**Supplementary data**

## Methods

### Safety evaluation in animals.

Male and female ICR mice weighing 18-20 g were purchased from the Institute of Laboratory Animal Science (Beijing, China). The mice were randomly divided into 3 groups with four mice each (2 male plus 2 female per dose level). The three groups of mice received RUT once intragastrically at 0 (1% CMC-Na as control), 500, or 1000 mg/kg, respectively. Body weight and survival were monitored. Seven days later, animals were sacrificed. Blood samples were taken for liver and kidney function examination. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN) and creatinine (CRE) levels were assayed using commercially available kits (Biosino bio-technology & science inc.). The livers, kidneys, and hearts were fixed in 10% formaldehyde at room temperature for histological examination using H&E staining.

For acute toxicity tests, ICR mice were intragastrically given RUT once in a single-dosing experiment at 0, 500, 1000, or 2000 mg/kg, and monitored for 7 days.

Plasma ALT and AST levels were also measured in $ApoE^{-/-}$ mice on HFD treated with or without RUT (20 mg/kg) after 8 weeks using the above kits (Biosino bio-technology & science inc.).

### FRET LXRα/β coregulator peptide interaction assay

FRET LXRα/β coregulator peptide interaction assay was performed as described in the original article method.

**Inflammatory factors determination.**

Plasma in ApoE$^{-/-}$ mice treated with or without RUT for 8 weeks was collected as in the method in the original article. Inflammatory markers including TNF-α, MCP-1, IL-8 and IL-6 expressions in plasma were examined using commercially kits (CUSABIO BIOTECH CO., LTD.) according to the instructions.

**Result**

**RUT had a good safety of RUT *in vivo*.**

As RUT targets several molecules within the RCT network, the *in vivo* safety of the compound was evaluated in mice. The animals were treated orally with RUT at 0, 500, 1000 mg/kg, and were followed up for 7 days. Results showed that RUT treatment didn't cause any detectable morphology change in liver, heart and kidney tissues of the ICR mice (*Supplementary Figure 1*), and didn't damage liver and kidney functions in the treated subgroups at 500 or 1000 mg/kg (*Supplementary Table 1*). In addition, acute toxicity test in ICR mice showed that no animal died in the 7-day treatment, indicating that the LD50 of RUT was above 2000 mg/kg in oral administration.

In addition, plasma ALT and AST levels were in ApoE$^{-/-}$ mice on HFD treated

with or without RUT (20 mg/kg) after 8 weeks didn't damage liver functions (*Supplementary Table 2*). In all, our results suggested a good safety of RUT *in vivo*.

**RUT modulated the interaction of corepressors and coactivators with LXRα or LXRβ LBD.**

As shown in *Supplementary Figure 2*, distinct patterns of coregulator recruitment to LXRα/LXRβ were observed in response to RUT and T0901317. Coactivator peptides exhibited partial recruitment to both LXRα and LXRβ LBDs by RUT compared with T0901317, including TRAP220/DRIP-2, D22, TRAP220/DRIP-250, PGC1α and SRC3-3. Corepressor peptide SMRT ID2 was partially displaced from both LXRα and LXRβ LBDs by RUT compared with T0901317. Corepressor peptide NCoR ID2 was partially displaced from LXRβ LBD but not LXRα LBD by RUT compared with T0901317.

**RUT inhibited some inflammatory factors expressions**

RUT is known to be anti-inflammatory. Several inflammatory markers in the serum were then examined in ApoE$^{-/-}$ mice treated with or without RUT for 8 weeks. As shown in *Supplementary Figure 3*, RUT inhibited TNF-α, MCP-1 and IL-8 expressions, but not IL-6, which indicated that RUT had an anti-inflammatory effect and might contribute to the good anti-atherosclerotic effect.

**Figure 1**

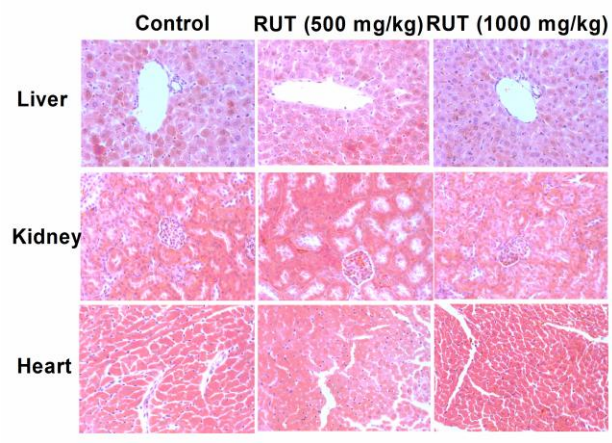
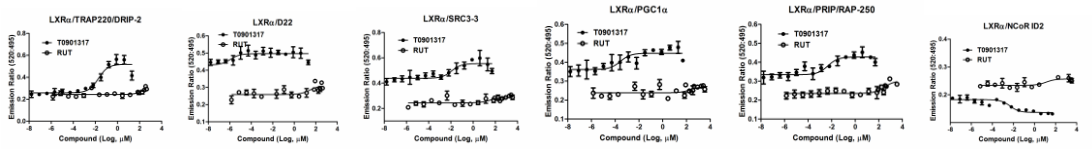



Figure 1. Safety evaluation of RUT in ICR mice

ICR mice were divided into 3 groups with four mice each. They were untreated or orally treated with RUT at 0, 500, or 1000 mg/kg in single-dose. Seven days later, blood samples were taken for liver and kidney function examination. Animal organs were taken as well for histological examination using H&E staining (400×). RUT treatment didn't cause morphology change in liver, heart and kidney tissues of the ICR mice.

## Figure 2

**A**




**B**

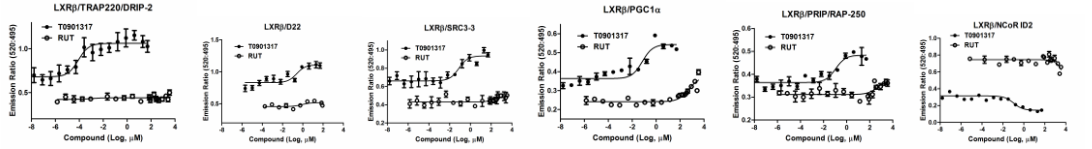



Figure 2. TR-FRET assay.

(A-B) TR-FRET assay was used to examine corepressor peptide displacement from or coactivator recruitment to human LXRα (A) or LXRβ (B) LBD in response to T0901317 or RUT. The data were calculated as the ratio of 520 nm/495 nm. Figures are representative of at least two independent experiments.

**Figure 3**

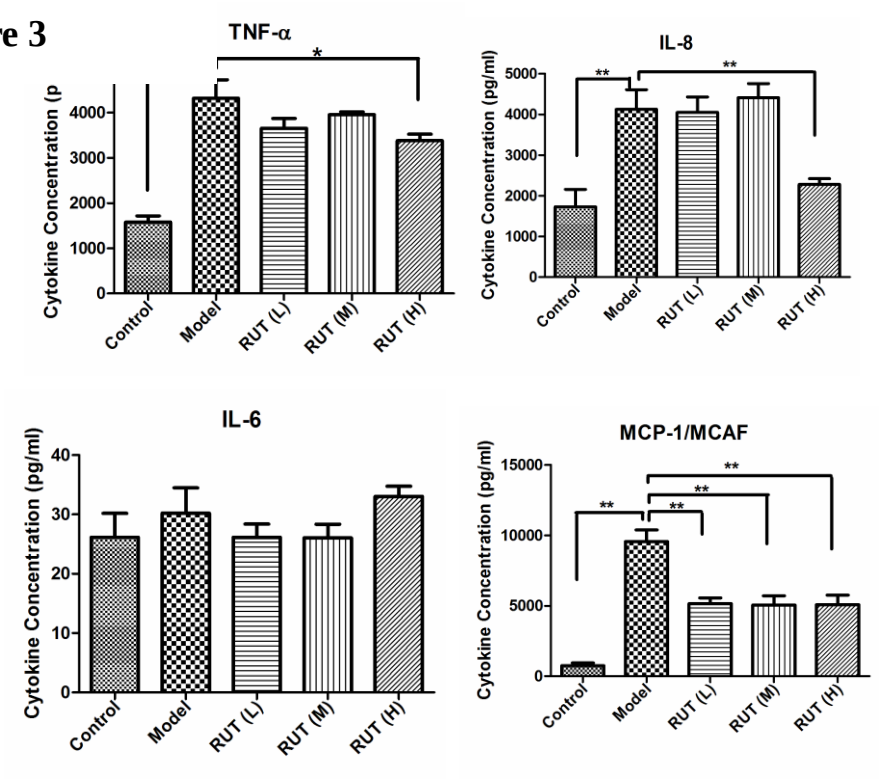



Figure 3. RUT inhibited TNF-α, MCP-1 and IL-8 expressions. Plasma in ApoE$^{-/-}$ mice treated with or without RUT for 8 weeks was collected as in the method in the original article. Inflammatory markers including TNF-α, MCP-1, IL-8 and IL-6 in plasma were examined as described in the methods. n=12 per group. $^{**}P<0.01$, $^{*}P<0.05$.

Table 1. Effect of RUT on liver and kidney functions in ICR mice with or without RUT treatment.

**Table 1.** Effect of RUT on liver and kidney functions of the subgroup of mice with or without RUT treatment in ICR mice.

| | n | AST (U/L) | ALT (U/L) | BUN (mM/L) | Cre (μM/L) |
|---|---|---|---|---|---|
| Control group | 4 | 75.33 ±3.30 | 23.25 ±2.28 | 5.88 ±0.58 | 47.43 ±12.56 |
| RUT group (500 mg/kg) | 4 | 91.67 ±16.50 | 28.50 ±7.76 | 6.00 ±0.62 | 43.62 ±7.76 |
| RUT group (1000 mg/kg) | 4 | 102.75 ±11.28 | 27.25 ±5.72 | 6.45 ±0.47 | 39.22 ±3.69 |

**Table 2** Effect of RUT on liver functions of the subgroup of mice with or without RUT treatment in ApoE$^{-/-}$ mice.

| | n | AST (U/L) | ALT (U/L) |
|---|---|---|---|
| Control group | 6 | 98.50±5.72 | 34.75±2.86 |
| Model group | 6 | 105.67±9.57 | 32.75±5.40 |
| RUT group (20 mg/kg) | 6 | 89.67±6.60 | 32.00±9.80 |