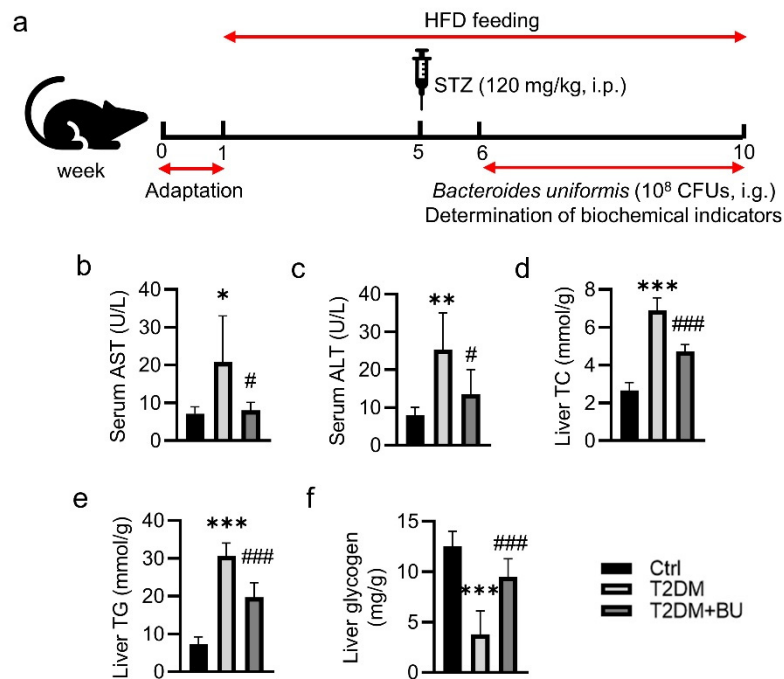
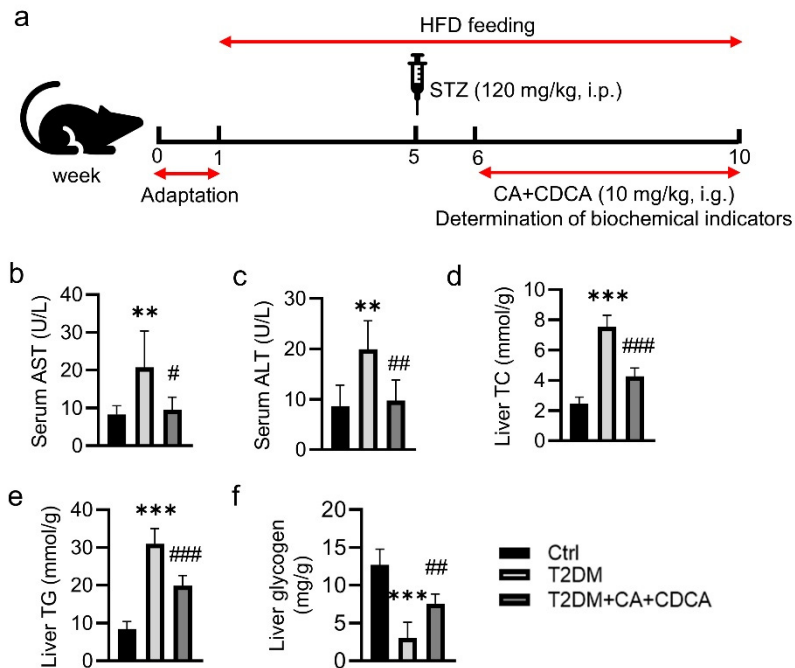


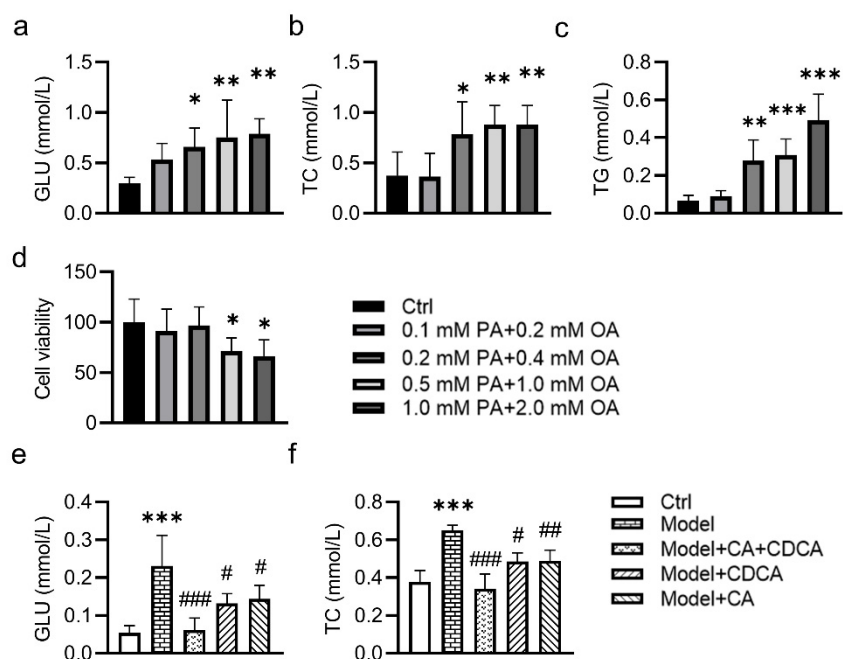
## Supplementary material and data



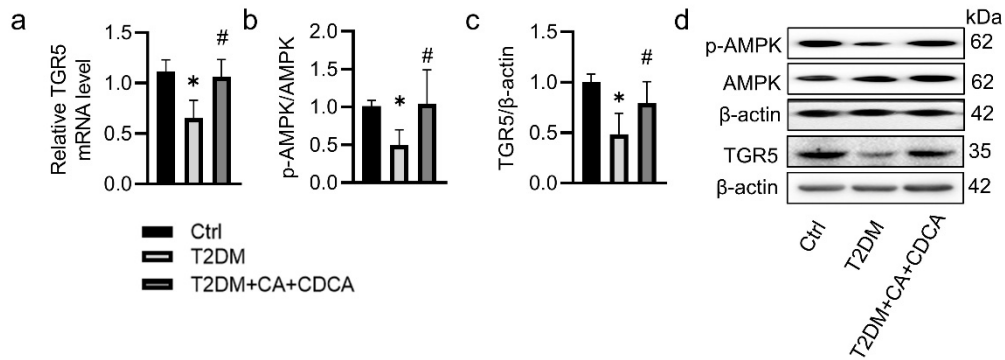
**Supplementary Figure S1.** (a) Experimental protocol. (b-c) The levels of serum AST, ALT. (d-f) The content of liver TC, TG and glycogen. Data were represented as mean  $\pm$  SD (n=6). \*P < 0.05, \*\*P < 0.01, \*\*\*P < 0.001 vs Ctrl; #P < 0.05, ###P < 0.001 vs T2DM. Ctrl, control; T2DM, type 2 diabetes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



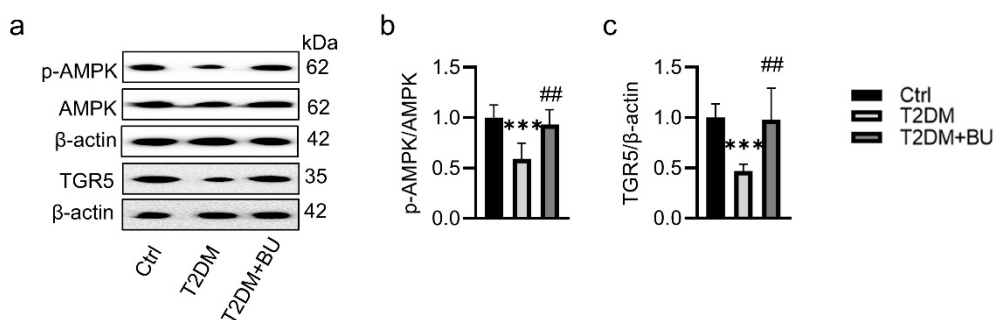
**Supplementary Figure S2. (a)** Experimental protocol. **(b-c)** The levels of serum AST, ALT. **(d-f)** The content of liver TC, TG and glycogen. Data were represented as mean  $\pm$  SD (n=6). \*\*P < 0.01, \*\*\*P < 0.001 vs Ctrl; #P < 0.05, ##P < 0.01, ###P < 0.001 vs T2DM. Ctrl, control; T2DM, 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  $\mu$ 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.

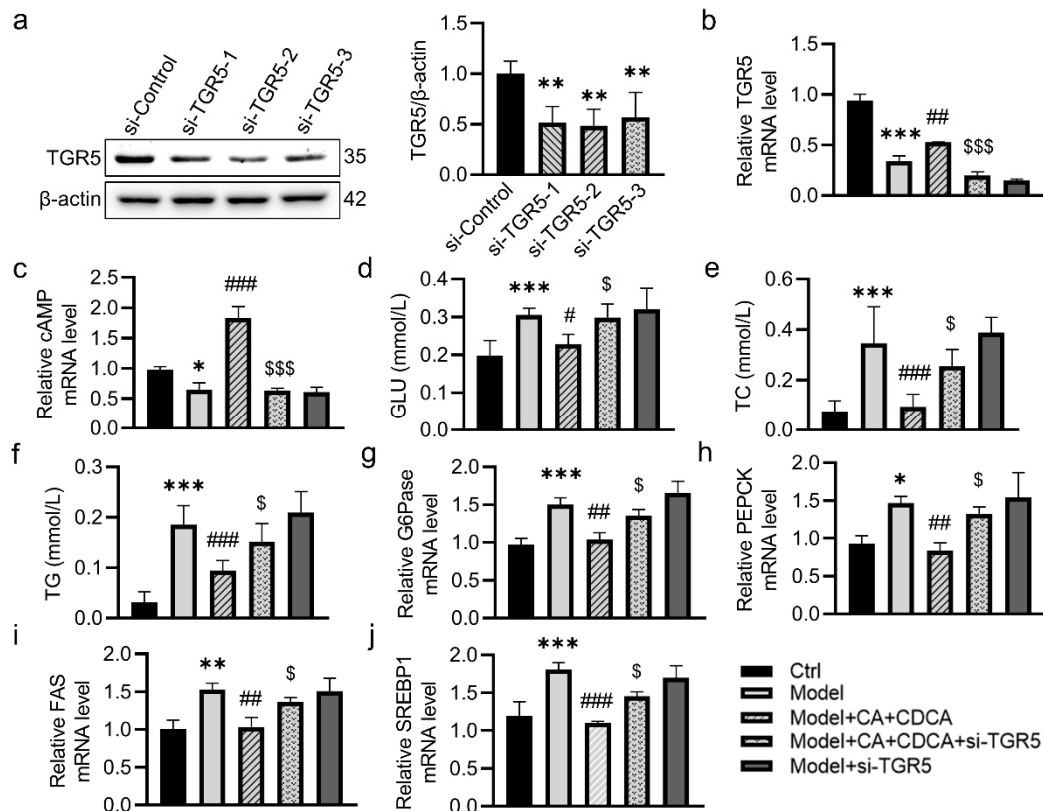


**Supplementary Figure S4. Effect of CA and CDCA on TGR5/cAMP/AMPK signaling pathway in T2DM mice.** (a) The relative mRNA levels of TGR5. (b-d) Representative blots and quantification of p-AMPK/AMPK and TGR5. Data were represented as mean  $\pm$  SD (n = 3-6). \* $P$  < 0.05, \*\* $P$  < 0.01 vs Ctrl; # $P$  < 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.



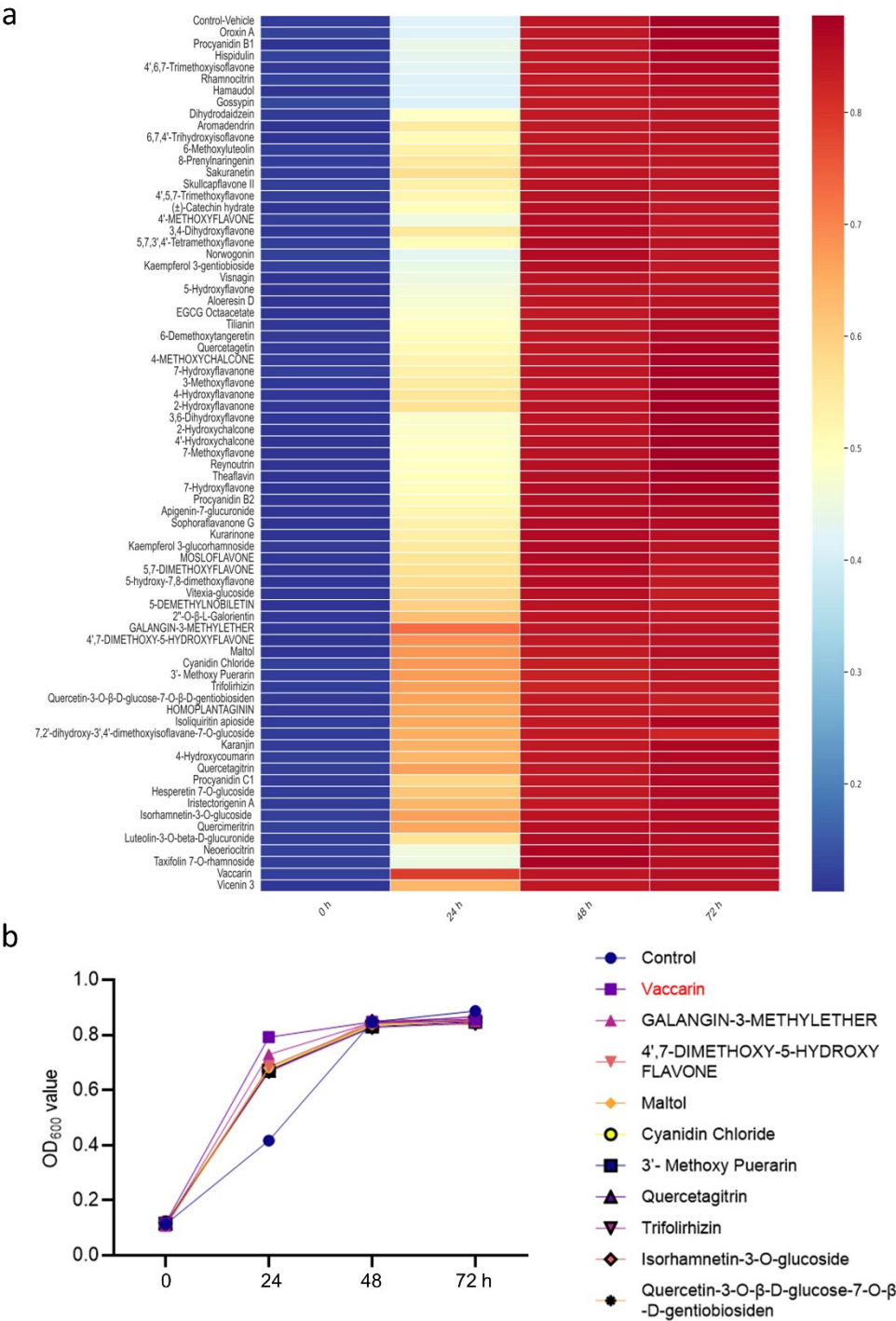
**Supplementary Figure S5. Effect of CA and CDCA on TGR5/cAMP/AMPK signaling pathway in T2DM mice.** (a) Representative blots of p-AMPK/AMPK and TGR5. (b-c) Quantification of p-AMPK/AMPK and TGR5. Data were represented as mean  $\pm$  SD (n = 6). \*\*\* $P$  < 0.01 vs Ctrl; # $P$  < 0.05 vs T2DM. Ctrl,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

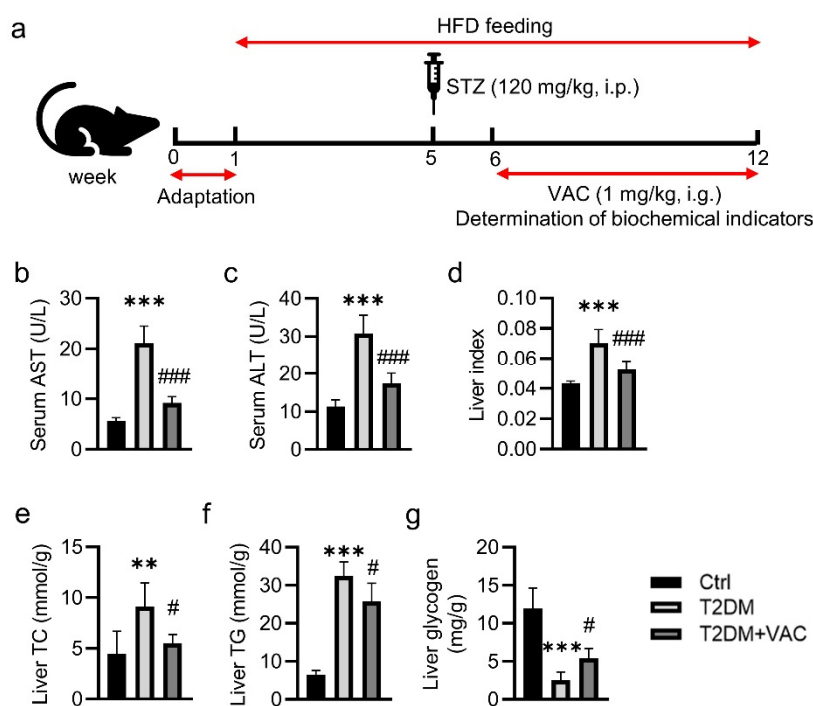


**Supplementary Figure S6. Deficiency of TGR5 prevented the effects of CA and CDCA on carbohydrate and lipid metabolism.** (a) Representative blots and quantification of TGR5. (b) The relative mRNA levels of TGR5. (c-e) The content of GLU, TC and TG. (f-i) The mRNA levels of G6Pase, PEPCK, FAS, and SREBP1. 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  $\mu$ M) on the growth of *B. uniformis* *in vitro*, as assessed by OD<sub>600</sub> 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	$\beta$ -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.**

<b>Gene</b>	<b>Forward primer (5'-&gt;3')</b>	<b>Reverse primer (5'-&gt;3')</b>
$\beta$ -actin	ATCATGTTTGAGACCTTCAACA	CATCTCTTGCTCGAAGTCCA
G6Pase	ACTGGCTCAACCTCGTCTTTA	CGGAAGTGTTGCTGTAGTAGTCA
PEPCK	GAAAAAACCTGGGGCACAT	TTGCTTCAAGGCAAGGATCTCT
FAS	AGCTGCCAGAGTCGGAGAAC	GTAGCCACGAGTGTCTCG
SREBP1	ACAGTGACTIONCCCTGGCCTAT	GCAATGGACGGGTACATCTTCAA
TGR5	CTGCTGGCTGCTTCTTCCTGAG	ACGAGGAGGCAGGACCAGTAAC

**Table S3. The primer sequences used in mice.**

<b>Gene</b>	<b>Forward primer (5'-&gt;3')</b>	<b>Reverse primer (5'-&gt;3')</b>
$\beta$ -actin	AGCTGAGAGGGAAATCGTGC	TCCAGGGAGGAAGAGGATGC
G6Pase	CCGGATCTACCTTGCTGCTC	GCATTGTAGATGCCCCGGAT
PEPCK	TGGAAGGTCGAATGTGTGGG	CAGTAAACACCCCCATCGCT
FAS	TGCTTGCTGGCTCACAGTTAAGAG	TTTCACGAACCCGCCTCCTCAG
SREBP1	GGATGCGGCTGTTGTCTACCATAAG	CCAGGTTAGAAGCAGCAAGATGTCC
TGR5	GCCTGGAACTCTGTTATCGCTCATC	GAAGCACTCGTAGACACCTTTGGG