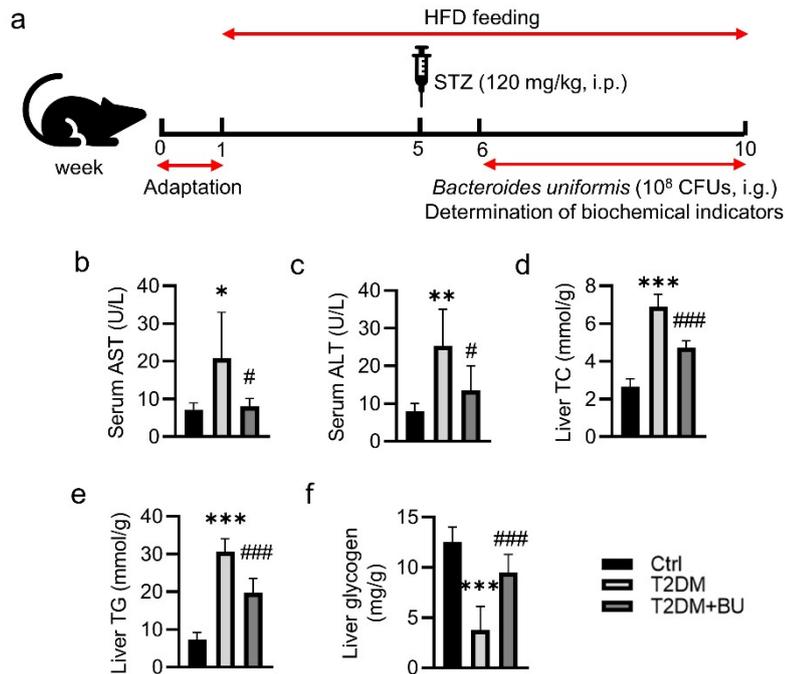
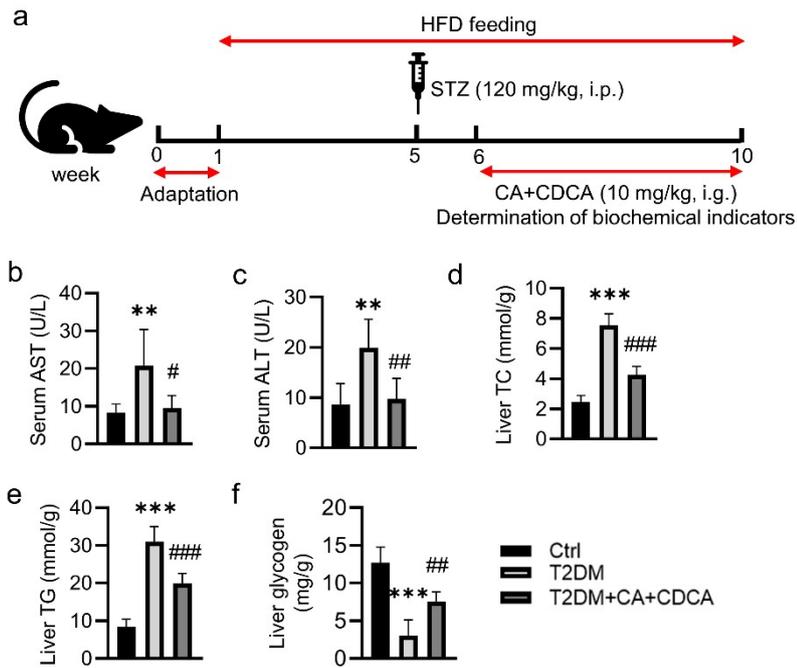


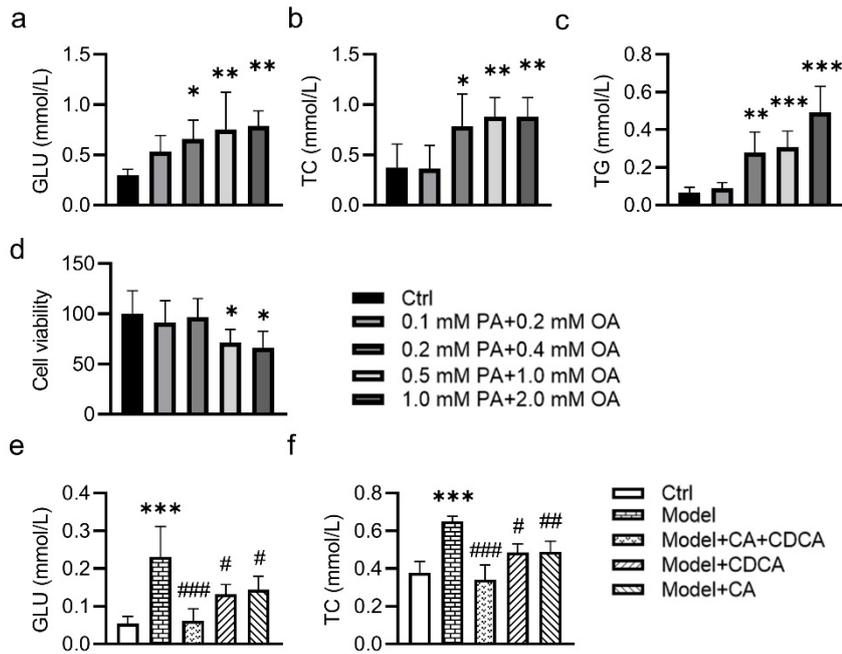
Supplementary material and data



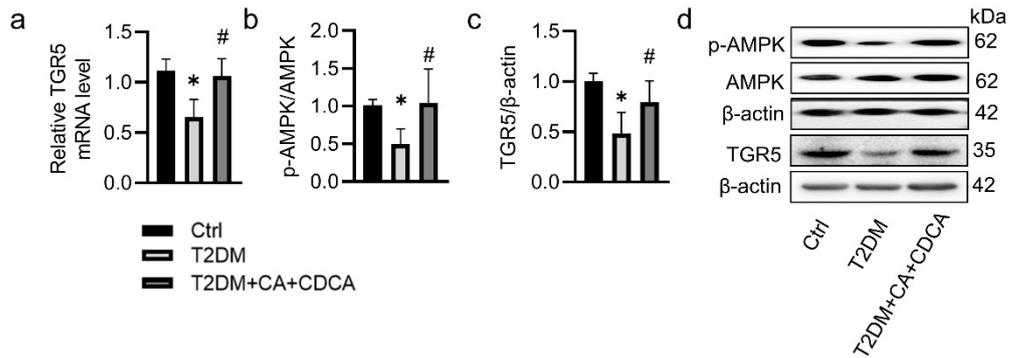
Supplementary Figure S1. (a) Experimental protocol. **(b-c)** The levels of serum AST, ALT. **(d-f)** The content of liver TC, TG and glycogen. Data were represented as mean \pm SD (n=6). *P < 0.05, **P < 0.01, ***P < 0.001 vs Ctrl; #P < 0.05, ###P < 0.001 vs T2DM. Ctrl, control; T2DM, type 2 diabetes mellitus; BU, *Bacteroides uniformis*; AST, Aspartate aminotransferase; ALT, Alanine aminotransferase; TC, total cholesterol; TG, triglycerides.



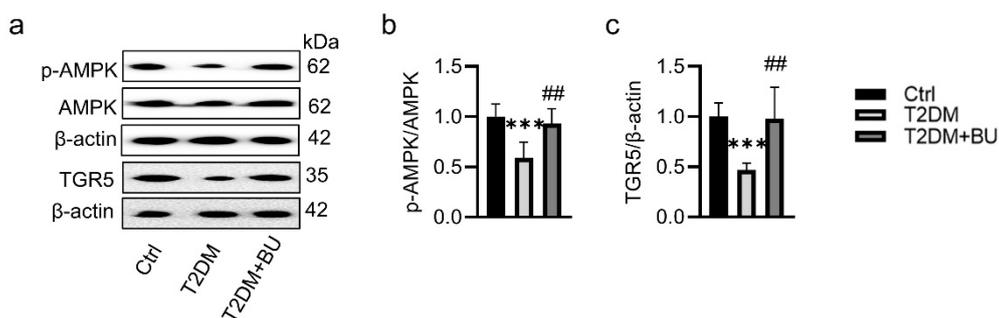
Supplementary Figure S2. (a) Experimental protocol. **(b-c)** The levels of serum AST, ALT. **(d-f)** The content of liver TC, TG and glycogen. Data were represented as mean \pm SD (n=6). **P < 0.01, ***P < 0.001 vs Ctrl; #P < 0.05, ##P < 0.01, ###P < 0.001 vs T2DM. Ctrl, control; T2DM, type 2 diabetes mellitus; STZ, streptozocin; HFD, high-fat diet; AST, Aspartate aminotransferase; ALT, Alanine aminotransferase; TC, total cholesterol; TG, triglycerides; CA, cholic acid; CDCA, chenodeoxycholic acid.



Supplementary Figure S3. Effect of different concentrations of CA and CDCA on PA/OA on insulin resistance and lipid deposition. (a-d) HepG2 cells were treated with different concentrations of PA and OA for 24 h. The levels of GLU, TC and TG were determined. Cell viability was measured by CCK-8 assay. **(e-f)** HepG2 cells were pre-incubated with 50 μ M CA, CDCA or, CA and CDCA for 30 min, and then treated without or with 0.5 mM of PA and 1 mM of OA for 24 h. The levels of GLU and TC were measured. Data were represented as mean \pm SD (n=3-6). * P < 0.05, ** P < 0.01, *** P < 0.001 vs Ctrl; # P < 0.05, ## P < 0.01, ### P < 0.01 vs Model. PA, palmitic acid; OA, oleic acid; GLU, glucose; TC, total cholesterol; TG, triglycerides; CA, cholic acid; CDCA, chenodeoxycholic acid.

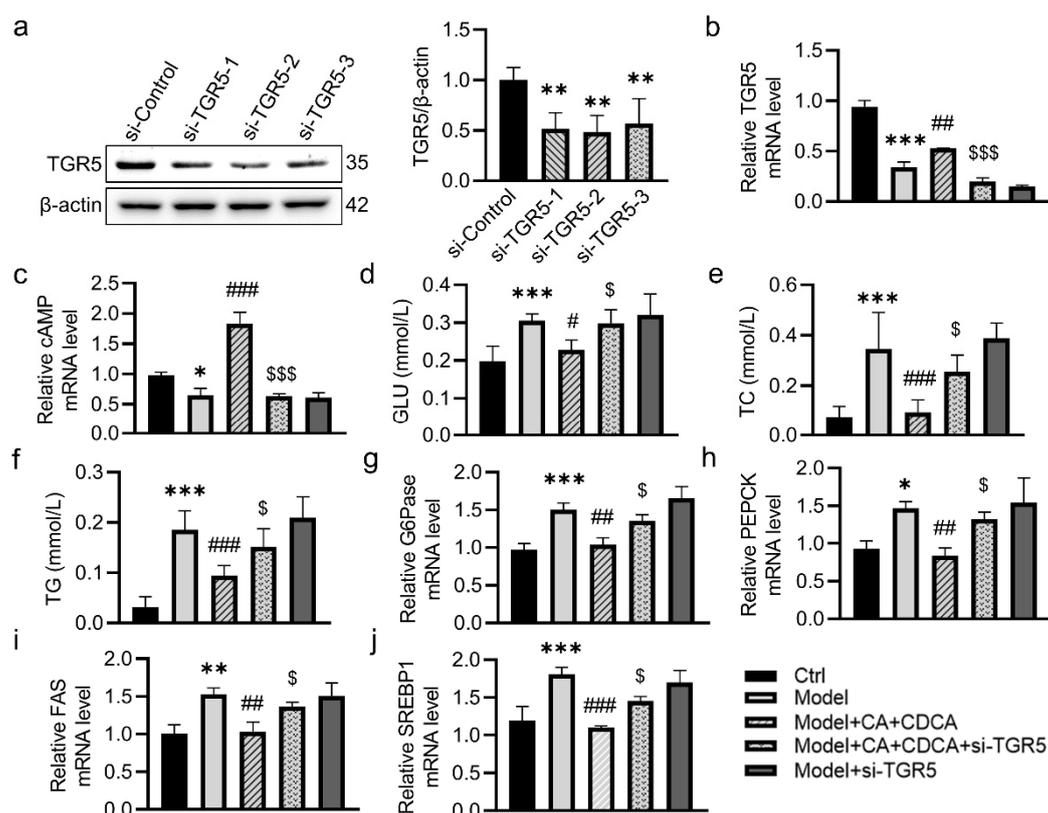


Supplementary Figure S4. Effect of CA and CDCA on TGR5/cAMP/AMPK signaling pathway in T2DM mice. (a) The relative mRNA levels of TGR5. (b-d) Representative blots and quantification of p-AMPK/AMPK and TGR5. Data were represented as mean \pm SD (n =3-6). * $P < 0.05$, ** $P < 0.01$ vs Ctrl; # $P < 0.05$ vs T2DM. Ctrl, control; T2DM, type 2 diabetes mellitus; TGR5, Takeda G protein-coupled receptor 5; AMPK, adenosine monophosphate activated protein kinase; p-AMPK, phosphorylated adenosine monophosphate activated protein kinase; CA, cholic acid; CDCA, chenodeoxycholic acid.



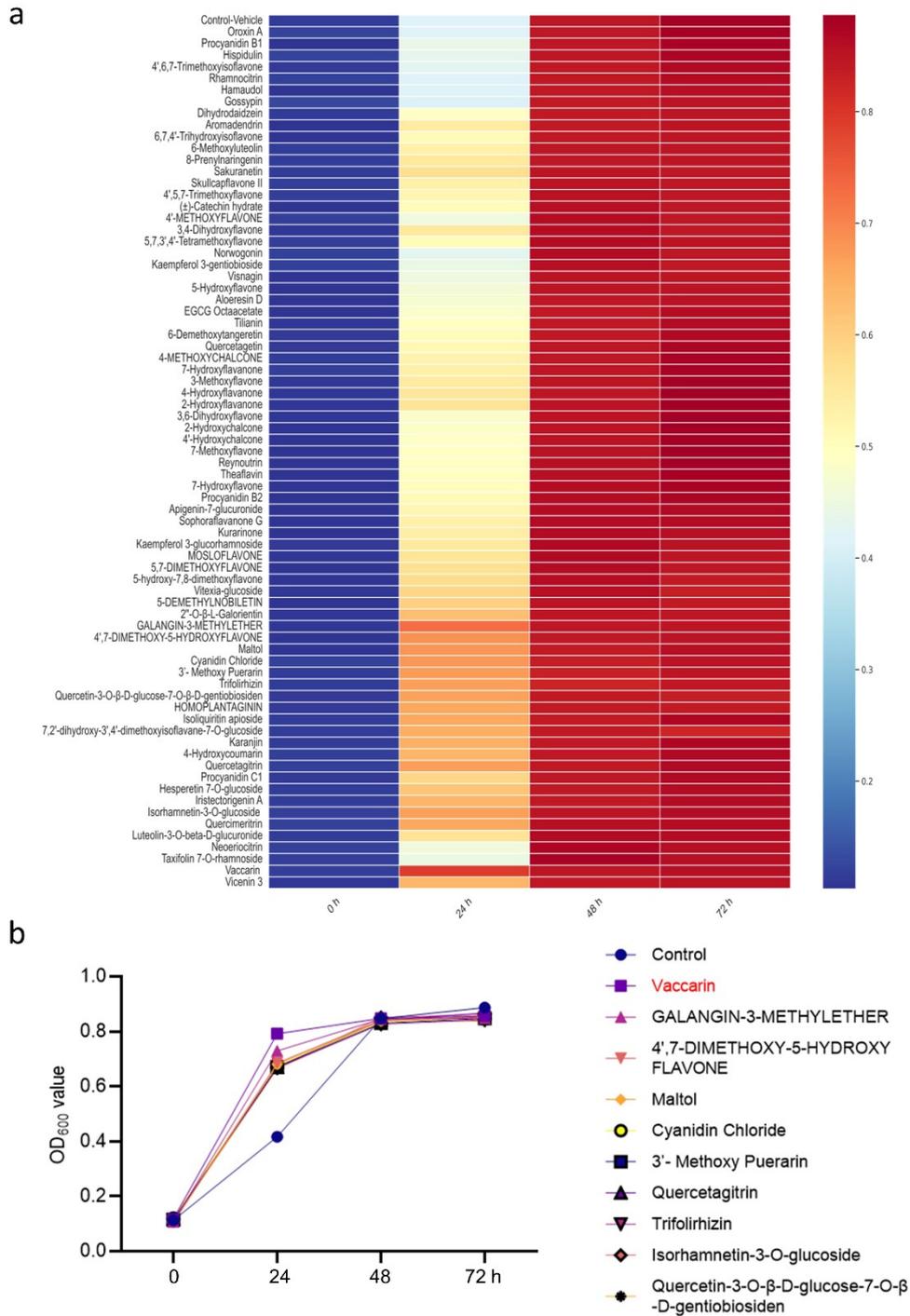
Supplementary Figure S5. Effect of CA and CDCA on TGR5/cAMP/AMPK signaling pathway in T2DM mice. (a) Representative blots of p-AMPK/AMPK and TGR5. (b-c) Quantification of p-AMPK/AMPK and TGR5. Data were represented as mean \pm SD (n = 6). *** $P < 0.01$ vs Ctrl; # $P < 0.05$ vs T2DM. Ctrl, control; T2DM, type

2 diabetes mellitus; BU, *B. uniformis*; TGR5, Takeda G protein-coupled receptor 5; AMPK, adenosine monophosphate activated protein kinase; p-AMPK, phosphorylated adenosine monophosphate activated protein kinase.

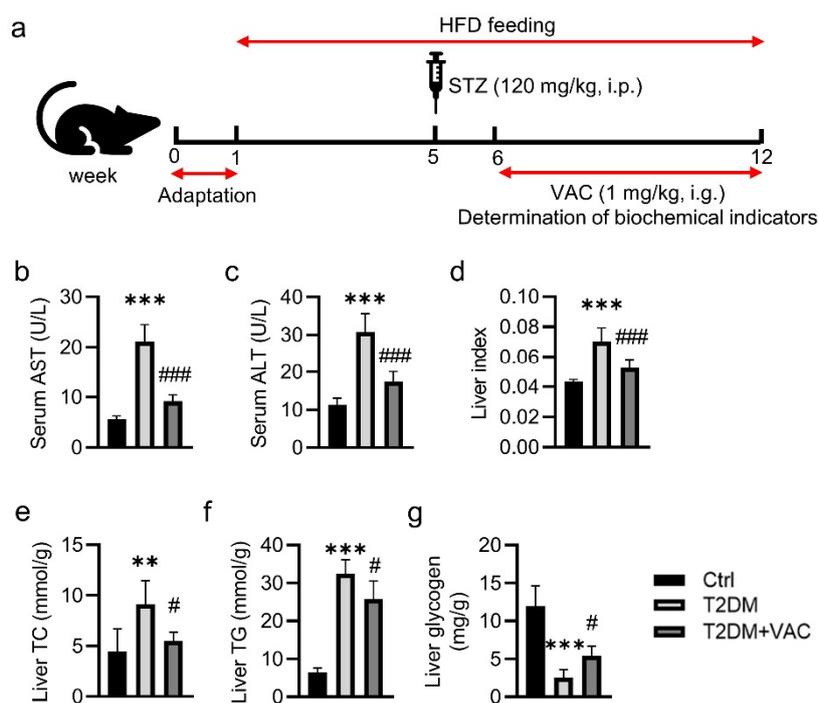


Supplementary Figure S6. Deficiency of TGR5 prevented the effects of CA and CDCA on carbohydrate and lipid metabolism. (a) Representative blots and quantification of TGR5. (b) The relative mRNA levels of TGR5. (c-e) The content of GLU, TC and TG. (f-i) The mRNA levels of G6Pase, PEPCK, FAS, and SREBP1. Data were represented as mean \pm SD (n = 3-6). * P < 0.05, ** P < 0.01, *** P < 0.001 vs Ctrl; # P < 0.05, ## P < 0.01, ### P < 0.01 vs Model. \$ P < 0.05, \$\$\$ P < 0.01 vs Model+CA+CDCA. Ctrl, control; CA, cholic acid; CDCA, chenodeoxycholic acid; TGR5, Takeda G protein-coupled receptor 5; GLU, glucose; TC, total cholesterol; TG,

triglycerides; G6Pase, glucose-6-phosphatase; PEPCK, phosphoenolpyruvate carboxykinase; FAS, fatty acid synthase; SREBP1, sterol-regulatory element binding protein 1.



Supplementary Figure S7. Effect of different natural flavonoids on the growth of *B. uniformis*. (a) Heatmap showing the effects of 79 compounds (10 μ M) on the growth of *B. uniformis* *in vitro*, as assessed by OD₆₀₀ value. (b) The growth curve of *B. uniformis* induced by top-ten saponins at indicated time points.



Supplementary Figure S8. (a) Experimental protocol. **(b-c)** The levels of serum AST, ALT. **(d)** The liver index. **(e-g)** The content of liver TC, TG and glycogen. Data were represented as mean \pm SD (n=6). **P < 0.01, ***P < 0.001 vs Ctrl; #P < 0.05, ###P < 0.001 vs T2DM. Ctrl, control; T2DM, type 2 diabetes mellitus; VAC, vaccarin; AST, Aspartate aminotransferase; ALT, Alanine aminotransferase; TC, total cholesterol; TG, triglycerides.

Table S1. Primer sequences used for measurement of the bacteria in the gut.

Species	Gene	Sequence
Mice	β -actin	F: 5'-AGCTGAGAGGGAAATCGTGC-3' R: 5'-TCCAGGGAGGAAGAGGATGC-3'
Mice	<i>B. uniformis</i>	F: 5'-TAGCGGTGAAATGCTTAG-3' R: 5'-CATCGTTTACTGTGTGGA-3'

Table S2. The primer sequences used in HepG2 cells.

Gene	Forward primer (5'->3')	Reverse primer (5'->3')
β -actin	ATCATGTTTGAGACCTTCAACA	CATCTCTTGCTCGAAGTCCA
G6Pase	ACTGGCTCAACCTCGTCTTTA	CGGAAGTGTTGCTGTAGTAGTCA
PEPCK	GAAAAAACCTGGGGCACAT	TTGCTTCAAGGCAAGGATCTCT
FAS	AGCTGCCAGAGTCGGAGAAC	GTAGCCCACGAGTGTCTCG
SREBP1	ACAGTGACTIONCCTGGCCTAT	GCATGGACGGGTACATCTTCAA
TGR5	CTGCTGGCTGCTTCTTCCTGAG	ACGAGGAGGCAGGACCAGTAAC

Table S3. The primer sequences used in mice.

Gene	Forward primer (5'→3')	Reverse primer (5'→3')
β -actin	AGCTGAGAGGGAAATCGTGC	TCCAGGGAGGAAGAGGATGC
G6Pase	CCGGATCTACCTTGCTGCTC	GCATTGTAGATGCCCCGGAT
PEPCK	TGGAAGGTCGAATGTGTGGG	CAGTAAACACCCCCATCGCT
FAS	TGCTTGCTGGCTCACAGTTAAGAG	TTTCACGAACCCGCCTCCTCAG
SREBP1	GGATGCGGCTGTTGTCTACCATAAG	CCAGGTTAGAAGCAGCAAGATGTCC
TGR5	GCCTGGAACTCTGTTATCGCTCATC	GAAGCACTCGTAGACACCTTTGGG