**Supporting Information**

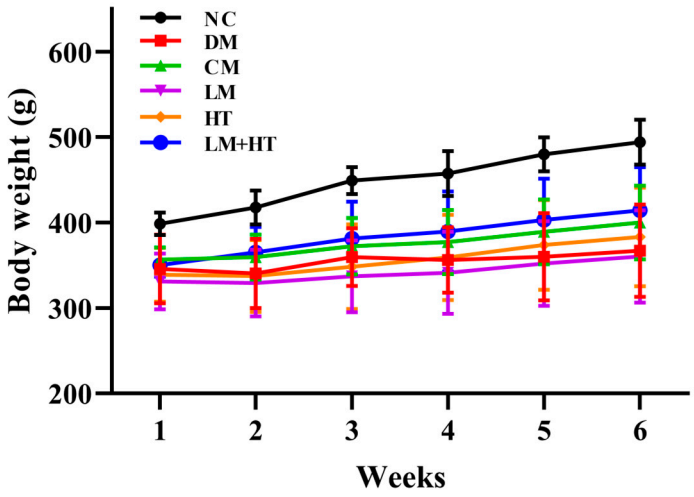



**Figure S1** Effect of combination of hesperetin and metformin on body weight in diabetes rats. NC, normal diet control group. DM, diabetes mellitus group. CM, conventional dose metformin (300 mg•kg$^{-1}$•day$^{-1}$) group. LM, low-dose metformin (100 mg•kg$^{-1}$•day$^{-1}$) group. HT, hesperetin (50 mg•kg$^{-1}$•day$^{-1}$) group. LM+HT, low-dose metformin+hesperetin (100 mg•kg$^{-1}$•day$^{-1}$ metformin+50 mg•kg$^{-1}$•day$^{-1}$ hesperetin).

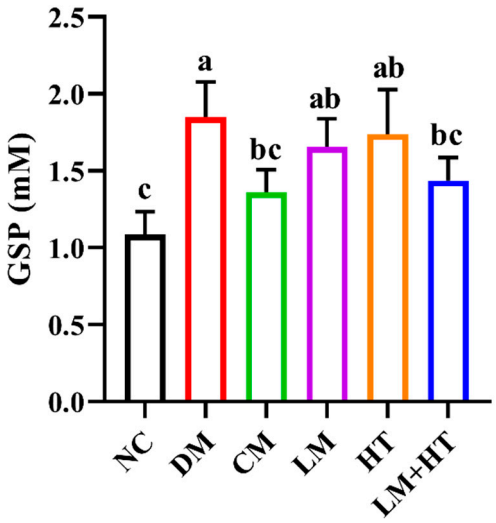



**Figure S2** Effect of combination of hesperetin and metformin on glycosylated serum protein (GSP) in serum. Data were presented as the mean ± SD. Different letters represented significance between the two groups ($p$<0.05). NC, normal diet control group. DM, diabetes mellitus group. CM, conventional dose metformin (300 mg•kg$^{-1}$•day$^{-1}$) group. LM, low-dose metformin (100 mg•kg$^{-1}$•day$^{-1}$) group. HT, hesperetin (50 mg•kg$^{-1}$•day$^{-1}$) group. LM+HT, low-dose metformin+hesperetin (100 mg•kg$^{-1}$•day$^{-1}$ metformin+50 mg•kg$^{-1}$•day$^{-1}$ hesperetin).

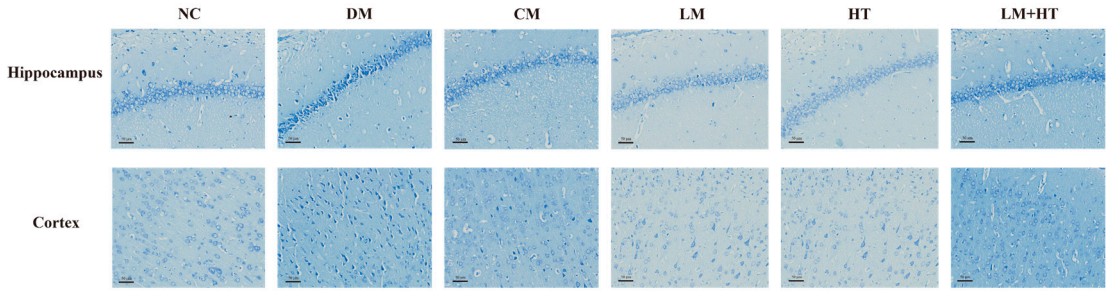



**Figure S3** Effect of combination of hesperetin and metformin on nissl staining of hippocampus. NC, normal diet control group. DM, diabetes mellitus group. CM, conventional dose metformin (300 mg•kg$^{-1}$•day$^{-1}$) group. LM, low-dose metformin (100 mg•kg$^{-1}$•day$^{-1}$) group. HT, hesperetin (50 mg•kg$^{-1}$•day$^{-1}$) group. LM+HT, low-dose metformin+hesperetin (100 mg•kg$^{-1}$•day$^{-1}$ metformin+50 mg•kg$^{-1}$•day$^{-1}$ hesperetin).

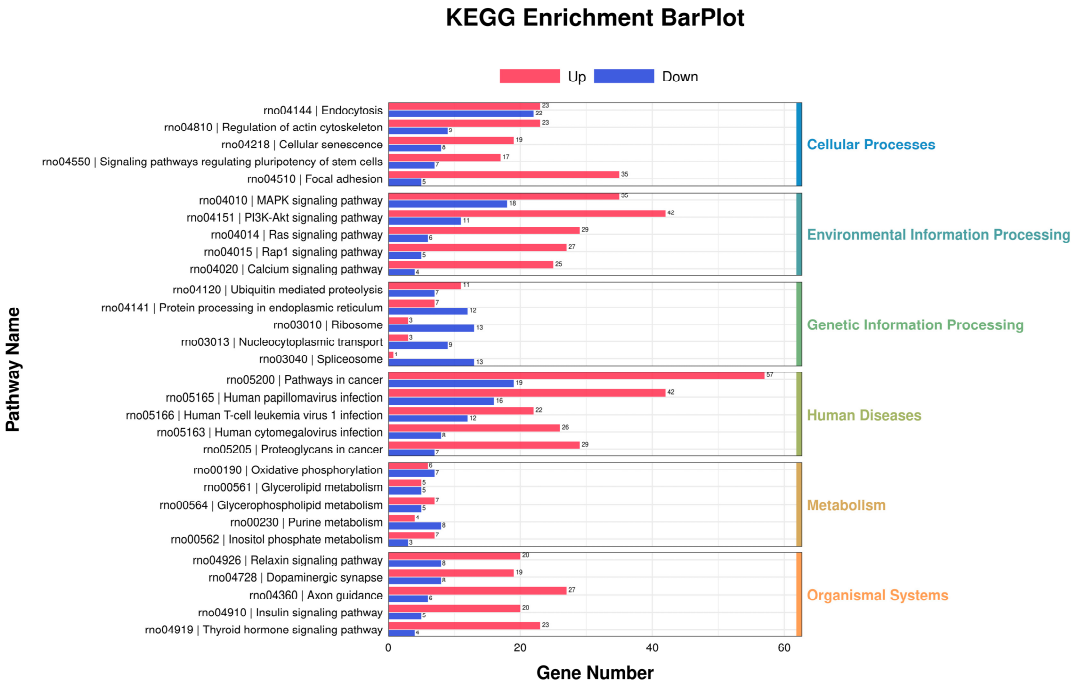



**Figure S4** Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment of transcriptome analysis.

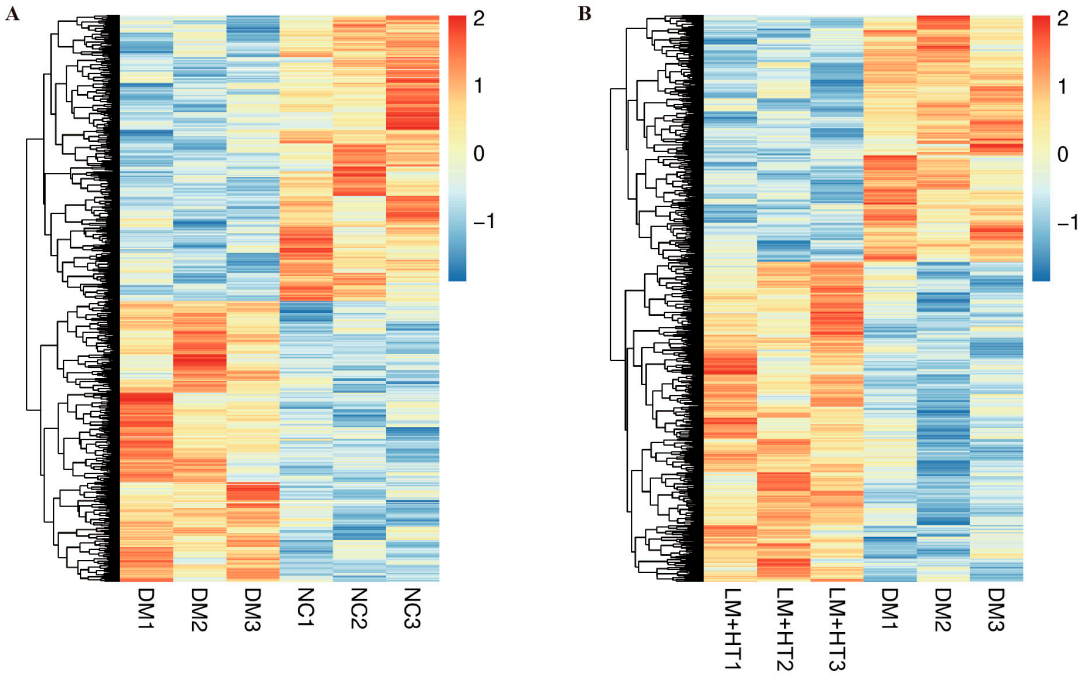



**Figure S5** Heatmap of differentially expressed genes in transcriptome analysis. (A) DM vs NC. (B) LM+HT vs DM. NC, normal diet control group. DM, diabetes mellitus group. LM+HT, low-dose metformin+hesperetin (100 mg•kg$^{-1}$•day$^{-1}$ metformin+50 mg•kg$^{-1}$•day$^{-1}$ hesperetin).

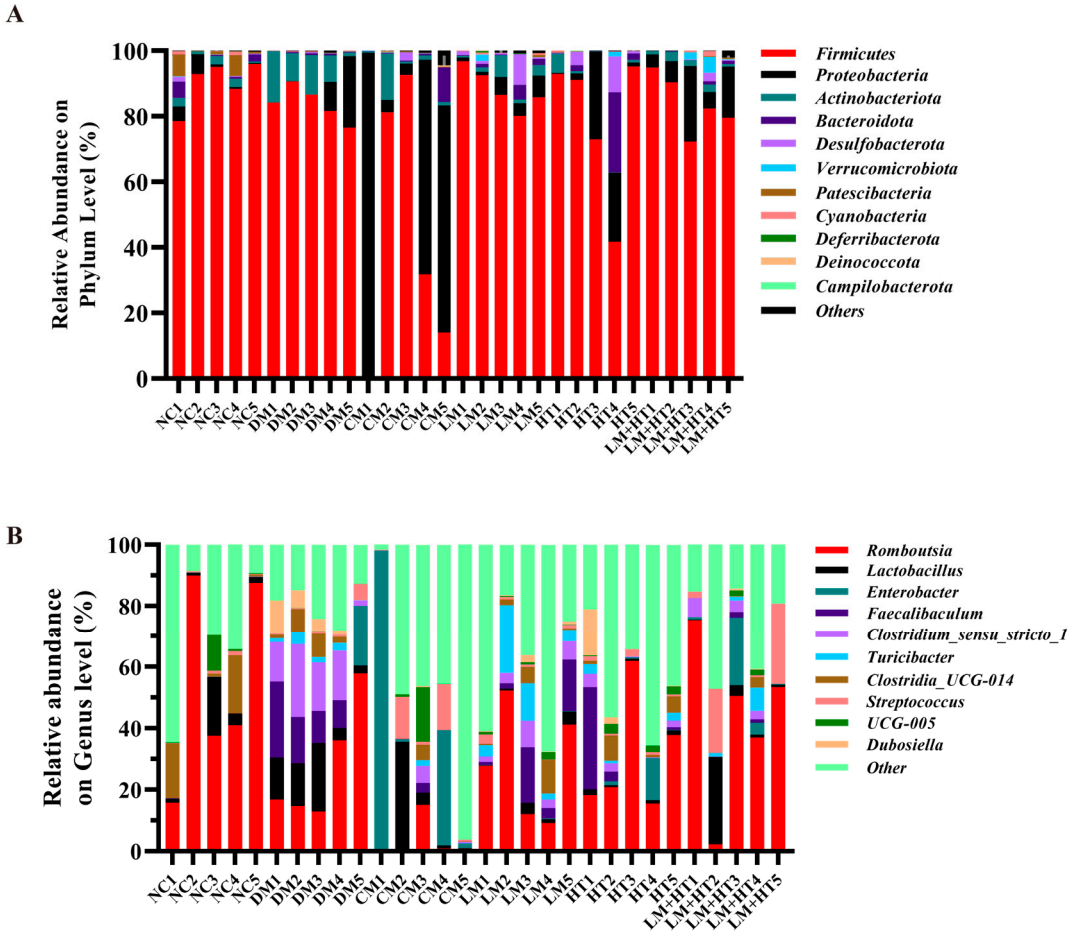



**Figure S6** Relative abundance in Phylum level (A) and Genus level (B). NC, normal diet control group. DM, diabetes mellitus group. CM, conventional dose metformin (300 mg•kg$^{-1}$•day$^{-1}$) group. LM, low-dose metformin (100 mg•kg$^{-1}$•day$^{-1}$) group. HT, hesperetin (50 mg•kg$^{-1}$•day$^{-1}$) group. LM+HT, low-dose metformin+hesperetin (100 mg•kg$^{-1}$•day$^{-1}$ metformin+50 mg•kg$^{-1}$•day$^{-1}$ hesperetin).

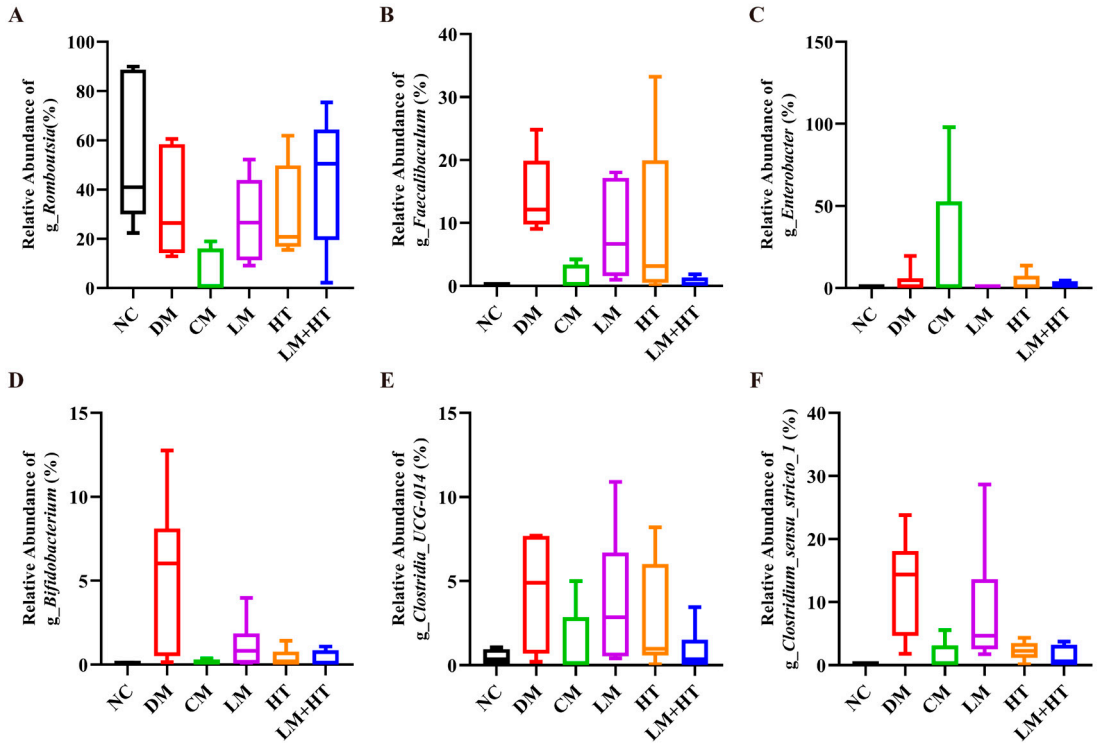



**Figure S7** Effect of combination of hesperetin and metformin on relative abundance of (A) g_*Romboutsia*, (B) g_*Faecalibaculum*, (C) g_*Enterobacter*, (D) g_*Bifidobacterium*, (E) g_*Clostridia_UCG-014*, (F) g_*Clo_Clostridium_sensu_stricto_1*. NC, normal diet control group. DM, diabetes mellitus group. CM, conventional dose metformin (300 mg•kg$^{-1}$•day$^{-1}$) group. LM, low-dose metformin (100 mg•kg$^{-1}$•day$^{-1}$) group. HT, hesperetin (50 mg•kg$^{-1}$•day$^{-1}$) group. LM+HT, low-dose metformin+hesperetin (100 mg•kg$^{-1}$•day$^{-1}$ metformin+50 mg•kg$^{-1}$•day$^{-1}$ hesperetin).

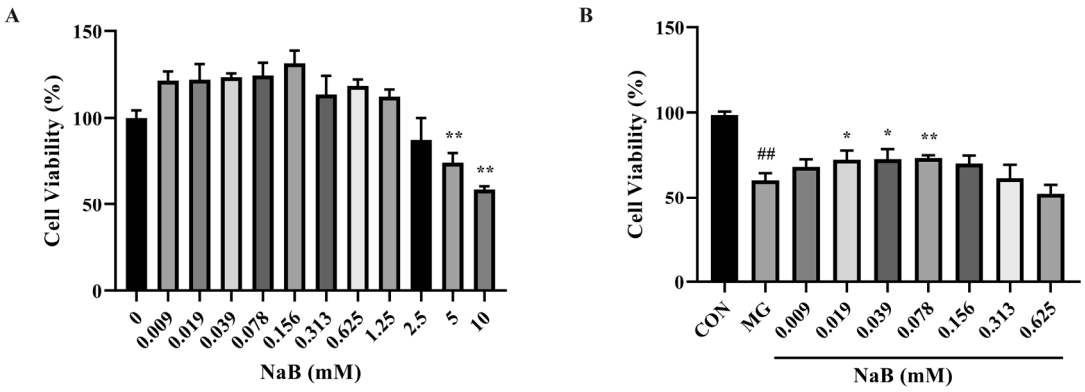



**Figure S8** Cell viability. (A) Cell viability of treatment with NaB in PC-12 cells. Data were presented as the mean ± SD. ***p*<0.001 vs 0 group. (B) Cell viability of treatment with MG and NaB in PC-12 cells. Data were presented as the mean ± SD. ##*p*<0.01 vs CON group. **p*<0.05 vs MG group. **p*<0.01 vs MG group. CON, control group. MG, methylglyoxal group. NaB, sodium butyrate group.

Table S1 Primer sequences used in the quantitative real-time PCR analysis

| **Target mRNA** | **Primer sequence (5'-3')** | **Fragment size (bp)** |
|---|---|---|
| *Bdnf* | F: TGGAACTCGCAATGCCGAACTAC<br>R: TCCTTATGAACCGCCAGCCAATTC | 88 |
| *β-Actin* | F: TGTCACCAACTGGGACGATA<br>R: GGGGTGTTGAAGGTCTCAAA | 165 |