Gold nanoparticles: A potential Therapeutic Target for Diabetic Nephropathy through Regulation of miR-192, miR-21, autophagy, apoptosis and fibrosis

Laila Ahmed Eissa, Salma. M. Eraky, Samar. M. Al Tantawy
Department of Biochemistry, Faculty of Pharmacy, Mansoura University, Mansoura 35516, Egypt +20-50-2247496

6TH Heart in Diabetes Conference

Introduction

Diabetic nephropathy (DN) is a global epidemic that eventually causes end-stage renal failure, with few therapeutic interventions. Several studies reported that gold nanoparticles (AuNPs) have a potent antidiabetic effect. Sodium-glucose cotransporter2 (SGLT2) inhibitors like dapagliflozin (DAPA) showed a prominent Reno protective effect in DN.

Background

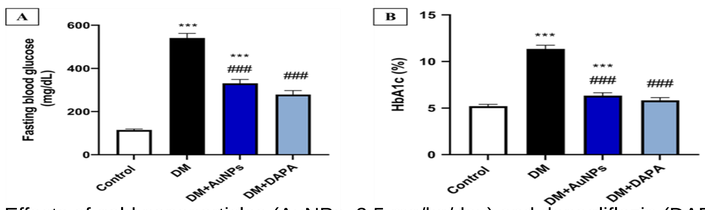
DN pathogenesis is complicated and involves the alteration of intracellular metabolism associated with hyperglycemia, which leads to hemodynamic and metabolic degradations, resulting in renal fibrosis, inflammation, oxidative stress, ultimately leading to renal failure. Beclin-1 is one of the first effectors of mammalian autophagy that has been implicated in DN. The microtubule-associated protein 1A/1B-light chain 3 protein (LC3) is a hallmark of autophagy that contributes to the fusion, maturation, and elongation of the autophagosome-lysosome . MiRNAs (miRs) are critical epigenetic regulators of gene expression, in addition to providing novel insights to interpret the molecular pathways linked to multiple diseases, such as DN. Numerous trials have revealed miR-192 contribution to DN's fibrogenesis process caused by transforming growth factor-beta1 (TGF-β1) MiR-21 is one of the most crucial miRs that result in renal fibrosis. Recent experimental research has reported that miR-21 inhibitors resulted in significant enhancement of the kidneys' functional in animal models. Consequently, miR-21 could be a promising therapeutic target for DN. Dapagliflozin (DAPA) is a highly selective inhibitor of SGLT2. It is evident that DAPA had a protective effect against DN

Method

AuNPs were synthesized using a modified sodium citrate approach. Forty male Sprague Dawley rats were used with a weight ranging between 180 to 250 g. They were maintained in standard temperature conditions, about 20-25◦C, with 12-hour light/12-hour dark regular cycles, and had free water as well as food access for one week. , the induction of diabetes was done by intraperitoneally injecting 55 mg/kg of freshly prepared STZ. Rats were categorized into four groups: Group 1 (control), Group 2 (diabetic group), Group 3 (AuNPs): diabetic rats were treated with 20 nm AuNPs (2.5 mg/kg/day) for seven weeks. Group 4 (DAPA group): diabetic rats administrated DAPA (2 mg/kg/day) for seven weeks. We collect urine to measure albumin and creatinine concentration by special colorimetric kits. Blood samples were used for the preparation of serum and plasma for measuring blood glucose levels, createnine, catalase (CAT) and malodialdehyde (MDA). Kidney tissues were used for the miR and real-time PCR analysis for apoptotic and autophagic markers by using Qiagen special kit.

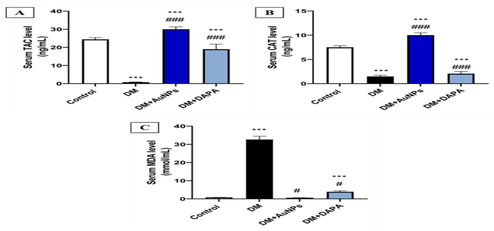
Results

- **AuNPs and DAPA effect on the levels of blood glucose and HbA1c:**



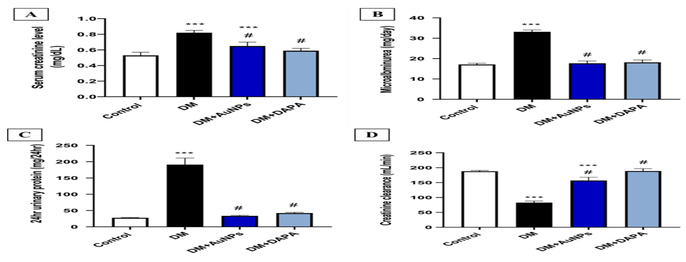
Effects of gold nanoparticles (AuNPs, 2.5 mg/kg/day) and dapagliflozin (DAPA, 2 mg/kg/day) on blood glucose level (A) and HbA1c (Glycated haemoglobin) (B) in a model of type 1 diabetes mellitus (DM) induced in rats by a single injection of 55mg/kg streptozotocin. Values are presented as Mean ± SEM. Number of animals in each group = 8.

- **AuNPs and DAPA effect on antioxidant markers (TAC, CAT, and MDA)**:



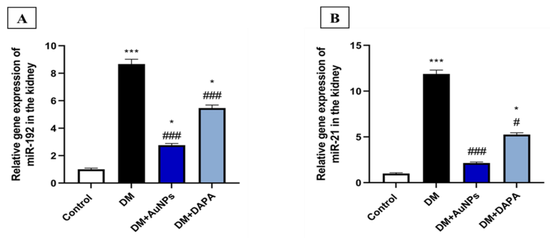
Effects of gold nanoparticles (AuNPs, 2.5 mg/kg/day) and dapagliflozin (DAPA, 2 mg/kg/day) on serum total antioxidant capacity (TAC) (A), catalase (CAT) (B) and malondialdehyde (MDA) (C) levels in a model of type 1 diabetes mellitus (DM) induced in rats by a single injection of 55mg/kg streptozotocin.

- **AuNPs and DAPA effect on renal functions**



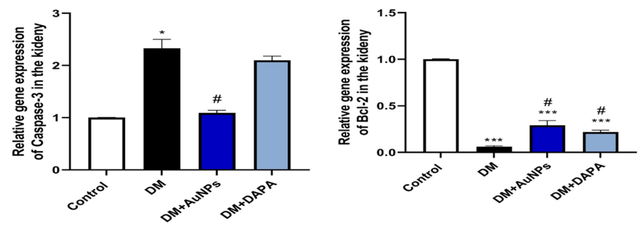
Effects of gold nanoparticles (AuNPs, 2.5 mg/kg/day) and dapagliflozin (DAPA, 2 mg/kg/day) on serum creatinine levels (A), microalbuminuria (B), 24hr urinary protein (C), and creatinine clearance (D) in a model of type 1 diabetes mellitus (DM) induced in rats by a single injection of 55mg/kg streptozotocin.

- **Effect of AuNPs and DAPA on miR-192 and miR-21**



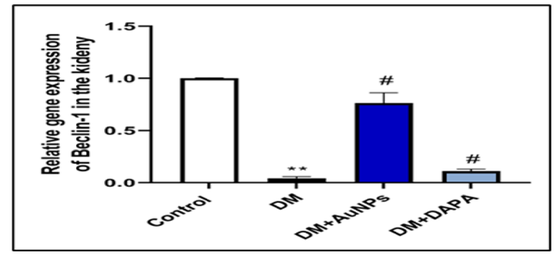
Effects of gold nanoparticles (AuNPs, 2.5 mg/kg/day) and dapagliflozin (DAPA, 2 mg/kg/day) on relative gene expression of microRNA-192 (miR-192) (A) and microRNA-21 (miR-21) (B) in a model of type 1 diabetes mellitus (DM) induced in rats by a single injection of 55mg/kg streptozotocin.

- **AuNPs and DAPA effect on the renal expression of apoptosis markers**



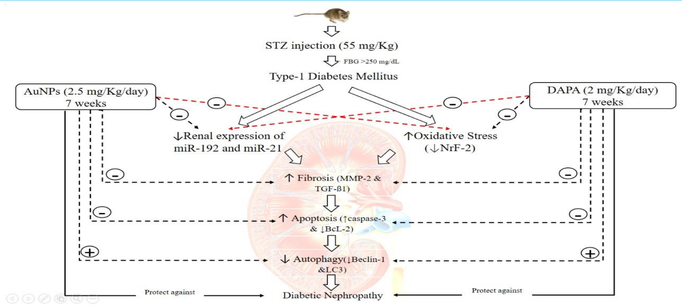
Effects of gold nanoparticles (AuNPs, 2.5 mg/kg/day) and dapagliflozin (DAPA, 2 mg/kg/day) on relative gene expression of Caspase-3 (A) and Bcl-2 (B) in a model of type 1 diabetes mellitus (DM) induced in rats by a single injection of 55mg/kg streptozotocin. Values are presented as Mean ± SEM. Number of animals in each group = 8.

- **AuNPs and DAPA effect on the renal expression of autophagic markers**



Effects of gold nanoparticles (AuNPs, 2.5 mg/kg/day) and dapagliflozin (DAPA, 2 mg/kg/day) on relative gene expression of Beclin-1 in a model of type 1 diabetes mellitus (DM) induced in rats by a single injection of 55mg/kg streptozotocin. Values are presented as Mean ± SEM. Number of animals in each group = 8.

Graphical Abstract



Conclusion

This study's findings illustrated a potential protective AuNPs and DAPA efficiency on DN. AuNPs were superior to DAPA in inhibiting miR-192 and miR-21. Moreover, AuNPs were superior to DAPA in increasing the expression of antiapoptotic markers (Bcl-2) and autophagic markers (Beclin-1 and LC-3). Indeed, AuNPs demonstrated a favorable impact on alleviating hyperglycemia adverse effects in renal tissue by affecting various molecular pathways, including their effect on downregulating miR-192 and miR-21, which are implicated in initiating most of the hyperglycemia-related adverse effects on the kidney.

References

1- Alomari, G., et al., Gold nanoparticles attenuate albuminuria by inhibiting podocyte injury in a rat model of diabetic nephropathy. Drug delivery and translational research, 2020. 10(1): p. 216-226.
2- Kawanami, D., et al., SGLT2 inhibitors as a therapeutic option for diabetic nephropathy. International journal of molecular sciences, 2017. 18(5): p. 1083
3- Oraby, M.A., et al., *Dapagliflozin attenuates early markers of diabetic nephropathy in fructose-streptozotocin-induced diabetes in rats.* Biomedicine & Pharmacotherapy, 2019. 109: p. 910-920.

.