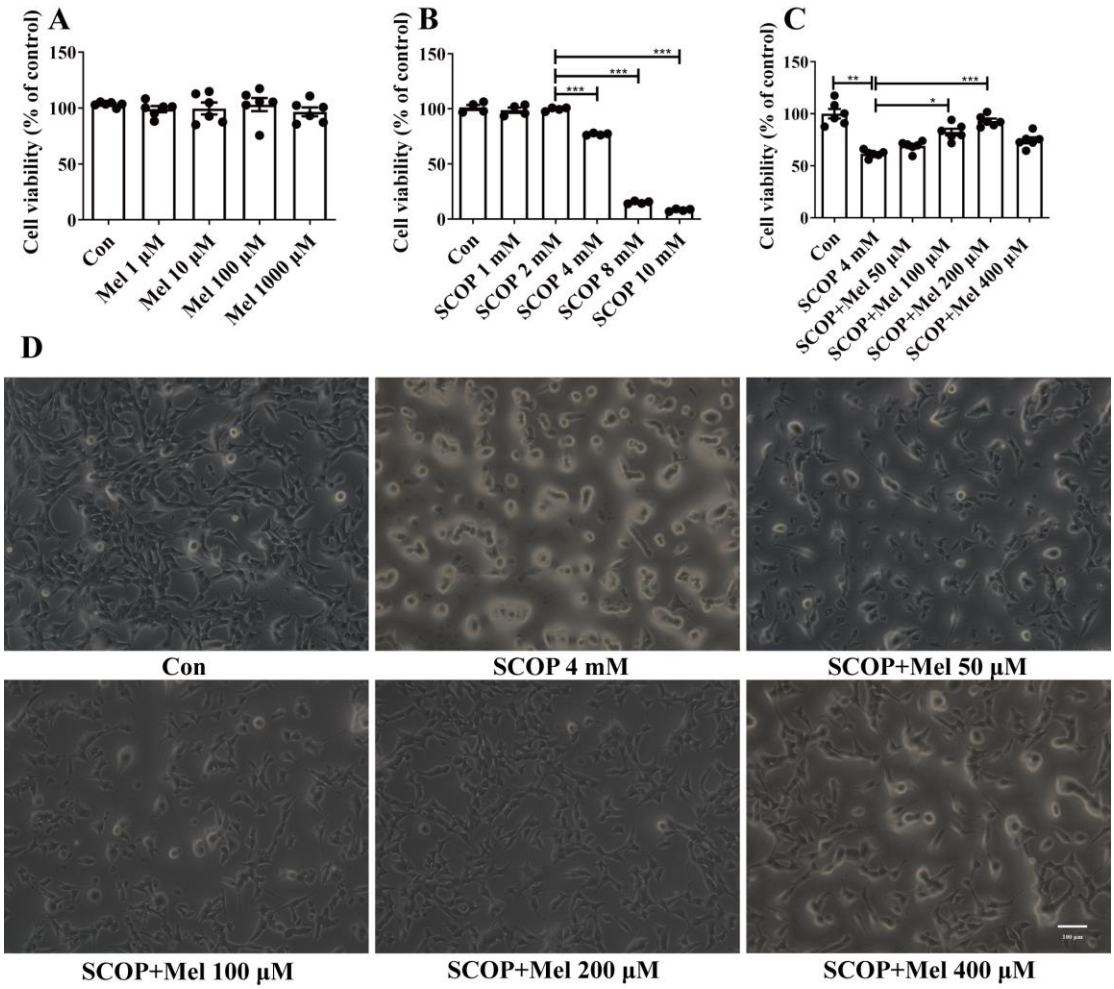
5’-GATCAAGATCATTGCTCCTCCTG-3’, reverse, 5’-AGGGTGTAAAACGCAGCTCA-3’.

Supplementary Fig. 1.



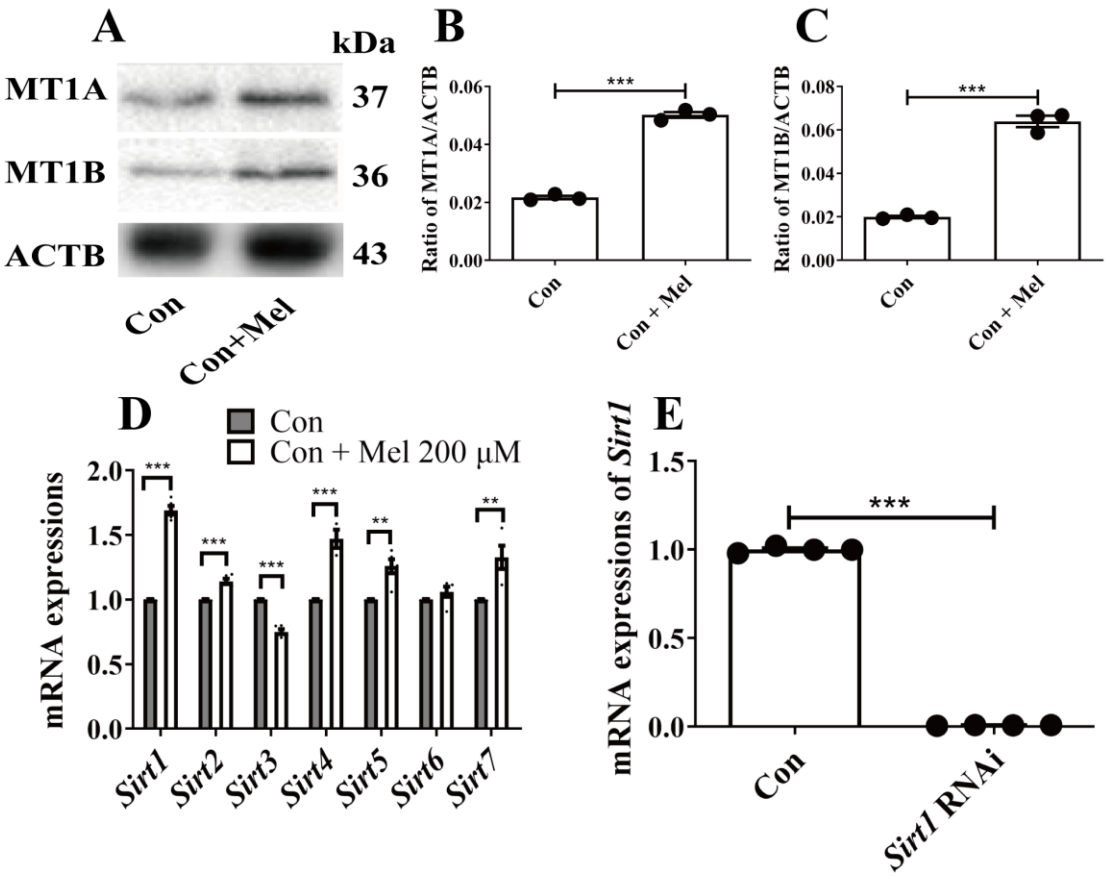
Supplementary Fig. 1. The trajectory of animal behavior. The track diagram of DAY1 and DAY5 (A), trajectory map of exploration (B) and trajectory map of learning (C).

Supplementary Fig. 2.



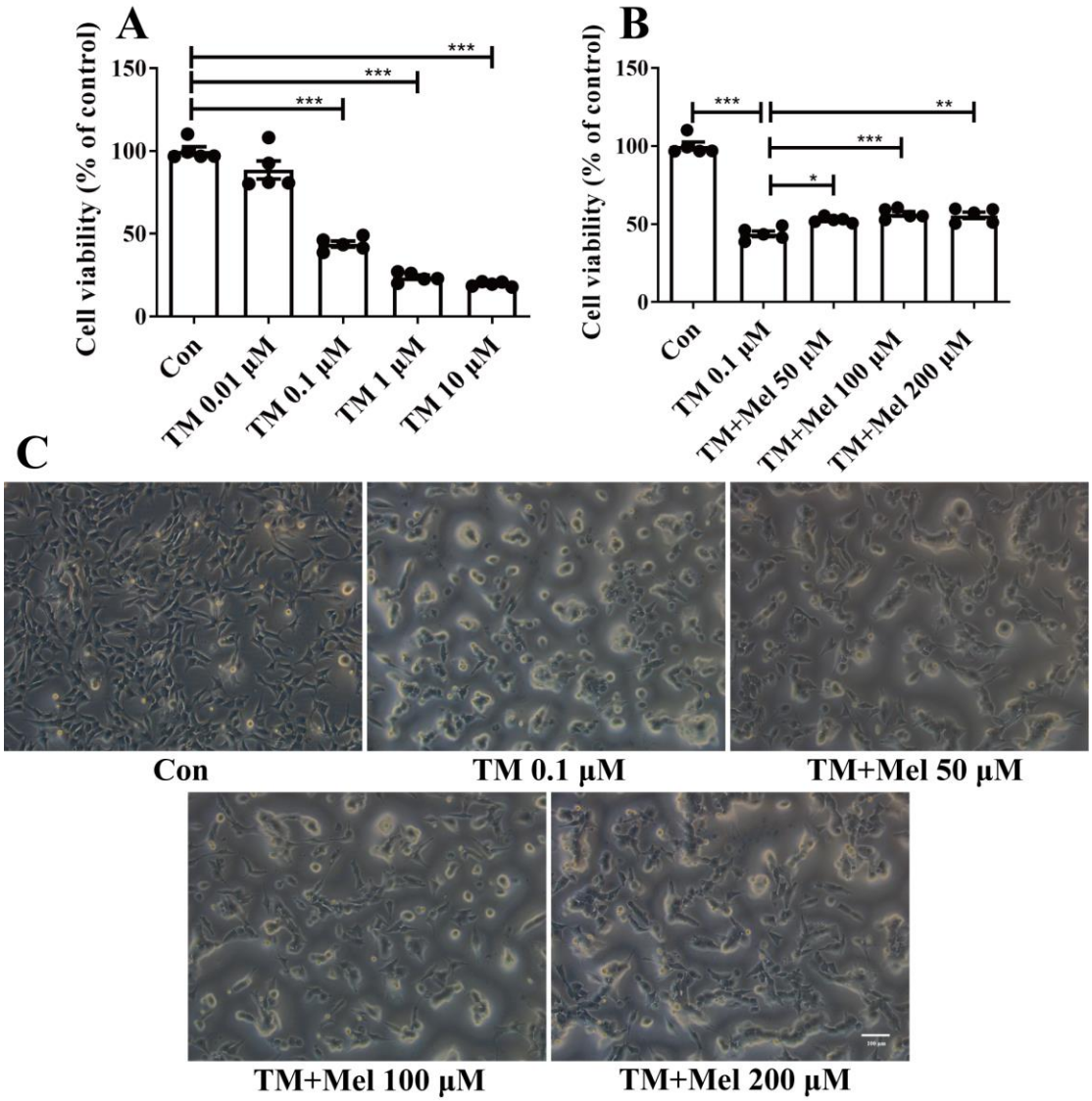
Supplementary Fig. 2. Effects of melatonin on SCOP-induced HT22 cell death. The cell viability after different concentrations of melatonin (24 h) (A), SCOP (24 h) (B) and adding melatonin for 24 h and then with or without SCOP (4 mM) for 24 h (C) (*p < 0.05, **p < 0.01, and ***p < 0.001). The bars indicate SEM. Morphological changes of SCOP-induced HT22 cells with or without melatonin (D). Scar bar = 100 μm.

Supplementary Fig. 3.



Supplementary Fig. 3. The expression of melatonin receptors and sirtuins family in melatonin-treated HT22 cells. (A-C) Expression of MT1A (B) and MT1B (C) proteins in melatonin-treated HT22 cells by western blot. The relative expression of *Sirt1-7* mRNAs was analyzed by quantitative RT-PCR (D). The mRNA expression of *Sirt1* after adding *Sirt1* RNAi 24 h by quantitative RT-PCR (E) (*$p < 0.05$, **$p < 0.01$, and ***$p < 0.001$, *vs.* control). The bars indicate SEM.

Supplementary Fig. 4.



Supplementary Fig. 4. Effects of melatonin on TM-induced HT22 cell death. The cell viability after different concentrations of TM (24 h) (A) and adding melatonin for 24 h and then with or without TM (0.1 μM) for 24 h (B) (*$p < 0.05$, **$p < 0.01$, and ***$p < 0.001$). The bars indicate SEM. Morphological changes of SCOP-induced HT22 cells with or without melatonin (C). Scar bar = 100 μm.