Pakistan J. Zool., vol. 58(4), pp 1715-1723, 2026 **DOI**: https://dx.doi.org/10.17582/journal.pjz/20241128151257

Assessment of Antidiabetic Activity of Ba Doped Zinc Oxide Nanoparticles in Swiss Webster Albino Mice (*Mus musculus*)

Muhammad Maqsood Ahmad Khan[1], Muhammad Khalil Ahmad Khan[1]*, Tehreem Tariq[2], Shoaib Siddique[3]*, Munazza Perveen[1], Muhammad Shahzad Ahmed Khan[4], Samina Tabassum[4], Muhammad Imran[1] and Allah Ditta[1]

[1]*Department of Zoology, University of Okara, Okara, Pakistan.*
[2]*Department of Physics and Astronomy Gallelio Galilei, University of Padova, Italy.*
[3]*Chemical and Materials Engineering, National Yunlin University of Science and Technology, Yunlin 640301, Taiwan.*
[4]*Department of Epidemiology and Public Health, The Islamia University of Bahawalpur, Pakistan.*

Article Information
Received 28 November, 2024
Revised 28 June 2025
Accepted 10 July 2025
Available online 15 January 2026 (early access)
Published 25 May 2026

Authors' Contribution
MMAK, TT and MP: Validation, methodology, investigation, formal analysis
MKAK and SS: Writing – review & editing, validation, supervision, methodology, investigation, formal analysis, conceptualization
ST: Methodology, data curation
MSAK: Methodology
MI and AD: Visualization

Key words
Piper nigrum, Alloxan, ZnO nanoparticles, Ba-doped ZnO nanoparticles, Glibenclamide, Diabetes treatment, Albino mice

ABSTRACT

Herein, for the very first time, barium-doped ZnO nanoparticles (Ba-ZnO NPs) with varying Ba concentrations were fabricated using black pepper (*Piper nigrum*) leaf extract to investigate antidiabetic properties. Ba-ZnO NPs were characterized using XRD, SEM, UV–Vis, and FT-IR techniques to assess their structural, morphological, optical, and functional properties. Albino mice of the Swiss Webster strain were assigned to different experimental groups for in vivo evaluation of their antidiabetic potential. The control group was maintained, while diabetes was induced in experimental mice using alloxan (160 mg/kg body weight). Separate groups received treatments of *Piper nigrum* leaf extract (220 mg/kg body weight), pure ZnO NPs (210 mg/kg body weight), Ba-doped ZnO NPs (200 mg/kg body weight), and glibenclamide (12 mg/kg body weight) over 36 days. Ba-doped ZnO NPs significantly reduced glucose and cholesterol levels in diabetic mice and enhanced total protein, albumin, insulin, and HDL levels. However, nitrogenous parameters (urea, uric acid, and creatinine) were not significantly affected. These findings indicate that Ba-doped ZnO NPs possess potential as a biocompatible and non-toxic therapeutic agent for diabetes, owing to their unique physicochemical properties.

INTRODUCTION

Diabetes mellitus is an escalating global public health problem characterized by chronic hyperglycemia, which is resultant of the various extraordinary abnormalities in insulin secretion (Balaji *et al*., 2019). It is an epidemic worldwide in point of frequency, incidence, and impact. The findings from epidemiological studies showed that the disease disorder has increased in its incidence over the last few decades (Lovic *et al*., 2020). It was further established that in the year 2014, 422 million people, which constituted almost 8.5% of the adult world's population, were living with diabetes, and adults with the disease trait would rise to 642 million by the year 2040 (Aljin *et al*., 2018; Singla, 2022). The heightened severity of the resultant diabetes pandemic and the concomitant criticality of effective management and preventive measures come into vivid perspective (Hartmann-Boyce *et al*., 2020). Public health and healthcare systems are impacted by numerous diabetes complications such as stroke, hypertension, dyslipidemia, obesity, metabolic syndrome, diabetic nephropathy, retinopathy, neuropathy, peripheral vascular disease, and coronary artery disease. To manage diabetes, lifestyle changes are necessary for proper diet and exercise (Association, 2019; Lambrinou *et al*., 2019). However, new insulin-delivery mechanisms, glucose-monitoring devices, artificial pancreas technology, and advanced medications can improve glycemic control, treatment burden, and patient compliance (Domingo-Lopez *et al*.,

* Corresponding author: dr.khalil@uo.edu.pk, shoaibmsaddique@gmail.com
0030-9923/2026/0004-1715 $ 9.00/0

2022). However, diabetes management is challenging because of pharmacological side effects, nonadherence of the patient, and progression of the disease (Aditama *et al*., 2020). Insulin management issues might also be difficult for patients and doctors to manage such as injection site reactions, hypoglycemia, weight gain, allergic reactions, and lipodystrophy (Buse *et al*., 2021; Haider, 2023).

Nanotechnology is a modern area of research that concerns the examination and control of materials at very small level (Behl *et al*., 2022). Due to the unique features of nanomaterials, scientists and engineers at various levels can collaborate and make discoveries that will promote sustainable development for the betterment of human existence and the development of novel approaches to addressing social problems (Gavilán *et al*., 2023; Ghosh *et al*., 2023; Palit and Hussain, 2020). When introduced into biological systems, nanostructures can interact with immune systems, resulting in a range of biological actions (Ashraf *et al*., 2021). These activities rely on a number of the nanostructures physicochemical characteristics, such as their size, shape, surface area, and surface chemistry (Ernst *et al*., 2021; Ray *et al*., 2021). Nanoparticle-based diabetes treatments are a subject of increasing research as new therapies enhance the function of β-cells, insulin sensitivity, and glucose levels. Nanoparticle-based therapies have continued to revolutionize the paradigm of diabetes management due to the emergence of new drug delivery, imaging, and regenerative medicine approaches (Alzate-Correa *et al*., 2022; Vijayakumar *et al*., 2019).

Recently, there has been a surge of interest in ZnO treating diabetes since it is biocompatible, nontoxic, and possesses unique physicochemical features (Singh *et al*., 2021). Nano ZnO remediate redox imbalance in diabetic tissues by scavenging reactive oxygen species (Abd El-Khalik *et al*., 2022). ZnO protects the pancreatic β cells from death, ensures insulin levels remain intact, and also protects from diabetes-related eye complications like nephropathy, neuropathy, and retinopathy (Sharma *et al*., 2023). Nano ZnO possesses anti-inflammatory properties; it also remediates diabetes mellitus type 2 chronic inflammatory reaction since the accumulation of inflammation leads to diabetic complications as well as insulin resistance and β cell death. ZnO mitigates inflammation increasing tissue insulin sensitivity lowering insulin resistance and breaks down the inflammatory cascade (Abdulmalek *et al*., 2021; Hassan *et al*., 2021). ZnO NPs excessive diabetic wound and ulcer healing, enhance fibroblast hyperplasia and angiogenesis (Ezhilarasu *et al*., 2020). Transition metal, notably barium-based nanostructures have received unprecedented attention to serve as potential candidates for establishing imaging, diagnostics, therapies, drug delivery, and other avenues of applications (Khorasani *et al*., 2023). Further, nanostructures doped with barium are far more bioactive and effective for mechanistic activation compared to metal nanostructures without barium ions. It makes these particles connect to particular molecules, cells, and tissues related to the occurrence of diabetes mellitus (Abdullah *et al*., 2023). Thus, metal nanostructures, specifically barium-based, activate or inhibit the enzymes, receptors, and transcription factors to subsequently influence glucose metabolism and insulin signaling into the tissues that promote glucose entry and use as well as glycogen synthesis (Bauri *et al*., 2023). It must be emphasized that metal nanostructures pass through the cell membranes and tissue matrices due to their respective physicochemical properties to attack and target the biomolecules and therapeutic drugs toward particular organs and areas in the body (Azharuddin *et al*., 2019).

This study aims to evaluate the antidiabetic performance of barium-doped zinc oxide nanoparticles (Ba-ZnO NPs) synthesized through a green synthesis approach using black pepper (*Piper nigrum*) leaf extract. Undoped ZnO and Ba-ZnO NPs were synthesized and extensively characterized using SEM, XRD, UV-vis, and FT-IR to analyze their optical, physical, and chemical properties. The antidiabetic efficacy of Ba-ZnO NPs was investigated by assessing key biochemical markers, including blood glucose levels, urea, uric acid, serum creatinine, and protein levels, to evaluate kidney function and metabolic status. Additionally, lipid profiles, such as cholesterol and triglycerides, were measured to assess changes in lipid metabolism commonly associated with diabetes. The theoretical framework focuses on the potential of Ba-ZnO NPs to influence glucose metabolism, insulin sensitivity, oxidative stress, and inflammation, ultimately improving glycemic control and metabolic health. The significant findings presented in this work highlight the potential of Ba-ZnO NPs in biomedical applications, photocatalysis, and environmental remediation.

MATERIALS AND METHODS

Preparation of nanoparticles

In a typical synthesis, *Piper nigrum* leaves were first cleaned and washed thoroughly with water. After allowing the leaves to air dry, they were finely ground into powder. A total of 20 g of the *Piper nigrum* powder was then mixed with 200 mL of double-distilled water (DDW), and the mixture was agitated for one hour at 80 °C. Following this, the mixture was boiled and subsequently filtered using Whatman No. 1 filter paper. The filtrate was then centrifuged for five min at 5,000 rpm. After centrifugation, a 0.25 M solution of $Zn(NO_3)_2$ was added dropwise to the leaf extract, and the resulting mixture was stirred at room

temperature for two hours. The combination formed a white precipitate of zinc hydroxide ($Zn(OH)_2$) after standing for six hours. ZnO nanopowder was made by calcining the white leftovers for four hours at 500°C after they had been dried for two hours at 100°C. Similar procedures were used to make Ba-ZnO NPs, which involved adding 0.25 M solutions of Ba $(NO_3)_2$ and $Zn(NO_3)_2 \cdot 6H_2O$. After adding the Piper nigrum extract solution, the mixture was mixed and left to stand at room temperature. Ba-ZnO NPs were produced by coarsely calcining the precipitates for four hours at 500°C after they had been dried in an oven at 100°C. A schematic representation of the synthesis route is exhibited in Supplemenatry Figure S1.

Evaluation of nanoparticels

Different diagnostic techniques were used to comprehensively analyze the synthesized nanomaterials. Absorption spectra were analyzed with the use of a UV-Vis spectrophotometer with a model C7200 at the wavelength from 200 to 600 nm. Through the use of UV-Vis spectroscopy, it was possible to measure the absorbance and transmittance of light by the nanomaterials, which offered significant knowledge of the optical properties, bandgap energy, and electronic transitions. X-ray diffraction analysis was conducted using Cu-Kα radiation, which enabled the analysis of the synthesized nanomaterials in the 2θ interval from 30° to 80°. XRD helped obtain valuable information on the synthesized nanomaterials' crystalline structure, phase composition, and lattice parameters. FTIR spectroscopy was executed using the FTIR spectrometer with a model L1600235. It helped to identify the functional groups and chemical bonds identified in the synthesized nanomaterials, which gave meaningful insights of the molecular structure, nature of surface chemistry, and interaction with the surrounding molecules. Scanning electron microscopy and energy-dispersive X-ray spectroscopy were used to examine the samples with MAIA3 Tescan instrument, which helped to analyze the samples from different perspectives. SEM provided the opportunity to visualize the surface structure, size, and shape of the synthesized nanostructures. EDX spectroscopy facilitated the elemental analysis and identification of the samples' chemical composition and element distribution.

Experimental design

Swiss Webstar strain albino mice (60 healthy males, 30±3 g) were obtained from VRI, Lahore, Pakistan, and housed in steel cages (12×18). The mice were acclimatized for one week under controlled conditions (humidity 60–65%, temperature 26–30°C, 12-h light-dark cycle) with ad libitum access to food and water. Diabetes Induction: A dose of 150 mg/kg STZ, dissolved in 0.1 M citrate buffer (pH 4.5), was administered intraperitoneally to 16 h fasted mice. After 6 h, food and water were provided, and 5% glucose solution (1 mL/kg) was given for 24 h to prevent hypoglycemic shock. Diabetes was confirmed three days post-STZ injection (glucose >200 mg/dL). Mice were randomly assigned to six groups each containing 10 mice: (i) D1 (Control): received distilled water and food. (ii) D2 (Diabetic Group): diabetes induced using alloxan. (iii) D3: treated with *Piper nigrum* extract. (iv) D4: treated with zinc oxide nanoparticles (ZnO NPs). (v) D5: treated with Ba-ZnO NPs, and (vi) D6: treated with a standard antidiabetic drug.

In Vivo and biochemical evaluation of antidiabetic activity

Treatments continued weekly for six weeks. Blood samples were collected from the tail vein, and blood glucose levels were measured using an i-QARE DSW Taiwan glucometer at 0, 1, 2-, 4-, and 6-h post-treatment (triplicate readings) (Alene *et al*., 2020). The percentage reduction in blood glucose levels was calculated using:

$$(Gb - Gp) / Gb \times 100 \quad ....(1)$$

Where Gb is the baseline glucose level and Gp is the post-treatment glucose level. Plasma insulin levels were determined using rat insulin ELISA kits (RayBiotech, USA) (Wang *et al*., 2024). Biochemical parameters, including urea, creatinine, and total protein levels, were measured using commercial kits (Biotechnical, Brazil; Merck, India) (da Costa *et al*., 2024). Triglycerides and cholesterol were analyzed using triglycerides/GB and cholesterol/HP kits. HDL and LDL levels were determined using Yantai Ausbio kits (China), while liver lipids were extracted using the Folch method (Zhang *et al*., 2024). For histopathological analysis, pancreas, liver, and kidney samples were fixed in Bouin's solution for 24 h, embedded in paraffin, sectioned (5 µm), and stained with hematoxylin-eosin. Microscopic examination was performed using an Olympus CX41 microscope. Statistical analysis was carried out using one-way ANOVA, followed by Duncan's multiple range test (DMRT). Results were expressed as mean ± SD, with statistical significance set at $p < 0.05$ (Martinez *et al*., 2024).

RESULTS AND DISCUSSION

Charaterizatoion of Ba-ZnO NPs

Figure 1A, B shows SEM images of undoped and 5% Ba-doped ZnO nanopowders. The undoped ZnO displays a mix of spherical and elongated particles with rough surface textures (Fig. 1A), while Ba-doped ZnO exhibits more irregular and densely packed particles (Fig. 1B), indicating that Ba incorporation influences particle size,

shape, and distribution. This morphological shift may enhance surface area and reactivity.

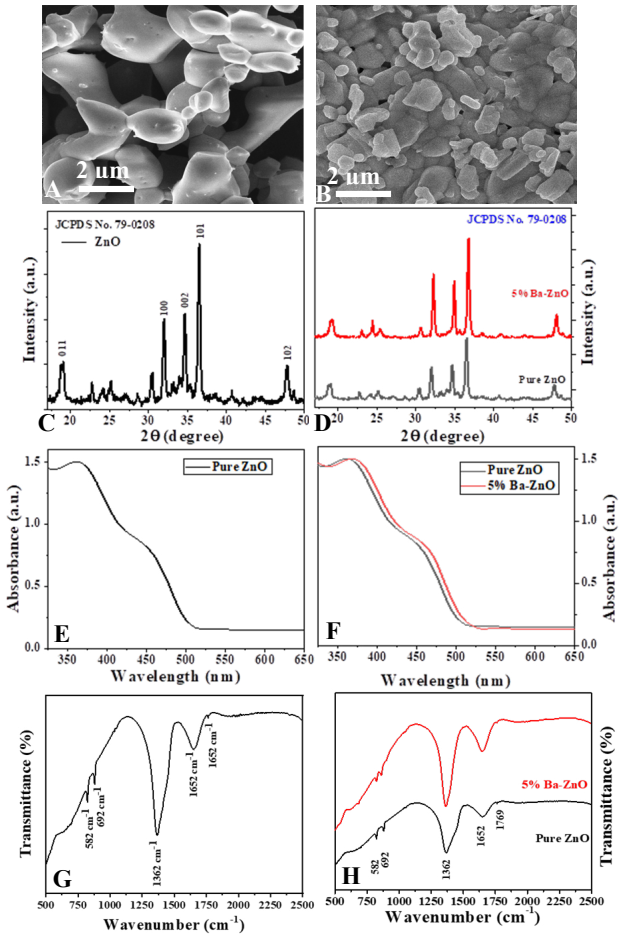

Fig. 1. Characterization of Pure ZnO and Ba-ZnO NPs. (A, B) SEM images of pure ZnO (A) and 5% Ba-ZnO (B), (C, D) X-ray diffraction patterns of pure ZnO NPs (C), and pure ZnO and 5% Ba-doped ZnO (D), (E, F) UV-Vis spectrum of pure ZnO (E) and pure ZnO and 5% Ba-ZnO NPs (F). (G, H) FT-IR spectrum of pure ZnO (G) and pure ZnO and 5% Ba-ZnO NPs (H).

XRD analysis in Figure 1C, D, confirms the wurtzite hexagonal phase in both samples. Ba-ZnO shows additional peaks at 25°, 42.5°, and 48°, absent in pure ZnO, likely corresponding to Ba phases. The dominant ZnO peaks remain intact, suggesting Ba is incorporated without major structural disruption. The decrease in crystallite size with Ba doping was calculated using Scherrer's formula, attributed to lattice strain and defect formation.

$$D = \frac{K\lambda}{\beta_G \cos\theta} \quad \ldots(2)$$

Optical properties were examined using UV–vis spectroscopy (Fig. 1E, F). The absorbance peak of pure ZnO appears at 363 nm, while Ba-ZnO shifts to 381 nm, indicating a redshift and bandgap narrowing due to Ba incorporation. This shift suggests enhanced visible light absorption, beneficial for optoelectronic applications. FTIR spectra (Fig. 1G, H) further confirm structural modification. Peaks around 437 cm^{-1} indicate Zn–O bonds, while new bands near 574 cm^{-1} suggest Zn–Ba–O bond formation. Carboxylate group vibrations at 1446–1643 cm^{-1} are also more pronounced in Ba-ZnO, consistent with enhanced surface interactions due to doping. Docking results (Figs. 2, 3) show Ba-ZnO exhibits stronger binding affinities with diabetes-related proteins compared to pure ZnO, except for 1XU9. Enhanced interactions, reflected in improved docking scores, may result from changes in electronic structure and surface charge. Ba-ZnO showed particularly strong binding to glucokinase (1V4S) and 11β-HSD enzymes (2BEL, 1XU7, 1XSE), indicating potential for therapeutic applications in diabetes. These results support the multifunctionality of Ba-doped ZnO as a promising candidate for biomedical and catalytic uses.

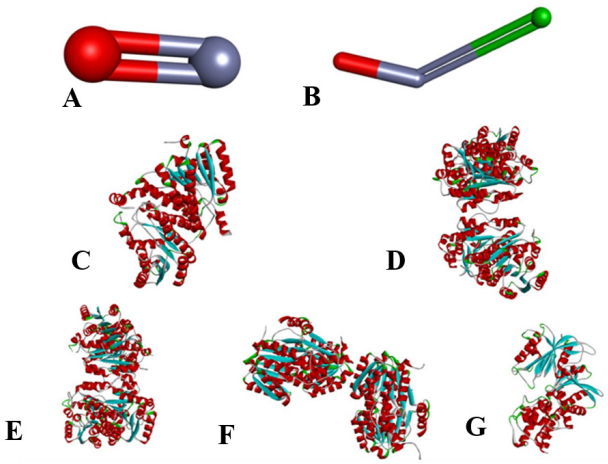

Fig. 2. Structure of (A) ZnO red atom shows oxygen and grey represents Zn and (B) Ba doped ZnO, green atom represents Ba and (C–G) Ribbon diagrams of various protein structures.

Effect of Ba-ZnO NPs on biochemical components of diabetic mice

As illustrated in Figure 4A-J, the biochemical parameters varied significantly among the experimental groups. Blood glucose levels (Fig. 4A) were substantially elevated in the diabetic control (D2), confirming disease induction, while the normal group (D1) maintained physiological levels. Treatments with Piper nigrum extract (D3), ZnO NPs (D4), and Ba-doped ZnO (D5) showed progressive

improvements, with Ba-ZnO producing the greatest reduction after the standard drug (D6), highlighting its superior hypoglycemic potential. Urea (Fig. 4B), uric acid (Fig. 4C), and creatinine (Fig. 4D) levels, which increased in D2 as markers of renal stress, were moderately lowered in D3–D5, with D5 approaching the efficacy of D6. Total protein levels (Fig. 4E) dropped in D2 but improved with treatment, especially in D5 and D6, suggesting recovery of protein synthesis and metabolic function. Insulin levels (Fig. 4F) were significantly reduced in D2 but recovered in all treated groups, with Ba-ZnO (D5) showing a higher effect than ZnO (D4) and extract (D3), and slightly trailing the standard drug (D6). Total cholesterol (Fig. 4G) and triglycerides (Fig. 4H) were elevated in D2 but effectively reduced in D5, indicating enhanced lipid-lowering ability. HDL cholesterol (Fig. 4I), which was suppressed in D2, improved with all treatments, with D5 outperforming D3 and D4. LDH levels (Fig. 4J), indicative of cellular damage, were highest in D2 and D4 but markedly reduced in D5. Ba-ZnO demonstrated greater therapeutic impact than ZnO and Piper nigrum, closely approaching the effects of standard treatment across multiple parameters. Blood glucose serves as a vital energy source for animals, and increased glucose levels are frequently employed as

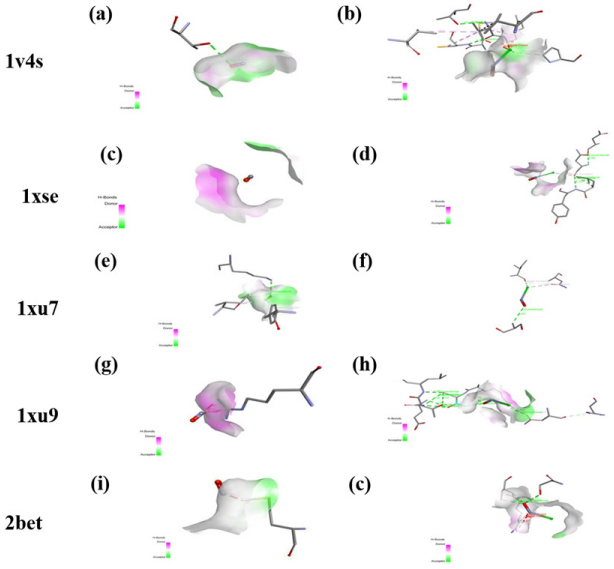

Fig. 3. Interaction of all proteins selected for analysis with ZnO and Ba-doped ZnO.

Table I. Docking scores of all proteins with ZnO and Ba-ZnO.

Prediction	Defrock confi-dence	SMINA affinity	SMINA minimized affinity	SMINA minimized RMSD
1V4S-ZnO	0.23	-0.74112	-0.76609	0.16612
1V4S-BaZnO	0.71	-1.16281	-1.55797	1.22554
1XSE-ZnO	0.04	-0.54555	-0.75332	2.19228
1XSE-BaZnO	1.14	-0.79424	-0.93339	0.71707
1XU7-ZnO	1.06	-0.27547	-1.16661	1.04752
1XU7-BaZnO	-0.21	-0.62517	-0.96241	0.52686
1XU9-ZnO	-0.16	-0.94692	-1.11633	0.35968
1XU9-BaZnO	3.83	2.26024	-0.47371	1.18813
2BEL-ZnO	0.8	3.19618	-0.32732	1.62777
2BEL-BaZnO	-0.05	-1.15778	-1.36313	1.19462

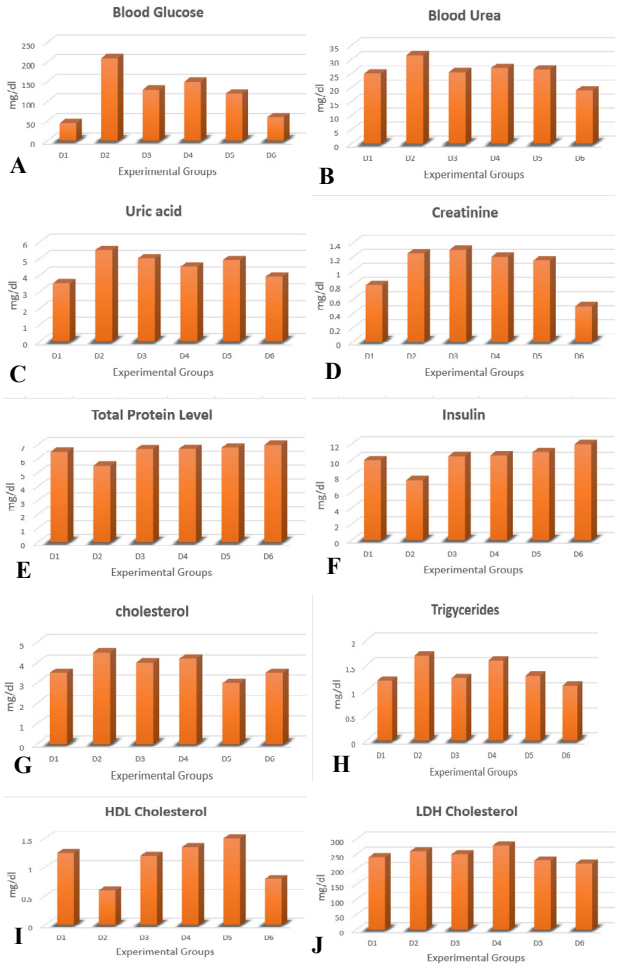

Fig. 4. (A) Blood Glucose level, (B) Urea level, (C) Uric Acid level, (D) Serum creatinine level, (F) Protein level, (F) Insulin level, (G) Total cholesterol level, (H) Total triglycerides level, (I) HDL cholesterol level, and (J) LDH cholesterol level in mice across different groups treated with Piper nigrum extract, ZnO NPs, Barium doped ZnO NPs and standard medication.

a stress signal causing diabetic effects. *P. nigrum* extract and ZnO NPs significantly reduce blood glucose levels compared to the D2, demonstrating potential antidiabetic effects. These results coordinate with earlier research conducted by Rehman *et al*. (2023), Meydan *et al*. (2022), and Ahmed *et al*. (2022), highlighting the effectiveness of natural extracts and nanostructures for lowering blood glucose levels. The combined medication, as (Raimundo *et al*., 2020) evidenced, enhances the antidiabetic effects consistent with our conclusions. The analysis of blood glucose and insulin levels starkly highlighted the insulin secretion seen in those with the disease. Compared to the control group, insulin release had noticeably diminished, as described by (Park *et al*., 2023). Treatment using an extract of *P. nigrum* leaves led to a boost in insulin amounts, signifying its probable role in restoring the natural discharge of this hormone. Prior investigations exploring plant-derived therapies had produced congruent results, according to (Ungurianu *et al*., 2019). What's more, the amalgamation of *P. nigrum* extract alongside pure ZnO and Ba-ZnO yielded a synergistic effect, implying the feasibility of utilizing nanomaterial conduits for drug transport. In all interventions tested, glibinclamide (GLC) medication brought about the most substantial insulin elevation, surpassing other options, corroborating its primacy as a front-line therapeutic approach (Shahzadi *et al*., 2022). Lipid profiles serve as an excellent biomarker for evaluating the adaptation ability, health, and dietary status of an organism. The HDL cholesterol levels were reduced in the disease group, but there was a slight increase due to the *P. nigrum* extract treatment. The therapy, which includes ZnO nanopowder and Ba-ZnO, showed the highest increase, which showed a high possibility of having synergy. The LDL cholesterol levels increased in the disease group and were slightly reduced due to *P. nigrum* extract treatment. On the other hand, the therapy of Ba-ZnO NPs was reduced significantly, which also had the possibility of synergy. Meanwhile, GLC medication had the lowest amount of LDL cholesterol levels. Analysis of total cholesterol revealed an elevated rate for the disease group that slightly decreased after exposure to *P. nigrum* extract, ZnO, and Ba-ZnO NPs but Ba-ZnO NPs had excellent effects in terms of a decrease in cholesterol levels, indicating that there was a synergistic effect of the applied drugs. GLC medicine had the most optimal cholesterol level, which was consistent with the fact that this treatment was optimal for managing and controlling the disease. The total triglyceride level was high for the disease group, but did not decrease considerably after *P. nigrum* extract treatment. At the same time, Ba-ZnO therapy had considerable positive changes and indicated interaction between the drugs, which is a positive effect and could be used for further studies to demonstrate the effects of treatment. Serum urea and creatinine were measured to assess normal renal functioning. A change in the concentration of creatinine and urea may lead to renal dysfunction (Abd El-Khalik *et al*., 2022). In the present study, a non-significant decrease in uric acid levels was observed in the disease group following exposure to plant extract, ZnO, and Ba-ZnO. However, a significant reduction was seen with GLC treatment in the D6 group. Uric acid levels significantly decreased in the diseased group treated with ZnO, while creatinine levels showed a significant reduction with GLC exposure and a non-significant decrease with plant extract, ZnO, and Ba-ZnO treatments. Serum creatinine levels, which are indicative of renal function, suggest that *P. nigrum* leaf extracts may have potential renoprotective effects (Insaf and Raju, 2019).

CONCLUSION

The present study demonstrated that Ba-doped ZnO nanoparticles exhibit promising antidiabetic potential in vivo. Albino mice of the Swiss Webster strain were utilized to evaluate the therapeutic effects of various treatments following diabetes induction with alloxan. Among the treatments tested, Ba-doped ZnO nanoparticles notably reduced blood glucose and cholesterol levels while enhancing total protein, albumin, insulin, and HDL levels in diabetic mice. Although no significant changes were observed in nitrogenous waste parameters (urea, uric acid, and creatinine), the overall findings suggest that Ba-doped ZnO nanoparticles are biocompatible and non-toxic, with favorable physicochemical properties that support their potential as an effective therapeutic agent for diabetes management.

DECLARATIONS

Acknowledgment

This study was supported financially by the National Science and Technology Council, the Republic of China (NSTC 112- 2221-E-224-013-MY3).

Funding

The study received no external funding.

Ethical statement

All procedures involving Swiss Webster Albino Mice (*Mus musculus*) were carried out in strict accordance with the guidelines for animal welfare and ethical conduct in the use of laboratory animals. The experimental protocols were reviewed and approved by the Institutional Animal

Ethics Committees of the University of Okara (Pakistan), the University of Padova (Italy), and the National Yunlin University of Science and Technology (Taiwan).

Supplementary material

There is supplementary material associated with this article. Access the material online at: https://dx.doi.org/10.17582/journal.pjz/20241128151257

Generative AI or AI-assisted technology statement

During the preparation of this work, the authors did not use generative AI or AI-assisted technologies to create or edit the content. The authors themselves carried out all writing, analysis, and revisions.

Statement of conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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