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Enhanced Therapeutic Effect Of Selenium Nanoparticles On The Treatment Of Induced Diabetes In Rats

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Abstract
This study evaluated the therapeutic impacts of the selenium-insulin nanocarrier in comparison with free, uncoated insulin. The insulin was encapsulated with selenium nanoparticles using an eco-friendly chemical synthesis method. The prepared nanocarrier was characterized by UV-visible spectroscopy within the wavelength range of 208.50–407.50 nm, as well as by (XRD) analysis, which revealed that the nanocarrier exhibited a polycrystalline thin film structure. Furthermore, (FESEM) analysis showed that the particles had a spherical morphology with nanoscale diameters ranging between 40–110 nm. The experimental animals were divided into four groups: the first as healthy, non-diabetic control; the second diabetic, untreated rats; the third diabetic rats treated with the selenium-insulin nanocarrier; and the fourth diabetic rats treated with free, uncoated insulin. Renal function markers were evaluated, revealing that the urea level in the diabetic control group reached (314.0a ± 13.64), while the healthy control group recorded (50.48b ± 1.21). The urea level in the diabetic group treated with free insulin was (128.8b ± 56.76), whereas the group treated with the selenium-insulin nanocarrier exhibited a level of (58.43b ± 10.89). Additionally, the creatinine level in the healthy control group was (0.26a ± 0.02), while the diabetic control group showed a level of (3.52a ± 2.27). Creatinine in the diabetic group treated with the selenium-insulin nanocarrier was (0.33a ± 0.04), while that in the free insulin-treated group was (1.15a ± 0.81). The results indicated that the untreated diabetic group significantly increased in urea and creatinine levels, which reflected kidney damage. In contrast, the group receiving the selenium-insulin nanocarrier showed a notable decrease in these markers when compared to the group treated with free insulin, suggesting a protective effect on kidney function. These findings suggest that the selenium-insulin nanocarrier is important in protecting the kidneys from diabetes-induced damage, enhancing hepatic function, improving insulin bioavailability, and providing protection against insulin degradation.
Keywords: *Enhanced therapeutic, Nanoparticle, Selenium, Treatment.*

INTRODUCTION

Diabetes is a lifelong, escalating metabolic disease marked by constantly elevated blood sugar. It arises because of a defect in the secretion and/or insulin function, or both [1]. Type 1 diabetes mellitus (T1DM) is an autoimmune condition in which the immune system mistakenly attacks and destroys the insulin-producing beta cells in the pancreas, causing insufficient insulin production. It may appear at any age, although it is most often identified in children, teens, and young adults. People with T1DM need lifelong insulin therapy to control their condition [2].

Type 2 diabetes mellitus (T2DM) was 90% of all diabetes cases, making it the most common form. It is characterized by the body's cells being unable to respond correctly to insulin. Insulin resistance, the body cells not responding as much to the insulin, makes it a different type compared to others. The pancreas could possibly produce inadequate insulin to supply the body, in the long run. Type 2 diabetes commonly comes with a connection to age, obesity, lack of exercise, and undesirable lifestyle habits such as poor nutrition [3,4]. According to the 2017 report by the International Diabetes Federation Atlas (IDFA), the rate of diabetes among adults is rising rapidly, and 451 million people are estimated to have diabetes all over the globe. By 2045, the number of people estimated to have diabetes could grow to 693 million. Close to half (49.7%) of the people with diabetes are estimated to stay undiagnosed. Additionally, 5 million diabetes-related deaths are estimated to occur globally among people aged 20–99 years [5].

As a result of insulin resistance, the metabolic problems of diabetes chiefly affect tissues such as the liver, muscle, and fat. Symptoms are a result of the severity of diabetes and the duration the condition has lasted. Hyperglycemia may cause symptoms of polyphagia, polydipsia, dysuria, weight loss, hunger, and visual disturbances, especially in children with complete insulin deficiency. Some diabetic patients,

particularly those with mild type 2 diabetes, are asymptomatic [6,7]. Insulin, a hormone which the pancreas produces controls blood sugar levels to treat diabetes. Diabetes impairs the body's capacity to efficiently utilize or create insulin, leading to a variety of short- and long-term complications. It is considered a common endocrine disorder in the world and is a significant public health concern, increasing morbidity, mortality, and financial burdens [8].Lately, different nanoparticles have been created to tackle diabetes and its connected issues, many research projects have emphasized the efficiency of nanotechnology in improving drug administration, upgrading glucose observation, and providing solutions to concerns associated with diabetes care, The potential of nanoparticles in diabetes treatment has been emphasized, demonstrating their superiority over conventional therapeutic approaches [9].Nanotechnology has proven to be a very promising field for the synthesis of nanostructures owing to their intriguing biological properties, thus being promising for therapeutic as well as diagnostic applications. Nanotechnology-based treatments are essential in the management and therapy of diabetes [10]. Presently, numerous nanoparticles are being utilized as alternative treatments because of their many biological functions, tackling diabetic issues and fighting inflammation, by raising the activity of glutathione peroxidase (GPx) and selenoproteins, selenium, a crucial antioxidant and anti-inflammatory trace element, assists in preventing reactive oxygen species (ROS) [11]. The biomedical use of selenium nanoparticles (Se-NPs) has shown their antioxidant characteristics [12]. Additionally, stabilizing substances like polysaccharides are used to increase the stability of selenium nanoparticles in solutions. These polysaccharides' hydroxyl groups enhance molecular activity and nucleation sites, thereby influencing The relationship between polysaccharides and selenium nanoparticles [13]. Interestingly, selenium reduces fasting serum insulin levels and insulin resistance index because of its insulin-mimetic effect. Furthermore, selenium nanoparticles were recently found to reduce the expression of MAPK, NF-κB, and TNF-α in rats [14].

MATERIALS AND METHODS

Selenium, nanoparticles were prepared and insulin (purity>98%) was used for coating. An eco-friendly biochemical approach was adopted to biocoating the selenium nanoparticles with insulin,10 mL insulin was mixed with 90 mL 2 mM Na_2SeO_3 solution to prepare the mixed solution. For the blank sample, 10 mL of distilled water was mixed with 90 mL of a 2 mM Na_2SiO_3 solution. The two flasks were shaken for 3 hrs in the dark to allow homogeneous mixing, The selenium nanoparticles formed were thereafter recovered and distilled (centrifuged). The dried SeNPs were kept at room temperature for subsequent analysis [15]. Selenium-insulin nanocarrier was well characterized using physiochemistry by different analytical techniques; to validate the surface plasmon resonance (SPR) properties of the nanoparticles, ultraviolet-visible (UV-Vis) spectroscopy was carried out at room temperature on a double-beam spectrophotometer (PD-303 UV). Crystallographic experiments were conducted using a Shimadzu XRD-6000 with Cu-Kα radiation (λ = 0.15418 nm) at 40 kV and 30 mA.

The Debye-Scherrer equation computed the average selenium-based formulation crystallite size. D is the crystallite diameter, k (0.94) the shape factor, λ the X-ray wavelength, β the full width at half maximum (FWHM), and θ the Bragg diffraction angle. Additionally, the morphology of the nanoparticles was tested by field emission scanning electron microscopy (FESEM) with Jeol JSM-6460 LV, enabling detailed observation of particle shape, surface structure, and distribution. Adult male albino rats, aged 3–4 months and 167–218 g, were reared in a closed cage facility at the Biotechnology Research Facility, Animal House of the University of Al-Nahrain. Rats were reared in laboratory-managed conditions at 22 ± 2°C and a 14-hour light: 10-hour dark photoperiod. We provided Pellet diet and ad libitum drinking water. Alloxan, dissolved at 150 mg/kg body weight, served to induce diabetes. The rats were then assigned to four groups of five animals per group, the first as the healthy, non-diabetic control, the second as a diabetic control, the third as diabetic rats with free insulin therapy, and the fourth as diabetic rats with the selenium-insulin nanocarrier. Blood was taken after 30 days of therapy by direct cardiac puncture while the animals were under anesthesia. Serum was separated and utilized for the analysis of the biochemical parameters: urea was assayed by [16], while creatinine was assayed by [17]. All the animals were dissected for the purpose of histological study. We removed the kidneys preserved them in 10% neutral buffered formalin [18].

Tissue segments of the kidneys were prepared for histology through standard histological procedures, involving dehydration in ethanol, clearing with xylene, and then embedded in hot paraffin wax. Thin sections of 5 μm were prepared by a microtome and stained with standard hematoxylin and eosin (H&E) using Harris's aqueous technique [19]. Histopathological analysis was made with a light microscope.

Statistical analysis:

The study used a one-way analysis of variance (ANOVA) for examining all data, and Duncan's multiple range to assess statistical differences between group means, with a 0.05 level of probability was statistically significant [20].

RESULTS AND DISCUSSION

Figure (1) illustrates the absorption spectrum obtained from the UV-Vis analysis of the selenium-insulin nanocarrier, showing ten distinct absorption peaks within the wavelength range of 208.50–407.50 nm. This reflects the complex chemical composition of the nanoparticles resulting from the encapsulation process, thereby confirming the successful formation of the nanocarrier. The outcomes observed in this study align closely with those previously documented by [21].

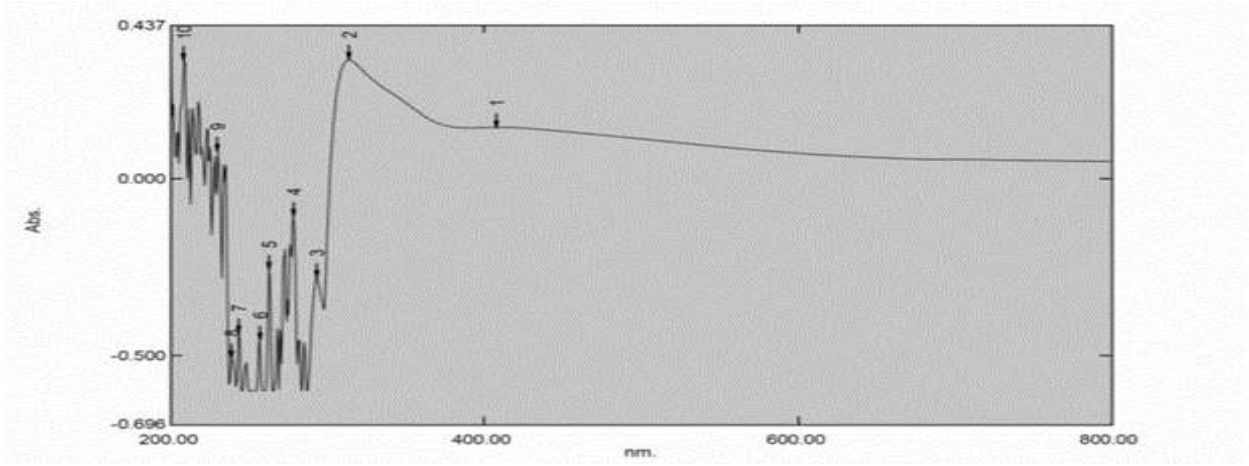

Figure (1): UV-Visible Spectral Analysis of the Selenium–Insulin Nanocarrier

The X-ray diffraction (XRD) pattern analysis of the selenium-insulin nanocarrier also revealed characteristic diffraction peaks. By analyzing these patterns and identifying the peak positions, distinct diffraction peaks were observed at the following crystallographic planes: (100), (101), (110), (102), (111), (200), and (201), as shown in Figure (2), which illustrates the polycrystalline thin film structure. These diffraction peaks were compared with the standard reference card (JCPDS No. 06-0362), and the results showed a good match with the international standard data, proving other's findings [22].

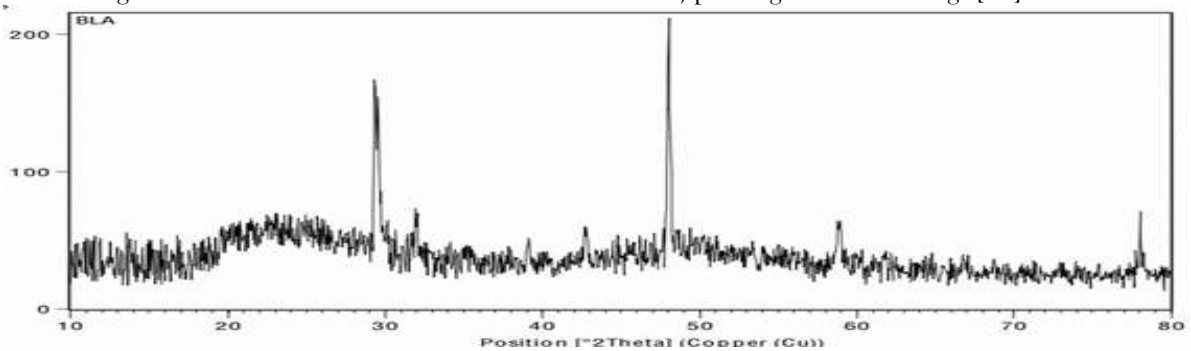

Figure (2): X-ray Diffraction (XRD) Analysis of the Selenium–Insulin Nanocarrier

The results also indicated that the particle size analysis of the selenium-insulin nanocarrier revealed spherical granules with nanoscale diameters ranging between 40–110 nm, distributed in a relatively uniform manner across different regions. In addition, the general surface distribution proved relatively smooth, which shows effective encapsulation of selenium with insulin at the nanoscale level. The results obtained in the present investigation are consistent with the findings reported by [23].

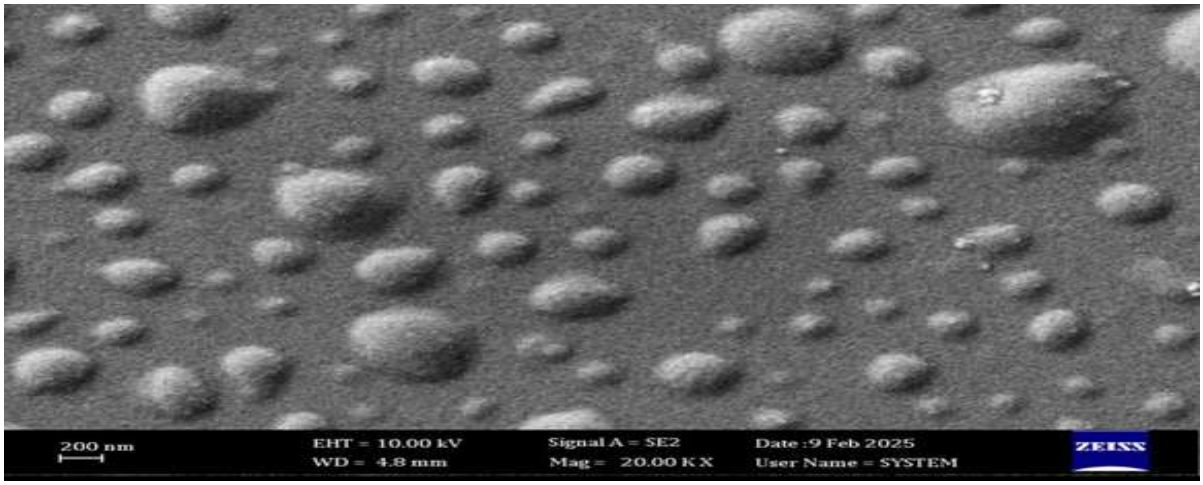

Figure (3): High-magnification FESEM image displaying the morphology of the selenium–insulin nanocarrier

Table (1) presents the serum urea and creatinine levels in diabetic and treated groups. The diabetic rats induced with alloxan exhibited a significant increase in urea levels, reaching 314.0 ± 13.64 a mg/dl, while the healthy control group showed considerably lower levels at 50.48 ± 1.21 b mg/dl. Administration of the selenium-insulin nanocarrier significantly dropped in urea levels in the sera (58.43 ± 10.89 b mg/dl) compared with the untreated diabetic group. Interestingly, the decrease in urea was higher when the nanocarrier of the selenium-insulin compound was used compared to the free insulin group (128.8 ± 56.76 b mg/dl). The result highlights that diabetes caused by alloxan disturbs kidney activity, causing extensive urea build-up in the blood. This agrees with earlier research [24], indicating that hyperglycemia arising because of beta-cell destruction inhibits glomerular filtration, hence the rise in urea concentration in the serum. Such dysfunction occurs, presumably, because of inadequate renal clearance and heightened urea production [25]. In addition, protein catabolism as an alternative energizing material is pushed by insulin lack, thus leading to excessive urea production [26]. Urease decrease after selenium-insulin nanocarrier therapy demonstrates better kidney functioning. Such findings are consistent with outcomes of earlier work [27], accommodating the prospect for selenium-containing nanocarriers to elevate insulin bioavailability at the renal level. Targeted delivery therapy could provide a protective effect versus diabetes-related nephropathy, specifically when insulin resistance or delivery inefficiency exists [28]. Selenium is also found to play a significant role through antioxidant activity, decreasing oxidative stress in the kidneys, a significant contributor to diabetic nephropathy and other renal diseases. By minimizing oxidative stress, selenium nanoparticles are found to maintain renal cells along with their functioning, thus normalizing the amount of urea [29]. The present work found a considerable rise in the level of the serum creatinine of diabetic rats prepared with alloxan, a level of (3.52 ± 2.27 a) mg/dl, as compared to the healthy non-diabetic control group, exhibiting a concentration of creatinine as (0.26 ± 0.02 a) mg/dl. Furthermore, the findings showed a notable decrease in serum creatinine levels in diabetic rats treated with the selenium-insulin nanocarrier (0.33 ± 0.04 a mg/dl) compared to the untreated diabetic control group. Furthermore, the concentration of the creatinine reduced notably when administering the selenium-insulin nanocarrier compared to the group of diabetic rats receiving free insulin, which indicated (1.15 ± 0.81 a) mg/dl. Those findings are consistent with the work carried out by [30]. This study also confirmed that the diabetes induction with alloxan had produced higher values of serum creatinine for the diabetic group compared with the healthy non-diabetic group, similar to the finding obtained by [31]. This elevation in creatinine levels can be attributed to the impaired renal filtration capacity in diabetic animals, resulting in the accumulation of nitrogenous waste and decreased nephron function, ultimately leading to elevated serum creatinine [32]. The encapsulation of selenium with insulin into nanoparticle-based carriers acts as a protective capsule, enhancing insulin delivery to cells, improving its absorption, and increasing its bioavailability [33]. Furthermore, selenium-loaded insulin improves insulin action by lowering blood glucose levels, thereby reducing stress on the kidneys and improving creatinine levels [34].

Table (1): Urea and Creatinine Levels in Diabetic and Treatment Groups

Experimental groups	Creatinine (mg/dl)	Urea (mg/dl)
Control	$0.26^{a} \pm 0.02$	$50.48^{b} \pm 1.21$
Diabetic control	$3.52^{a} \pm 2.27$	$314.0^{a} \pm 13.64$
Diabetes+Selenium	$0.33^{a} \pm 0.04$	$58.43^{b} \pm 10.89$
Diabetes+insulin	$1.15^{a} \pm 0.81$	$128.8^{b} \pm 56.76$

The histological study results, as shown in Figure (1), revealed a transverse section of the kidneys of healthy non-diabetic male rats. Numerous nephrons were observed, containing the Malpighian corpuscles with Bowman's capsule, proximal and distal renal tubules, and tubular epithelial cells, representing a normal histological kidney structure. In contrast, Figure (2) illustrates a transverse kidney section of male rats with alloxan-induced diabetes, showing histopathological alterations due to diabetes induction, such as congestion within the renal glomeruli, tubular necrosis, severe dilation of glomerular blood vessels, and inflammation compared to the non-diabetic relative to the non-diabetic control group, consistent with the observations noted in [35]. Figure (3) shows a transverse kidney section of diabetic rats treated with free insulin, where severe swelling and notable hypertrophy of tubular epithelial cells were observed, consistent with the study by [36]. Finally, Figure (4) demonstrates a transverse kidney section of diabetic rats treated with the selenium-insulin nanocarrier, revealing significant histological improvement compared to other groups. The glomerular diameter appeared near normal, with no marked increase in glomerular cellularity, no dilation of Bowman's capsule, and absence of congestion in blood vessels or renal tubules compared to the diabetic control group treated with free insulin. These results concur with findings by [37]. The adverse histopathological changes observed in the kidneys of diabetic rats are attributed to tubular shedding and renal tissue congestion in diabetic animals, with congestion and inflammatory cells resulting from oxidative stress [38]. Studies have shown that alloxan-induced diabetes in rats leads to renal lesions resembling human diabetic glomerulopathy, although not identical. Tubular damage, responsible for reabsorbing essential substances and excreting waste, includes tubular atrophy and dilation [39]. Similarly, alloxan-induced diabetes in mice causes glomerular changes that mimic human diabetic nephropathy, tubular injury, and interstitial fibrosis [40]. Selenium, as an essential micronutrient with antioxidant properties, plays a crucial role since diabetes induces increased oxidative stress, which damages renal tissues. Selenium nanoparticles can scavenge free radicals, thereby reduce oxidative stress and protecting kidney tissues from damage [41]. Additionally, selenium nanoparticles can modulate inflammatory pathways that are often overactivated in diabetic nephropathy. By reducing inflammation, these nanoparticles help preserve kidney structure, tissue integrity, and function [42].

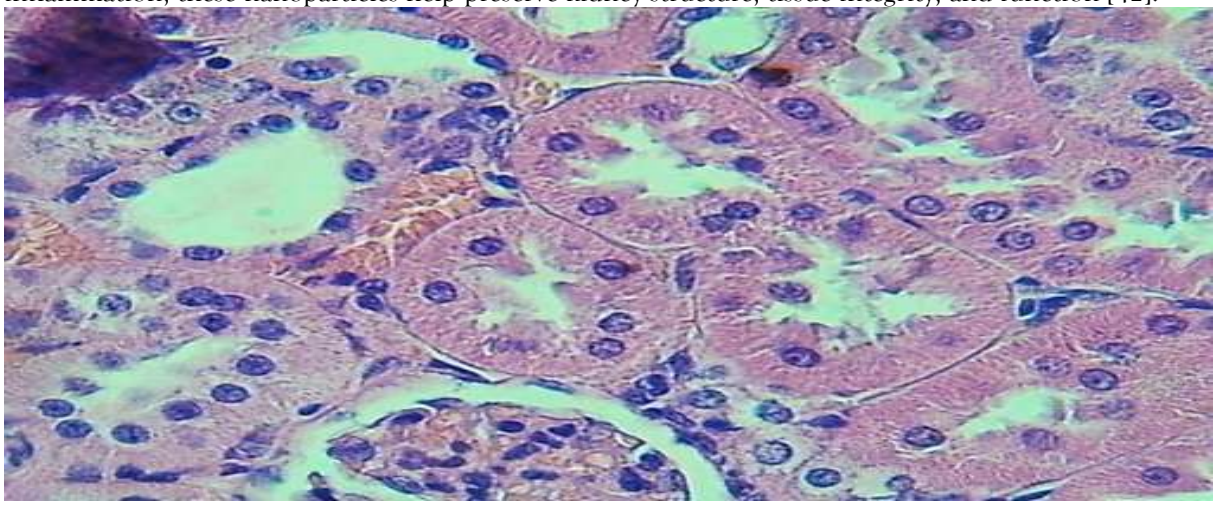

Figure (1): Transverse section of a healthy, non-diabetic rat kidney showing Bowman's capsule, glomerulus, and renal tubules (H&E stain) (X400).

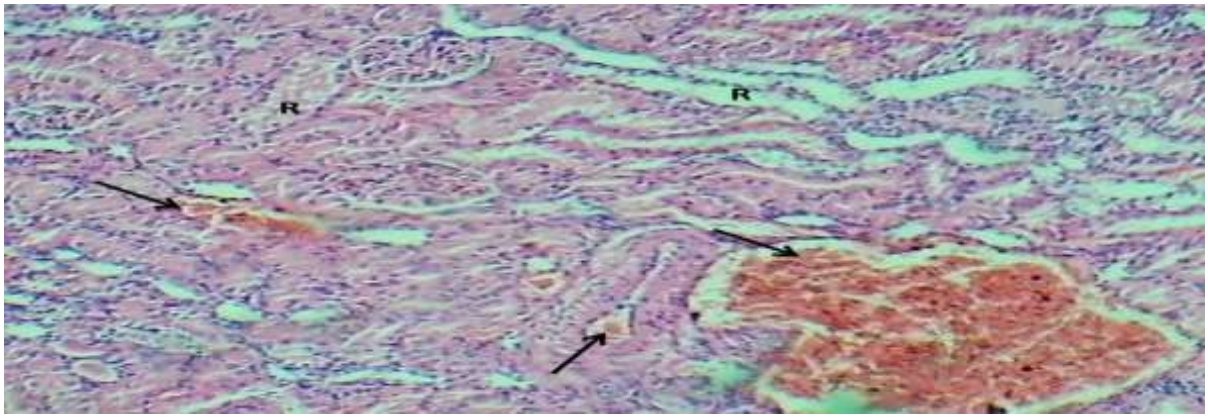

Figure (2): Cross-section of an untreated diabetic rat kidney showing shows moderate nephrosis that revealed vacular degeneration (R), with vascular dilation & congestion (Arrows). H&E.100x

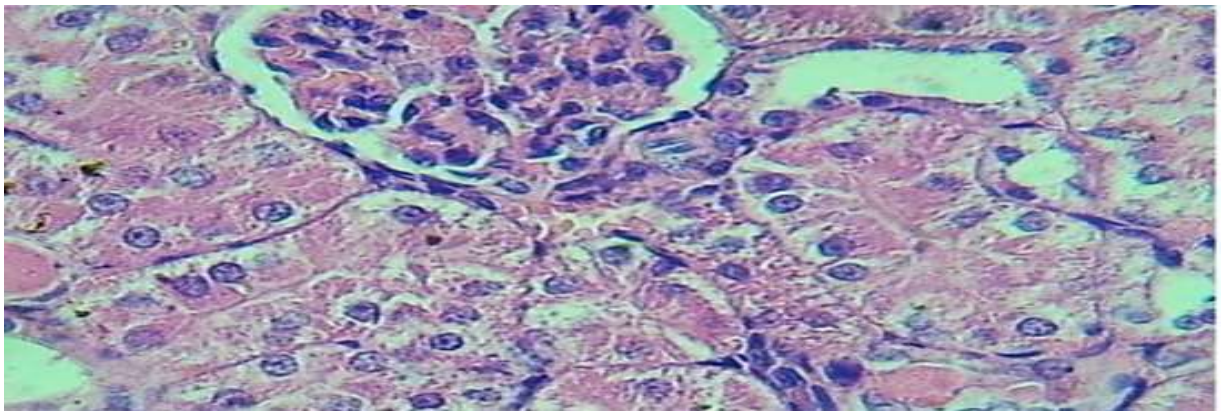

Figure (3): Cross-section of a diabetic rat kidney treated with free insulin showing severe swelling of the tubular epithelial cells with marked hypertrophy (H&E) (X400).

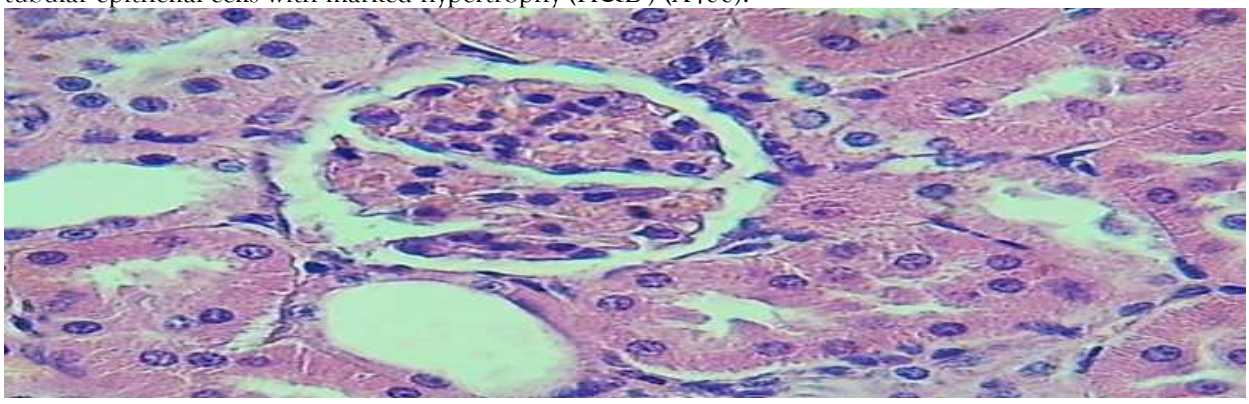

Figure (4): Cross-section of a diabetic rat kidney treated with the selenium-insulin nanocarrier showing tubular epithelial cells with improvement in the glomerulus (H&E) (X400).

CONCLUSIONS:

The results indicate that the use of an environmentally friendly nanoenhancer of insulin loaded onto selenium nanoparticles is an effective therapeutic strategy for reducing diabetic complications. This strategy demonstrated a significant improvement in physiological parameters, including decreased urea and creatinine levels compared to untreated animals and the free insulin-treated group, indicating improved kidney function. Histological examinations also revealed a significant improvement in kidney tissues in treated rats, with the disappearance of inflammatory and congestive changes. This is due to the improved antioxidant and anti-inflammatory properties of selenium nanoparticles, as well as their ability to enhance insulin effectiveness and its degradation within cells.

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