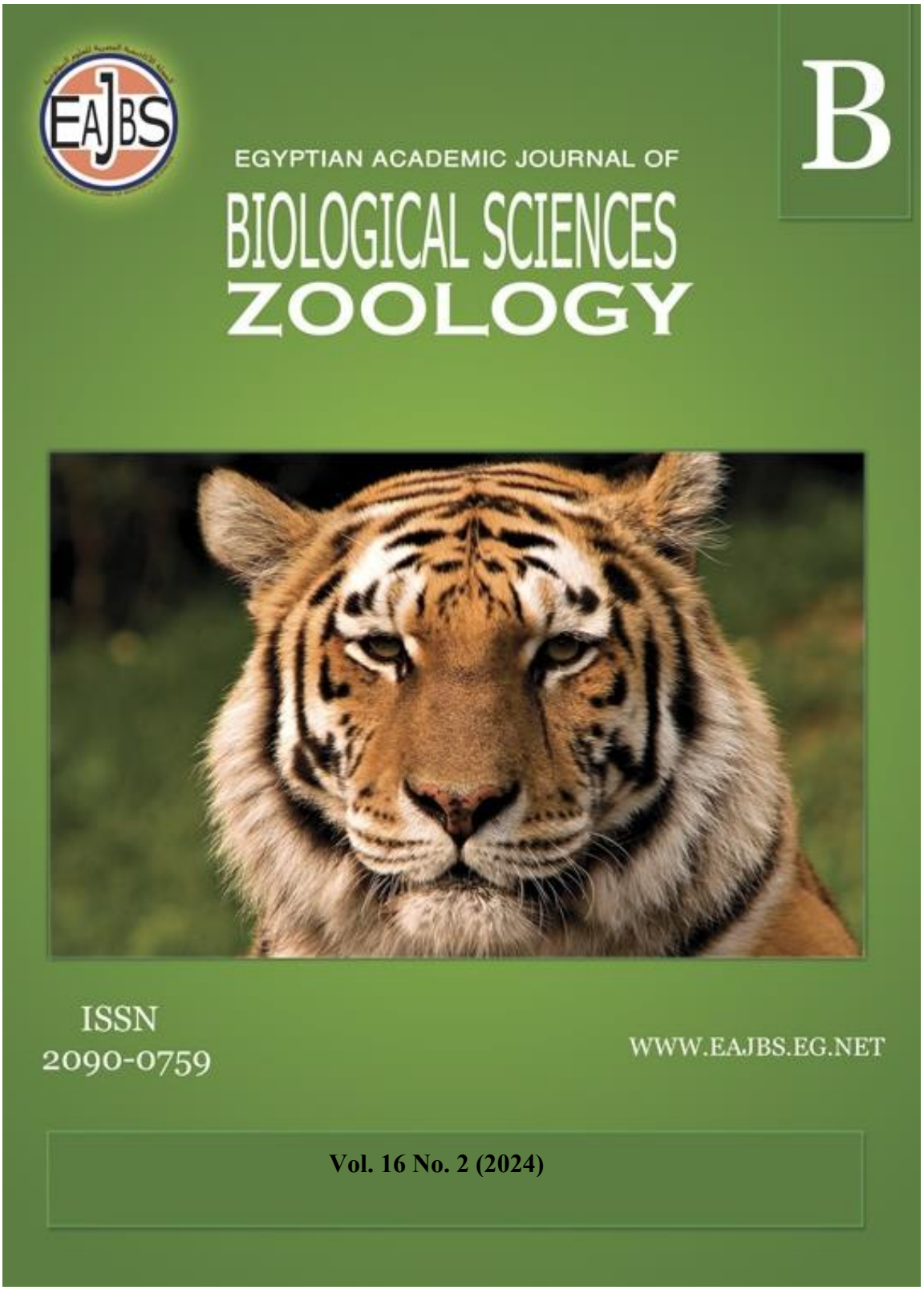

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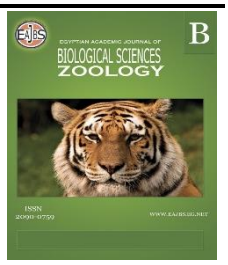

Metal and Metal Oxide Nanoparticles and Synergistic Therapy as A Novel Method for Managing Diabetic Nephropathy: A Brief Overview

Zainab M. Al Aamri[1*], Abdulkader M. Shaikh Omar[1,2,] and Salim M. El-Hamidy[1,2]
[1]Department of Biological Sciences, Faculty of Science, King Abdulaziz University, Jeddah, Saudi Arabia.
[2]Princess Rd. Najla Bint Saud Al-Saud Centre for Excellence Research in Biotechnology, King Abdulaziz University, Jeddah, Saudi Arabia.
*** E-mail** : zmosaedalaamri@stu.kau.edu.sa

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ABSTRACT

Diabetic nephropathy (DN) is another name for diabetic kidney disease (DKD). This is a prevalent issue among people with diabetes worldwide. This disease is a health condition affecting the renal glomeruli and causes diabetic nephropathy. Hyperglycemia is the most important contributing factor to the development of DN, where the blood vessels in the renal tissue may get damaged as a result of continuously elevated blood sugar levels, specifically the endothelial cells of the renal glomeruli, which leads to weak capillaries, affected glomerular filtration rate (GFR), the onset of albuminuria, and ultimately kidney damage. However, the reasons for this are unclear, making treatment hard and costly. It is correlated with an increased danger of reaching end-stage renal disease (ESRD). Recent research focuses on finding new therapeutic targets using nanomedicines to develop new therapeutic solutions for diabetes patients. Metal nanoparticle oxides such as Zn, Au and Ag Oxides, in addition to synergistic therapy using NP combinations such as Curcumin-Magnesium Oxide **(**Cur-MgO NPs), Metformin with Hollow mesoporous silica and cerium oxide nanocomposite particles (MET–HMSN–CeO2 NPs), selenium-metformin nanoparticles (Se-NPs- MET), Chitosan-selenium-metformin nanoparticles (Ch-Se-MEF NPs), Chitosan-ZnO (ZnO-CS NPs) and Silver-chitosan-ascorbic acid (Ag-NCs) show promise in the treatment of DN, as they can prevent its progression. This article presents a comprehensive overview of metallic nanoparticles and their associated oxides, highlighting their remarkable efficacy in the management of DN.

INTRODUCTION

Beta cells in the pancreas are specialized cells that create insulin in the body. If these cells are damaged or injured, it will cause diabetes mellitus (DM). This damage leads to hormonal imbalance and causes problems with insulin production. As a result, blood sugar levels become unregulated, which can have an impact on different organs in the body, including the reproductive system, kidneys, and liver (Lovic *et al*., 2020). DM is a medical condition characterized by high blood glucose concentrations. Diabetes that persists for an extended period can lead to macrovascular and microvascular

complications if left uncontrolled (Thipsawat, 2021). Most of these complications occur in the body due to increased oxidative stress, directly affecting the reduction of anti-oxidants within the body's cells (Zharkikh *et al*., 2020; Alkazazz and Taher, 2021; Thipsawat, 2021).

The World Health Organization has set new goals in 2022 to achieve by 2030 to reduce the risk of diabetes, including diagnosing 80% of cases and controlling blood sugar and blood pressure in people diagnosed with diabetes (WHO, 2022). The prevalence of DM is expected to increase globally, with the number of affected individuals estimated to reach 578 million by 2030 and 700 million by 2045, up from 463 million in 2021 (Zharkikh *et al*., 2020). A total of 537 million individuals worldwide are living with diabetes, with 73 million living in the Middle East and North Africa region. The number of these people is expected to increase to 135.7 million by the year 2045 (International Diabetes Federation, 2021).

Diabetes is becoming more prevalent worldwide, especially during the past two decades, including in the Kingdom of Saudi Arabia (KSA). The total rate of diabetes especially Type 2 in the KSA reached 16.4% out of a total population of 258,283 million people (Jarrar *et al*., 2023).

The Kingdom of Saudi Arabia's health sector (KSA) has been putting in immense effort to provide the best healthcare facilities for patients, especially those with ESRD. With the increasing number of patients in need of kidney transplantation, the government of Saudi Arabia has been educating people about the importance of organ donation after death. According to the Annual Report of the Saudi Centre for Organ Transplantation, kidney transplant operations have steadily increased, with 549 operations in 2020 alone and 14,190 operations between 1979 and 2020. This puts a significant burden on both the Saudi government and the families of patients. As the number of cases continues to rise every year, scientific research is focusing on finding new therapeutics to prevent diabetes complications. This will help to reduce the global burden on governments, especially healthcare sectors worldwide (Transplantation, 2024).

End-stage renal disease is mostly caused by diabetic nephropathy (Selby and Taal, 2020). DN refers to a chronic condition that develops over several years (Rossing and Flyvbjerg, 2024). DN is a severe condition that can have serious consequences (Liu *et al*., 2022). It is a prevalent complication in individuals diagnosed with type 2 DM, impacting approximately one-third of all patients with DM. Diabetic kidney disease (DKD) is another term that refers to DN; it is caused by the dysfunction of the kidneys due to DM. Additionally, studies have shown that DN has a significant relationship with depression among diabetics (Dagar *et al*., 2021). This condition, if left uncontrolled, will progress to ESRD (Thipsawat, 2021).

Researchers have found new ways to provide early treatments for DN using nanomedicine to create powerful therapeutics from nanoparticles. Because of their tiny dimensions, they can effortlessly infiltrate the kidney and deliver medication directly to the damaged region. This targeted approach has shown promising results in the early stages of treating DN. Nanoparticles can potentially revolutionize the treatment of this condition and potentially decelerate or even reverse its progression (Liu *et al*., 2022).

Recently, nanoparticles such as cerium, zinc oxide, magnesium, and selenium NPs products have been used to treat diabetics (Ashrafizadeh *et al*., 2020).

This article aims to present a comprehensive analysis of the significance of nanoparticles mainly metal and metal oxide and their possible application as an acceptable therapy for DN.

Diabetic Nephropathy (DN):

DN is a dangerous medical disorder that impacts individuals globally. It can lead to multiple systemic disorders and loss of kidney function. It is necessary to take early

detection and immediate action to stop renal function from further declining and to delay complications (Mizdrak *et al*., 2022).

Over the past 40 years, renin-angiotensin-aldosterone system (RAAS) blockade and sodium-glucose transport protein 2 (SGLT2) inhibitors have improved patient outcomes by slowing DKD progression (Sawaf *et al*., 2022).

T2DM is responsible for 90% of diabetes cases worldwide. Therefore, most of the patients who develop DN have T2DM. The probability of developing DN decreases in patients with T2DM over 30 years after diagnosis. Several factors, such as the duration since the first diagnosis, glycaemic control, blood pressure, and genetic susceptibility, influence the progression of the disease (Saeedi *et al*., 2019).

Several clinical symptoms can indicate the onset of DN. These include high albumin excretion in the urine and a low glomerular filtration rate. The pre-diabetic condition can lead to persistent high blood sugar levels, resulting in a gradual decline in kidney function (Dagar *et al*., 2021).

Since the degree of diabetic retinopathy (DR) has been associated with glomerular damage, DR is a good predictor of DN. In contrast to people with diabetes but not DN, those with DN had a larger proportion of DR cases, based on a recent study conducted by (Cai *et al*., 2024). This implies that DN patients have a higher prevalence of DR than diabetics without DN (Q. Wang *et al*., 2024).

Treatment Goals:

To stop diabetes from progressing to DN, it must be under control. Treatment for this chronic condition includes education as an essential factor. Enhancing knowledge and skills and changing patients' behaviours are the primary objectives of diabetes education, in addition to changing lifestyle modifications such as losing weight, getting more exercise, cutting back on sodium in food, and giving up smoking and lipid-lowering). Glycemic management and cardiovascular (CV) risk reduction are primarily dependent on developing self-care practices, following treatment recommendations, and building psychological resilience (Hermis and Muhaibes, 2024). Like other vascular issues linked to diabetes, DN requires comprehensive treatment that includes lifestyle modifications and maintaining blood pressure, cholesterol, and blood sugar targets (Sarafidis *et al*., 2019).

Histopathology of the Kidney Tissues Affected by DN:

In diabetic glomeruli, extensive interactions take place between podocytes, endothelium, and the mesangium. The growth of immature blood vessel production is facilitated by angiogenesis, which is promoted by specific features presented by a subset of glomerular endothelial cells. Consequently, vascular leakage, glomerular barrier breakdown, and ultimately glomerulosclerosis are the outcomes of this process. All of these factors work together to advance the progression of DN. Furthermore, the progression of this medical condition is influenced by glomerular endothelial cells, podocytes, and immune cells including macrophages, T lymphocytes, B lymphocytes, and plasma cells. These scientific findings have helped identify potential therapeutic targets for controlling the development of this disease (Charles *et al*., 2018). Several histological changes occur in the kidneys in patients with chronic diabetes that are left uncontrolled, such as reduced or absent glomeruli, necrotic nucleus, tubular cytoplasmic vacuolation, intratubular blood congestion, and loss of glomerular lobulation. Recent research has confirmed that certain nano-treatments, such as ZnO NPs, prevent or improve these histological changes (Othman *et al*., 2020).

Oxidative Stress and Antioxidant Status:

Oxidative stress, which disrupts the balance of redox signalling and damages molecules, is caused by the imbalance between antioxidants and oxidants. Any disruption to this balance triggers a stress response, which is recognized as a stress (Sies, 2020).

There are essential markers commonly used to detect oxidative stress in the body,

such as nitrite/nitrate (nitric oxide; NO), lipid peroxidation (LPO), and glutathione (GSH). On the other hand, several enzymes are commonly used to detect anti-oxidant levels in the body, including superoxide dismutase (SOD), catalase (CAT), glutathione reductase (GR) and glutathione peroxidase (GPx) (Othman *et al*., 2020).

Endoplasmic Reticulum (ER) stress participates in the advancement and pathogenesis of DN. The failure of the endoplasmic reticulum has been correlated with the progression of renal disease, especially in DN. When not effectively managed, this type of stress response leads to increased expression of proteins; thus, the cell produces too many proteins and the endoplasmic reticulum cannot handle the increased demand for folding, which leads to an accumulation of stress known as ER stress. Stress causes a build-up of misfolded proteins, which eventually leads to renal damage and cell death. However, ER stress inhibitors can help improve DN by reducing the expression of proteins such as RTN1A, which is often overexpressed in diabetic kidney cells, avoiding cell death and the development of kidney damage due to diabetes (Kumar and Maity, 2021).

Nanotechnology and Nanobiology:

The field of nanotechnology is a promising 21st-century technology. It is advancing quickly, with a particular focus on the manufacturing of nanoparticles ranging from one to 100 nanometres in size as mentioned in The National Nanotechnology Initiative (NNI) *(Abbasi et al*., 2020). Nanotechnology has offered innovative solutions to address this worldwide issue. Diabetes management is now an advanced and extremely promising field, offering specialized nanomedicine for more effective drug delivery and improved glucose management. It offers significant advancements in the treatment of Type 2 diabetes. Artificial pancreas systems that incorporate nanosensors and nanocarriers have the potential to completely revolutionize diabetes management by enhancing patient outcomes and treatment quality. Nanotechnology has recently attracted a lot of attention for its ability to explore and develop interventions related to diabetic complications, such as DN (Mandal *et al*., 2023).

Nanobiology, a branch of nanotechnology, is primarily concerned with the study of biological interactions at the nanoscale. It explores the complex interrelationships between chemistry, physics, and biology within a system and how the small size of these materials makes them superior to others in the medical field (Agrawal *et al*., 2021).

Nanoparticles:

Nanoparticles are tiny particles with distinctive chemical, physical, and biological properties that enhance their utility as therapeutic and diagnostic tools. Reducing materials to the nanoscale alters their characteristics and allows them to interact in a highly accurate way with the biomolecules of cells. It is also possible to precisely and carefully engineer their features. Because of their size, structure, and formulation, nanoparticles have special properties such as increased electrochemical reactivity, enhanced thermal conductivity, and a relatively large surface area compared to their volume. They have shown promising potential in terms of drug administration due to their accuracy in targeting combined with enhanced pharmacokinetic qualities (Silvera Batista *et al*., 2015; Wahba *et al*., 2016; Murali *et al*., 2017; Baig *et al*., 2021; Liu *et al*., 2022).

The latest discovery has shown that nanoparticles can be used to treat diabetes. They exhibit anti-diabetic activity and can reduce the damage caused by diabetes to the kidneys, pancreas, liver, and other body organs (Alkazazz and Taher, 2021).

When compared to conventional therapeutic techniques, the use of nanoparticles as nanocarriers has revolutionized the delivery of oral hypoglycaemic medicines, offering enhanced efficiency and improved control of blood glucose levels (Mandal *et al*., 2023).

Nanomedicine:

Nanomedicine refers to the use of nanotechnology in the field of medicine, and the materials used in this field must have at least one dimension within the nanoscale range.

Nanomedicines have numerous advantages compared to traditional pharmaceuticals, including increased solubility and stability, decreased toxicity, targeted accumulation at the site of disease, regulated release, and incorporation of diagnostic and treatment. These factors together contribute to an enhanced therapeutic result (Lv and Zhu, 2024).

Uncontrolled diabetes, whether type 1 or type 2, can progress to DN, renal cirrhosis, and ultimately reach the end stage of renal disease. Therefore, recent research is focused on developing new therapeutic methods, such as nanomedicines to prevent the progression of diabetes to DN, thus reducing the need for dialysis or kidney transplantation (Alkazazz and Taher, 2021).

Over the past few decades, nanomedicines have been created, designed, and scaled up at the macromolecular, and cellular scales (Mitchell *et al*., 2021). The use of nanopharmaceutical substances in nanomedicine has led to significant progress in disease detection, diagnosis, prevention, and management (Farjadian *et al*., 2019).

Nanoparticles & Kidney Targeting:

Nanoparticles (NPs) have various uses in the field of medicine due to their ability to penetrate biological barriers and improve the delivery of medications. With the widespread applications, novel strategies have emerged to treat renal diseases. Drugs, nucleic acids, and other distinct biophysical properties can create precisely regulated nanocarriers targeted to the kidneys. When these nanoparticles interact with kidney cells over extended periods of time, they can improve the absorption and retention of the particles in different cell types (Paul *et al*., 2023). Nanoparticles are extensively used in biomedicine because of their capability to interact with biological parts such as proteins, nucleic acids, receptors, and membranes (Yu *et al*., 2020). However, Metal nanoparticles are less hazardous than mineral salts and have a multidimensional influence on the organism (Ashrafizadeh *et al*., 2020).

Metal Nanoparticles (MNPs):

Metal nanoparticles have anti-diabetic activity via reducing oxidative stress, increasing anti-oxidant, sensitivity to insulin, and glucose utilization. Silver nanoparticles (Ag NPs) and zinc oxide nanoparticles (ZnO NPs) are highly effective in reducing the severity of complications associated with diabetes and lowering insulin resistance (Alkazazz and Taher, 2021). In the last few years, there has been a growing interest in the use of metal and metal oxide nanoparticles due to their possible application in various sectors including electronics, biological sensors, photocatalysis, biomedicine and the agricultural sector (Mishra *et al*., 2017).

Zinc Oxide Nanoparticles (ZnO NPs):

ZnO NPs Properties:

Zinc oxide nanoparticles (ZnO NPs) are distinguished from bulk ZnO by their small particle size (between 1 and 100 nm). They have an extremely high surface area in proportion to their volume, which leads to enhanced reactivity. Because of the many advantages of ZnO NPs, such as biological compatibility, low toxicity, and affordability, these particles have gained a lot of attention and are currently used on a large scale in many fields (Kalpana & Devi Rajeswari, 2018) (Asif *et al*., 2023).

Uses and Applications of ZnO NPs:

ZnO NPs are used in the food production and agricultural industries as food supplements (Youn and Choi, 2022). A recent study proved that ZnO nanoparticles (NPs) had greater effectiveness as supplements for fish growth and development than non-nano zinc oxide (Mahboub *et al*., 2020).

ZnO NPs are frequently employed in biomedical therapies, such as cancer therapy, due to their special chemical and physical features that aid in zinc delivery (Yang *et al*., 2020). Because of their unique optical and chemical properties, ZnO NPs are interesting candidates for various applications in the biological and biomedical fields. These include

bioimaging, drug delivery, biosensors, food packaging, optical and electrical fields, and biological and biomedical uses such as antimicrobial, antibacterial, antifungal, antioxidant, antidiabetic, anticancer, antiviral, and wound healing. Additionally, they show promise in combating certain drug-resistant microbes, providing an alternative to antibiotics. They also have other activities such as dietary supplements, food additives, and semiconductor materials. ZnO NPs have UV filter properties, making them widely used as sunscreen (Mishra *et al*., 2017; Kalpana and Devi Rajeswari, 2018; Asif *et al*., 2023; Fujihara and Nishimoto, 2024).

Any imbalance in zinc levels is thought to be one of the factors causing diabetes because zinc is essential for the synthesis and release of the hormone insulin (Chabosseau & Rutter, 2016; Olechnowicz *et al*., 2018).

Zinc is an essential mineral that both men and women should consume in daily amounts of 11mg and 8mg, respectively. This amount is generally considered sufficient for meeting the body's nutritional requirements for zinc (Youn and Choi, 2022).

Zinc deficiency commonly appears in children and adults with nutritional issues, as well as individuals with illnesses such as alcohol use, kidney problems, digestive tract abnormalities, inflammatory conditions, and cancer. It is classified as generally safe, meaning it is safe to use in accordance with recommended dosages (Youn and Choi, 2022).

Many changes occur after the induction of diabetes, such as a significant loss of weight, a decrease in zinc content in pancreatic and liver cells, high blood sugar levels, a significant presence of elevated oxidative stress, specifically lipid peroxidation (LPO) and nitric oxide (NO), and a decrease in insulin in the bloodstream. These changes result from a malfunction in the expression of pancreatic and hepatic RNA genes and the destruction of beta cells (Othman *et al*., 2020). All of these changes can lead to significant injury to renal tissue and the advancement of diabetes into DN if left untreated in the early stages (P. Paul *et al*., 2023).

Several studies have proven that ZnO NPs have a great future as a promising therapy for diabetes. They help to reduce DM complications, including DN. Zinc oxide nanoparticles (ZnO NPs) have the ability to reverse the alterations in tissues of the pancreas that result from diabetes (Wahba *et al*., 2016). They have an anti-diabetic activity effect as a treatment for DN by improving the natural balance of all indicators, such as restoring the balance between oxidants and antioxidants within the cells through microRNA modification and improving serum insulin, glucose tolerance and pancreatic β-cell function (Othman *et al*., 2020; Alkazazz & Taher, 2021).

Zinc Oxide NPs treatment enhanced renal function, prevented degenerative alterations, inhibited kidney fibrosis, inflammation, oxidative stress, abnormal blood vessel formation (angiogenesis) and delayed podocyte damage in rats with DN. ZnO NPs act as a successful strategy for slowing down the progression of DN (Alomari *et al*., 2021; Abd El-Khalik *et al*., 2022).

ZnO NP's Role in Gene Expression:

In a diabetic nephropathy model in rats, Zinc Oxide nanoparticle treatment largely reversed the anatomical and ultrastructural changes in the kidney by significantly increasing the mRNA expression of podocyte protein molecules, specifically nephrin and podocin. This repair process successfully restored the structural integrity of the glomerular filtration barrier, resulting in a renal structure that was hardly distinguishable from normal. One possible explanation for the beneficial effects of ZnO-NPs is their ability to activate autophagy by blocking the mTOR signalling pathway. This led to a decrease in p62 mRNA expression and an increase in beclin-1 and LC3 mRNA expression. Additionally, ZnO-NPs have the ability to prevent or inhibit programmed cell death (as evidenced by the reduction in p53 immune expression), as well as anti-inflammatory and antioxidant

effects (supported by the suppression of blood levels of HIF-1α, tissue nuclear factor kappa beta (NF-κB), and serum levels of COX-2 enzyme activity). These findings suggest a promising strategy for DN therapy (Abd El-Baset *et al*., 2023).

Zinc oxide nanoparticles (ZnONPs) exhibit superior anti-diabetic effects over other metal nanoparticles due to their enhanced cellular penetration, hepatic glycogenesis-induced stimulation of glycolysis, and elevated insulin levels. Together, all of these factors increase the GLUT-4 and INS genes' activity in skeletal muscles and other peripheral tissues, including adipose tissues. GLUT-4 is the main transporter of glucose, and its activity is stimulated by INS (a gene responsible for producing the hormone insulin inside the pancreatic beta cells**)**. ZnONPs have synergistic effects by increasing the activity and expression of an enzyme called glucokinase as well as the concentrations of insulin receptor A (IRA) and the glucose transporter protein (GLUT-2) (Bayrami *et al*., 2018). Zinc carriers are required for the mechanism of insulin production from pancreatic beta cells, enhancing insulin signalling and maintaining insulin structure (Siddiqui *et al*., 2020).

Modes of Action of ZnO NPs as Anti-Diabetic Agents:

Zinc oxide nanoparticles (NPs) have various physiological effects on the body's cells, including lowering blood sugar levels and preserving blood sugar balance. They achieve this by reducing oxidative stress in pancreatic cells and increasing insulin secretion. ZnO NPs also improve glucose tolerance, lower blood sugar levels, and regulate the lipid profile in the bloodstream. Additionally, they enhance insulin signals and sensitivity in muscle cells. Zinc oxide also helps to enhance insulin secretion and sensitivity, increase gluconeogenesis in the liver, and improve glucose uptake and storage in adipose tissue. All these changes contribute to regulating glucose levels and maintaining balance within the body (Jha *et al*., 2023), thereby reducing serious diabetes complications such as DN.

A recent study highlighted the potential benefits of zinc oxide nanoparticles as a therapy for rats with type 2 diabetes. The study reported a significant increase in blood glucose levels and elevated insulin and pancreatic interleukin-10 (IL-10) levels. ZnO NPs work to reduce pancreatic injury by enhancing the pancreas's antioxidant defense system and total antioxidant capacity (TAC), which have been compromised by oxidative stress (Ali, 2020).

Modes of Action of ZnO NPs as Antioxidant Agents:

Zinc is an important mineral for healthy growth and development, immune system function, and antioxidant protection (Skrajnowska and Bobrowska-Korczak, 2019). ZnO NPs, which had a spherical shape and a size of 39.2 nm, were used at 40 and 80 ppm as food supplements. They greatly reduced the amount of malondialdehyde (MDA) and improved the activity of antioxidant enzymes, including catalase and superoxide dismutase (SOD) (Hafez *et al*., 2020).

Modes of Action of ZnO NPs as Anti-inflammatory Agents:

Anti-inflammatory mechanisms of ZnO NPs involve inhibiting iNOS enzyme expression, pro-inflammatory cytokine release, myeloperoxidase, NF-κβ pathway, and mast cell breakdown (Agarwal and Shanmugam, 2020; Jan *et al*., 2021).

Gold Nanoparticles (AuNPs):

Gold nanoparticles efficiently lower high blood sugar levels in diabetic animal models, and no negative effects have been identified, according to a recent study conducted by Alomari *et al*. (2020). Results of the study showed that the use of AuNPs at a dose of 50 nm helped ameliorate podocyte injury, inhibit renal oxidative stress, improve renal function, and decrease extracellular matrix protein accumulation in experimental models of DN.

AuNPs and DAPA contribute to the protection against diabetic nephropathy (DN) in rats by influencing miR-192 and miR-21, as well as their downstream pathways, which

involve fibrosis, apoptosis, autophagy, and oxidative stress (Al-Tantawy *et al*., 2023).

High glucose (HG) concentrations induce glycol-oxidative stress in kidney cells, specifically proximal renal tubular epithelial cells (HK-2), and AuNPs are promising as prospective therapeutics to minimize the danger of DN developing (Y. Yu *et al*., 2021).

AuNPs have been found to have various health benefits. they have several actions, including inhibiting the activity of transforming growth factor-β, preventing glycation, reducing angiogenesis, lowering blood sugar levels, reducing inflammation, and acting as an antioxidant. Gold NPs treatment efficiently disrupts numerous pathogenesis variables in the rat model of DM and its associated consequences (Alomari *et al*., 2021).

The histological and immunohistochemical results suggest that AuNPs can decrease glomerular sclerosis and renal fibrosis caused by STZ, as well as protect against oxidative stress and its side effects in high blood sugar level situations. They can be applied as a preventive method to reduce DN and as an essential tool in the treatment of issues caused by high blood sugar levels (hyperglycemia) (Manna *et al*., 2019).

Silver Nanoparticles (Ag NPs):

Numerous studies have explored the possible advantages and uses of silver nanoparticles (Ag NPs) in the prevention and treatment of complications associated with diabetes. A recent study by Wang *et al*. (2023) demonstrated that mice administered silver nanoparticles experienced notable reductions in both blood glucose and urea levels, indicating that silver nanoparticles may play a role in diabetes management. The unique characteristics of the silver nanoparticles, which encompass nephroprotective potentials and antimicrobial, anti-inflammatory, and antioxidant properties, render them promising candidates for future therapeutic interventions by targeting multiple factors of the pathogenic process of DM (Paul *et al*., 2024).

The eco-friendly and biocompatible characteristics of Ag NPs highlight their potential as treatment agents for oxidative stress health-related conditions such as bacterial infections and DN (Prem *et al*., 2024).

Synergistic Therapy Using NPs:

With the goal of reducing dosage-related side effects and enhancing therapeutic efficacy in various illnesses, including diabetes and its complications, combination therapy, also known as synergistic treatment, holds great promise (Chinnaiyan *et al*., 2019). This technique, utilizing nanoparticles (NPs), shows great promise for the successful therapy of DN. The complex pathogenic mechanisms of DN include many pathway abnormalities that limit the efficacy of a singular therapeutic technique (Tong *et al*., 2020). Hybrid nanocarriers with homogeneous architectures can enhance their importance for biomedical applications. In these applications, nanomaterials work together to create novel medication delivery systems that target intracellular locations while minimizing the risk of toxicity. This collaboration creates a fundamental interaction at the (bio/nano) interface (Nanda and Yi, 2024).

1.Curcumin-Magnesium Oxide Nanoparticles (Cur-MgO NPs Conjugate):

Magnesium (Mg) has anti-diabetic properties by minimizing diabetes-related problems through raised levels of antioxidant enzymes, enhanced glucose consumption and improved insulin sensitivity (Ashrafizadeh et al., 2020). Magnesium can have an important effect on the medical management of insulin resistance (Alkazazz & Taher, 2021). In the latest research conducted by Shehata *et al*. (2020), the possible use of the combination of curcumin-magnesium oxide nanoparticles in the treatment of the diabetic rat model was highlighted. The findings of the study showed the efficacy of Cur-MgO NPs Conjugate for DM in rats that had been given STZ-induced diabetes for forty-five days at a dose of 10 mg/kg BW/day.

2. MET–HMSN–CeO2 NPs:

The anti-diabetic drug metformin (MET) is taken in combination with "Hollow

mesoporous silica nanocomposite particles" (HMSN) that contain traces of cerium oxide nanoparticles (CeO2 NPs). These particles have a high drug-loading capacity and exhibit renoprotective properties. The nanoparticles can reduce the symptoms of DN by mitigating oxidative stress, inhibiting cellular apoptosis, and providing kidney protection. Treatment with the MET–HMSN–CeO2 combinations significantly improves DN. This combination therapy shows promise as a treatment option for DN (Tong *et al*., 2020).

3. Selenium and Metformin Nanoparticles (Se-NPs-MET):

Combined selenium and metformin nanoparticles (Se-NPs-MET) as a promising therapeutic for diabetic complications and insulin resistance. The study by Abdulmalek and Balbaa (2019) showed that Se-NPs with MET had a significant effect on the values of anti-diabetic biomarkers compared to Se-NPs or MET alone.

4. Chitosan- selenium nanoparticles- Metformin:

Through the reduction of stress caused by oxidation and maintenance of glucose homeostasis, the combination treatment of chitosan-selenium nanoparticles and metformin, or Ch-SeNPs/MEF co-therapy, shows promise in maintaining renal health. This refers to a possible treatment strategy for DMT2-related nephropathy (Khater *et al*., 2021).

5. Zinc Oxide-Chitosan (ZnO-CS NPs):

The chitosan-ZnO composite membrane significantly speeds up the healing of diabetic wounds through improved pro-angiogenic impacts, re-epithelialization, and extracellular matrix (ECM) modification, when used as an adjuvant therapy alongside insulin injections Hussein *et al*., 2022). Zinc oxide-chitosan nanoparticles (ZnO-CS NPs) have been shown in a recent study to have protective effects against kidney damage in rats because of their antioxidant activity (Saad *et al*., 2023).

6. Silver/chitosan/ascorbic acid (Ag-NCs):

Ag-NCs nanocomposite was used on diabetic mice induced by STZ. The study demonstrated a decrease in blood levels of glucose, nitric oxide (NO), malondialdehyde (MDA), creatinine, urea, and uric acid. At the same time, there was a general increase in insulin, catalase (CAT), and superoxide dismutase (SOD) activities, as well as an increase in the quantity of glutathione (GSH). The histopathological examination showed a noticeable enhancement in renal architecture (Abu El Qassem Mahmoud *et al*., 2021).

Nanoparticles Are Useful but Need More Study:

There are a number of nanoparticles that can positively impact glucose regulation, such as Titanium dioxide nanoparticles (TiO2 NPs). On the other hand, multiple studies have provided evidence that these nanoparticles might have harmful effects and may accumulate in vital organs of the body, such as the liver, pancreas, kidneys, and lungs. This may result in inflammation, oxidative stress, and, eventually, tissue damage (Hu *et al*., 2020). TiO2 NPs cause hepatic cell damage characterized by fatty degeneration even though titanium (Ti) did not accumulate in the rat liver. This damage is not reflected in any changes in the blood markers that indicate liver injury or function. Regardless of their anti-diabetic properties, more studies are needed to determine appropriate therapeutic doses and avoid unknown risks *(*Chen *et al*., 2020).

Conclusion

Nanoparticles (NPs), particularly metal/metal oxide nanoparticles, have the potential to prevent kidney tissue damage in patients with DM and DN. This is achieved by increasing antioxidant levels in the body and inhibiting oxidative stress activity, exerting inflammatory and antioxidant effects by suppressing serum COX-2 enzyme activity and boosting the expression of GLUT-4 and INS genes. As a result, ZnO, Au, Ag, CeO2, and synergistic therapy using NP combinations can help prevent the progression of diabetes to nephropathy. Ag NPs and ZnO NPs are highly effective in reducing the severity of diabetes-related issues and improving insulin resistance. Metal nanoparticles

can directly target the affected area in the kidney. This targeted approach has shown promise in the early treatment of DN, which may slow or reverse DN progression.

Declarations:

Ethical Approval: The animal experiments were approved by the ethical committee of the faculty of pharmacy, KAU University, Jeddah, Saudi Arabia. (P140-2022).

Competing interests: The authors have declared that no competing interests exist.

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