شبكة المعلومات الجامعية

التوثيق الإلكتروني والميكروفيلم

# بسم الله الرحمن الرحيم

HANAA ALY

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# جامعة عين شمس

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# قسم

نقسم بالله العظيم أن المادة التي تم توثيقها وتسجيلها
علي هذه الأقراص المدمجة قد أعدت دون أية تغيرات

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تحفظ هذه الأقراص المدمجة بعيدا عن الغبار

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# Comparative Study of Native or Nano Quercetin on Epigenetic modification and Nephropathy Biomarkers post Challenges in Diabetic Hamsters

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# ABSTRACT

Diabetic nephropathy (DN) refers to the deterioration of kidney function and is one of the major public health problems, in spite of medical care developing. This disease is multifactorial and their current treatment strategies are only associated with symptomatic relief rather than curbing their progression. Phytochemicals have been consistently proposed as alternative therapy in modern medicine, but their efficacy is somewhat limited by rapid metabolism, insufficient permeability across membranes and decreased its bioavailability and stability in tissues. Fortunately, current advances in nanotechnology present opportunities to overcome such limitations in delivering active phytochemicals candidates.

The main goal of this study was to examine the possible regulatory effects of quercetin nanoparticles (QUNPs) in compare with native quercetin either with or without metformin on DN through different biological, epigenetic, molecular and biochemical measurements in addition of the histopathological changes in kidney tissues sections in DN hamsters. The first phase of this study used high resolution transmission electron microscope (HR-TEM) image to characterize QUNPs and the results revealed that average size of quercetin was in the nano-scale. The biological trial showed that DN hamsters consumed native or nano quercetin with or without metformin caused significant enhancement in nutritional parameters; change in body weight, feed intake, feed efficiency ratio, feed conversion ratio and relative weight of kidney (***P<0.05***) as compared to DN untreated group. QUNPs plus metformin treated group was the most effective by virtue of their small size and characteristics, followed by group consumed native quercetin with metformin. Diabetic and nephropathy biomarkers showed a significant improvement in all treated groups as well as increase expression of insulin receptor substrate -1 (IRS-1) and glucose transporter -4 (GLUT-4) genes. Our results illustrated that the effect of QUNPs plus metformin was the most effective in IRS-1 and GLUT-4 gene expression by 618.18% and 253.33%, respectively that correlated with inhibition of histone deacetylase activity (HDACs) by37.52% compared to DN untreated group which in turn improved diabetic and nephropathy biomarkers. Results of gene expression were confirmed by immunohistochemical analysis. Furthermore, antioxidant effects followed the same direction and were apparent through significantly increment in superoxide dismutase and glutathione peroxidase activities. Levels of metabolic dysfunction, inflammation and apoptosis also reflect the treatments on DN. The levels of inflammatory biomarkers decreased in all treated groups, while QUNPs with metformin was the most effective of all tested treatments, where the level of interleukin-6 and tumor necrosis factor-α was decreased by 47.37% 83.75%, respectively compared to DN untreated group. These results were confirmed by histochemical examinations in kidney tissues. Interestingly, all tested treatments significantly exhibit renal improvement; however, QUNPs with metformin was the most effective.

## LIST OF ABBREVIATIONS

| | |
|---|---|
| 4-AAP | 4-aminoantipyrine |

| | |
|---|---|
| A/G ratio | Albumin/globulins ratio |
| AChE | Acetylcholine esterase |
| ACR | Albumin: creatinine ratio |
| AGEs | Advanced glycation end products |
| AIDS | Acquired immunodeficiency syndrome |
| AIN-93 M | American Institute of Nutrition-93 for maintenance |
| AKT | Protein kinase B |
| ALEs | Advanced lipoxidation end products |
| AMP | Adenosine monophosphate |
| AMPK | Adenosine monophosphate activated protein kinase |
| AP-1 | Activator protin-1 |
| aPKC | Atypical protein kinase C |
| AR | Aldose reductase |
| ARIs | Aldose reductase inhibitors |
| ATP | Adenosine triphosphate |
| BCG | Bromocresol green |
| BMP | Bone-morphogenic protein |
| BSA | Bovin Serum Albumin |
| cDNA | Complementary DNA |
| CFTR | Cystic fibrosis transmembrane conductance regulator |
| CID | Chemical Industries Development |
| 3CLpro | 3-chymotrypsin-like protease |
| COVID-19 | Corona virus disease -2019 |
| COX | Cyclooxygenase |
| cPKC | Conventional protein kinase C |
| Ct | Critical threshold |
| DAG | Diacylglycerol |
| DHBS | 3,5-Dichloro-2-hydroxybenzene sulfonic acid |
| DKD | Diabetic kidney diseases |
| DM | Diabetes mellitus |
| DN | Diabetic nephropathy |
| DNA | Deoxyribonuclic acid |
| DPP 4 | Dipeptidyl peptidase 4 |
| EC | Endoplasmic cell |
| ECM | Extracellular matrix |
| EDTA | Ethylene diamine tetra acetic acid |

| | |
|---|---|
| Egr1 | Early growth response 1 |
| ELISA | Enzyme-linked immunosorbent assay |
| EMT | Epithelial-to- mesenchymal transition |
| eNOS | Endothelial nitric oxide synthase |
| ER | Endoplasmic reticulum |
| ERK | Extracellular signal-regulated kinases |
| ESRD | End-stage renal disease |
| FCR | Feed conversion ratio |
| FER | Feed efficiency ratio |
| FFA | Free fatty acids |
| G-6-Pase | Glucose-6-phosphatase |
| GBM | Glomerular basement membrane |
| GDM | Gestational diabetes mellitus |
| GFR | Glomerular filtration rate |
| GLcNAc | N-acetylglucosamine |
| GLP-1 | Glucagon-like peptide 1 |
| GLUT-4 | Glucose transporter 4 |
| GO | Glyoxal |
| GPx | Glutathione peroxidase enzyme |
| GR | Glutathione reductase |
| GSH | Reduced glutathione |
| GSSG | Oxidized Glutathione |
| $H_2O_2$ | Hydrogen peroxide |
| HAT | Histone acetyl transferase |
| Hb | Hemoglobin |
| HbA1c | Glycated hemoglobin |
| HDAC | Histone deacetylase |
| HF-HFr | High fat-High fructose |
| HFD | High- fat diet |
| HIV | Human immunodeficiency viruses |
| HOMA-IR | Homeostasis model assessment |
| HR-TEM | High Resolution-transmission Electron Microscope |
| HRP | Horseradish peroxidase |
| ICAM-1 | intercellular adhesion molecule-1 |
| IL-6 | Interleukin-6 |
| iNOS | Inducible nitric oxide synthase |
| INS-QT-LCNPs | Insulin-quercetin-loaded liquid crystalline nanoparticles |

| | |
|---|---|
| IR | Insulin receptor |
| IRS-1 | Insulin receptor substrate - 1 |
| LADA | Latent autoimmune diabetes of adulthood |
| LSD | Least significant differance |
| MAPK | Mitogen-activated protein kinase |
| MCP-1 | Monocyte chemoattractant protein-1 |
| MDA | Malondialdehyde |
| MGO | Methylglyoxal |
| MODY | Maturity- onset diabetes of the young |
| MRNA | Messenger ribonucleic acid |
| mTOR | Mammalian target of rapamycin |
| NaClO | Sodium hypochlorite |
| $NAD^+$ | Nicotinamide adenine dinucleotide |
| $NADP^+$ | Nicotinamide adenine dinucleotide phosphate |
| NADPH | Reduced nicotinamide adenine dinucleotide phosphate |
| NBT | Nitroblue tetrazolium |
| NDM | Neonatal diabetes mellitus |
| NEDA | N-(1-naphthyl)- ethylenediamine |
| NF-κB | Nuclear factors kappa B |
| NO | Nitric oxide |
| NOS3 | Nitric oxide synthase3 |
| NOX | NADPH oxidase |
| nPKC | Novel protein kinase C |
| NPs | Nanoparticles |
| $O_2$- | Superoxide anion |
| OD | Optical denisty |
| 8-OHdG | 8- hydroxydeoxyguanosine |
| PAI-1 | Plasminogen activator inhibitor 1 |
| PBMCs | Peripheral blood mononuclear cells |
| PBS | Phosphate buffer saline |
| PCR | Polymerase chain reaction |
| Pdx1 | Pancreatic and duodenal homeobox1 |
| PEPCK | Phosphoenolpyruvate carboxykinase |
| PFF | protein free filtrate |
| PI3K | Phosphatidylinositol 3-kinase |
| PKC | Protein kinase C |
| PLpro | papain-like protease |
| PMS | Phenazine methosulphate |

| | |
|---|---|
| PPARγ | Peroxisome proliferator-activated receptor gamma |
| PTP1B | protein tyrosine phosphatase 1B |
| QUNPs | Quercetin nanoparticles |
| RAGEs | Receptor for advanced glycation end products |
| RBCs | Red blood cells |
| RNA | Ribonuclic acid |
| ROS | Reactive oxygen species |
| rpm | Round per minute |
| RT-PCR | Reserve transcription-polymerase chain reaction |
| SARS-CoV-2 | Severe acute respiratory syndrome coronavirus -2 |
| SD | Standard deviation |
| SDH | Sorbitol dehydrogenase |
| SERCA | Sarco (endo) plasmic reticulum $Ca^{2+}$-ATPase |
| SGLT 2 | Sodium-glucose co-transporter 2 |
| SIRTs | Sirtuins |
| SOD | Superoxide dismutase enzyme |
| SPSS | Statistical Package for Social Science |
| STAT3 | Signal transducer and activator of transcription 3 |
| STZ | Streptozotocin |
| T1DM | Type 1 diabetes mellitus |
| T2DM | Type 2 diabetes mellitus |
| TBA | Thiobarbituric acid |
| TCA | Trichloroacetic acid |
| TEM | Transmission electron microscope |
| TGF-β | Transforming growth factor β |
| $T^m$ | Melting temperature |
| TMB | Tetra Methyl Benzidine |
| TNF-α | Tumor necrosis factor-α |
| TRX | Thioredoxin |
| TXNIP | Thioredoxin-interacting protein |
| UAE | Urine albumin excretion |
| UCC | Urinary creatinine concentration |
| UDP | Uridine diphosphate |
| UV | Ultraviolet |
| VEGF | Vascular endothelial growth factors |
| WHO | World Health Organization |

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