**Supplementary File**

1. **Collection of biological samples**

At the end of the experiment, an oral glucose tolerance test was carried out for all groups. After performing the glucose tolerance test, animals in all studied groups were exposed to overnight fasting and then were anesthetized to collect blood samples retro-orbital. Blood samples were centrifuged at 3000×g for 10 min in order to obtain serum samples which were used to determine serum glucose, insulin, urea, and creatinine levels. Later, animals were sacrificed through cervical dislocation and these organs were isolated in aliquots (muscle, pancreas, and kidney) tissues. Muscle and kidney tissues were isolated washed and divided into 3 aliquots; the first aliquot was used for DNA isolation for the assessment of mitochondria DNA copy number (mtDNA-CN), and the second was used for total RNA isolation for the assessment of gene expression, and the third aliquot was homogenized in phosphate-buffered saline PBS (0.1 M, pH 7.4) in ratio1:9. The homogenates were centrifuged at 10000×g for 10 min at 4 °C. The obtained supernatants were stored in aliquots for subsequent determinations of total protein level by the Lowery method and the protein levels of insulin receptor substrate-1 and -2 (IRS1 and IRS2), AMP-activated protein kinase (AMPK), the mammalian target of rapamycin at Ser 2448 (mTOR), the wingless-Type MMTV Integration Site Family, Member 3A (WNT3a), the inactive form of Glycogen synthase kinase-3β at Ser9 (GSK-3β), β-catenin, and Forkhead Box O1 (FOXO1). Also, the gene expression of kidney injury molecule-1 (Kim-1) and lipocalin-2 at the mRNA level (as markers of the renal damage) were assessed. Pancreas and muscle tissues were used for histopathological analyses.

1. **Biochemical and Molecular Biology Assays** 
   1. **Oral blood glucose tolerance test** **(OGTT)**:

After 4 weeks of treatment, animals were exposed to overnight fasting followed by collecting blood droplets from the tail vein directly onto the test strip (baseline), then a glucose solution was administered by oral gavage at a dose of 2.5 g/kg. After glucose administration, blood was collected at different time intervals (30, 60, 90, and 120 min) and the glucose level was determined using Glucometer (ACCU CHEK Active, Roche Co.). The **area under the curve (AUC)** was calculated for **blood glucose levels** during the OGTT according to the following equation:

**AUC=0.25× (Fasting value) +0.5× (30 min. value) +0.75× (30 min. value) +0.5× (120 min. value)**

* 1. **Gene expression analysis using quantitative real-time reverse transcriptase-polymerase chain reaction (qRT-PCR):**

The quantitative analyses of IRS1, IRS2, AMPK, mTOR, WNT3a, GSK-3β, β-catenin, and FOXO1 genes expression at mRNA level in muscle and kidney tissues, and Kim-1 and lipocalin-2 in kidney tissue were performed using qRT-PCR. The total RNA was extracted from the studied tissue using RNeasy Mini Kit (Qiagen, Germany) according to the manufacturer's instructions. The reverse transcription of the extracted RNA was done using MiScript II RT Kit (Qiagen, Germany) according to the manufacturer’s instructions. The obtained cDNA was then amplified and detected using specific primers for IRS1, IRS2, AMPK, mTOR. WNT3a, GSK-3β, β-catenin, FOXO1, Kim-1, and lipocalin-2 **(supplementary table)** by qRT-PCR assay using Rotor-Gene SYBR Green PCR Kit (Qiagen, Germany). Rotor-Gene Q-Pure Detection version 2.1.0 (build 9) (Qiagen, Valencia, CA, USA) was used to determine the threshold cycle (Ct), which is the point where the instrument first detects fluorescence above background noise. For each gene, the expression was calculated relative to 18SrRNA as a reference gene using the formula: 2-ΔΔCt.