Research Article

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Treatment of gestational diabetes by *Acroptilon repens* leaf aqueous extract green-formulated iron nanoparticles in rats

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Abstract: In recent years, researchers have been utilizing nanotechnology more and more to study diabetic complications, with a particular emphasis on prevention and treatment. In this investigation, we analyzed the effects of *Acroptilon repens* extract on iron nanoparticles (FeNPs), which demonstrated significant anti-diabetic characteristics both in living organisms and in laboratory settings. To assess the effectiveness of the FeNPs produced through the interaction of iron salt solutions stabilized by *A. repens* extract, we utilized a range of methodologies. The FeNPs were manufactured in a spherical shape, ranging in size from 10 to 60 nm. During the *in vivo* experiment, gestational diabetes was induced through streptozotocin (STZ) intraperitoneal injection. The animals were then categorized into four groups: FeNPs-60 μg/kg group, FeNPs-120 μg/kg group, normal pregnancy group, and gestational diabetes mellitus group ($n = 10$). FeNPs were administered intragastrically for 25 days. On the final day, the levels of ALP, AST, ALT, and blood glucose in the serum samples were assessed. Following tissue processing, 5 μm liver sections were prepared and the overall volume of the hepatic arteries, bile ducts, central vein, portal vein, sinusoids, hepatocytes, and liver, were approximated. FeNPs have the potential to reduce the elevated levels of ALP and AST enzymes. In gestational diabetes rats, the administration of FeNPs lead to a decrease in blood glucose levels. The administration of STZ significantly increased the volume of sinusoids and hepatocytes. However, after the treatment with a high dose of FeNPs, there was a notable decrease in their volume. In contrast, the volume of the bile ducts and portal vein remained unchanged in the experimental groups. Nevertheless, the volume of the hepatic arteries and central vein exhibited changes due to the presence of FeNPs. The current study showcases the hepatoprotective and anti-diabetic characteristics of FeNPs, providing a potential option as a supplement to prevent gestational diabetes mellitus while also offering hepatoprotective benefits.

Keywords: *Acroptilon repens* extract, iron nanoparticles, streptozotocin, gestational diabetes mellitus, liver

1 Introduction

Glycogenic hepatopathy is an uncommon occurrence in individuals with uncontrolled diabetes mellitus, presenting as a temporary impairment of liver function accompanied by heightened liver enzyme levels and hepatomegaly [1–3]. This condition arises due to the surplus glycogen reversible buildup in the hepatocytes. It is primarily observed in individuals who have had type 1 diabetes mellitus for a long time and is reported rarely in connection with type 2 diabetes mellitus. While it was initially noticed in children, it has since been revealed in adults and teenagers, both without and with ketoacidosis [4,5]. The correlation between glycogenic hepatopathy and hyperglycemia in diabetes remains poorly established. A crucial factor in the glycogenic hepatopathy development pathophysiology is the significant variation in insulin and glucose levels [5,6]. Clinically, it is challenging to differentiate between glycogenic hepatopathy and non-alcoholic fatty liver disease, with the latter being more common in diabetic patients and having the potential to advance to severe cirrhosis and liver disease [5–7]. Achieving proper glycemic regulate can cause the perfect resolution of histological, laboratory, and clinical disorders. Recently, there have been reports indicating the presence of liver fibrosis in varying degrees among patients with glycogenic hepatopathy [1,8,9]. Additional research is necessary to comprehend the biochemical

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abnormalities that contribute to glycogenic hepatopathy, develop noninvasive and efficient diagnostic examinations for this condition, and evaluate the implications of severe fibrosis, which can potentially advance to cirrhosis. The level of awareness regarding this condition among medical professionals, including specialists, is currently inadequate [1,9].

Nowadays, nanomaterials are being widely utilized in various fields, making their presence felt in every aspect of life. Additionally, the application of nanoparticles (NPs) in medical procedures has witnessed a significant rise [10–12]. NPs possess several applications in medicine, encompassing disease treatment and prevention, diagnostic nano-robots, diverse medical sensors, drug delivery systems, and imaging techniques. Nanocomposites have gained significant attention in the field of nanotechnology for their practical applications, particularly as anti-diabetic compounds and drug delivery systems for diabetes treatment [13–16]. The utilization of NPs for encapsulating drugs applied in diabetes treatment enhances the efficacy of drug delivery to pancreatic cells while minimizing toxicity and adverse effects on normal cells. In light of the diabetes rising prevalence and the limitations of conventional chemotherapy approaches, there is an urgent demand for innovative techniques development to address this disease [17–19]. It is imperative to focus on anti-diabetic medications that specifically target pancreatic cells, while also minimizing the drugs concentration to mitigate their toxic effects on normal cells. Hence, in order to precisely target the medication to the pancreas and minimize its adverse efficacies, we can utilize novel delivery techniques and employ NPs as carriers [10–15]. NPs ranging from 10 to 100 nm in size are commonly utilized to target medicinal and diagnostic agents. Over the past few years, there has been a notable increase in NPs utilization for preventing pancreatic cells loss, thereby minimizing the overall cytotoxicity of anti-diabetic medications [16–19].

Acroptilon repens is an *Asteracea* family member. It is herbaceous, characterized by its extensively branched stem and abundant foliage, adorned with vibrant purple and pink flowers. Geographically, *A. repens* thrives in semi-arid to semi-humid regions of Iran, particularly in areas with irrigated or rain-fed crops, or an annual rainfall ranging from 250 to 600 mm [20]. It is widely distributed across various regions, making it a common sight almost everywhere. *A. repens*, a perennial weed, thrives in corn and wheat fields, imparting a bitter flavor to their flour. It spreads through both rhizomes and seeds. Studies have revealed that *A. repens* generates phytotoxic substances, leading to competition with other plants. Additionally, research has documented that the root aqueous extract of *A. repens* hinders the growth of neighboring plants [20].

A research was performed to follow the impact of a plant extract on heart contraction and blood pressure. The findings revealed that the extract's ability to raise blood pressure is partially attributed to the norepinephrine release from cytoplasmic and intragranular stores before synapses. Additionally, the plant extract was found to cause premature ventricular contractions, which can be attributed to its blood pressure-raising effect [21]. Another research project involved the extraction of methanol extract and essential oil from the young branches and leaves of *A. repens* gathered in Shahrood, followed by analysis using GC-MS. The results revealed the presence of anthracene in the *A. repens* essential oil, while the methanolic extract contained morphinan as main compounds. Additionally, the study demonstrated the potent antibacterial properties of the *A. repens* methanolic extract [22–24]. *A. repens* has been found to contain various sesquiterpene lactones and flavones, known for their considerable toxicity [25,26]. The root of this plant has been identified to contain a toxic compound called 7,8-benzoflavone. Furthermore, the extraction from this plant has yielded the sesquiterpene lactone acropetline [27]. Additionally, *A. repens* also contains repin, which exhibits neurotoxic and cytotoxic effects [28]. *A. repens* not only exhibits harmful effects, but also possesses anti-fever properties [29]. Additionally, a report indicates that the extract of *A. repens* can inhibit the alpha glucosidase enzyme [30], thereby preventing glucose absorption from the intestine. This makes it beneficial in the hyperglycemia and diabetes treatment resulting from it. Furthermore, *A. repens* demonstrated antioxidant efficacies in *in vitro* experiments [31]. The experiment involved administering doses of 100 and 300 mg/kg of the extract to normal rats, 30 min before the glucose tolerance test. The results revealed that 300 mg/kg caused a remarkable decrease in serum glucose levels in rats [31]. Additionally, the study examined the effects of *A. repens* hydroalcoholic extract (300 mg/kg) on glucose levels, lipid levels, and indicators of liver and kidney function (creatinine, AST, and ALT) in both normal and diabetic rats [31].

Our research was conducted to address the scarcity of information on the utilization of iron nanoparticles (FeNPs) as a dietary supplement for preventing liver disorders associated with gestational diabetes, in comparison to iron salt. The study's primary objective was to examine the extent of liver damage caused by diabetes mellitus and explore the potential protective properties of orally administered FeNPs synthesized with *A. repens* extract.

2 Experimental

2.1 Preparation of *A. repens* extract

Fresh leaves of *A. repens* were harvested, thoroughly cleaned, and sun-dried. Subsequently, 100 g of the flowers was immersed in 2 L of deionized water and gently heated to 80°C for half an hour. The light-colored liquid obtained was cleaned up using Whatman-1 paper [32].

2.2 Synthesis of FeNPs

An established method (with slight adjustments) was employed for the eco-friendly FeNPs synthesis [32]. Initially, 10 mL of the *A. repens* extract (50 g/L) was combined with 30 mL of 0.02 M $FeCl_3{\cdot}6H_2O$. Subsequently, the mixture was agitated for 120 min at 55°C. Upon completion of the reaction time, FeNPs were produced. The transition in color from yellow to black signified the successful formation of FeNPs. The FeNPs that were acquired underwent three rounds of water washing and were then centrifuged at 10,000 rpm for 15 min. The black-colored purified NPs were obtained by air-drying the resultant pellet at 90°C for 2 h. Subsequently, the black powder underwent purification by washing with acetone.

2.3 Chemical characterization of FeNPs

The NPs absorbance value was measured by the UV-Vis test (200–800 nm). The morphology and structural characteristics of the NPs were checked by the field emission scanning electron microscopes (FE-SEM) test. ImageJ software was applied for determining the FeNPs size distribution. The specific functional group characteristics in stabilizing and reducing of the synthesized FeNPs were achieved via fourier transform-infrared spectroscopy (FT-IR) test. KBr method was employed for the FT-IR analysis, involving the preparation of a sample (0.3 g) of synthesized FeNPs mixed with KBr. The elemental composition of FeNPs was examined using energy dispersive X-ray (EDX) spectroscopy (LEO 1430 VP).

2.4 *In vivo* design

The study involved 50 pregnant rats weighing approximately 210 ± 5 g. To induce diabetes, a single dose of streptozotocin (STZ) at 60 mg/kg was administered to 40 animals at the start of the experiment. An individual was classified as diabetic if their blood glucose level enhanced 400 mg/dL. Subsequently, the subjects were divided into six subgroups through random selection. The subgroups included:

(1) Healthy control group: The animals received distilled water for 20 days.
(2) Negative control group: The diabetic animals received distilled water for 20 days.
(3) Positive control group: The diabetic animals received glibenclamide (20 mg/kg) for 20 days.
(4) FeNPs group (I): The diabetic animals received FeNPs (60 µg/kg) for 20 days.
(5) FeNPs group (II): The diabetic animals received FeNPs (120 µg/kg) for 20 days.

Following a 20-day treatment period, blood samples were collected from the heart for analysis of biochemical and stereological parameters. A 2 mL blood sample was obtained from the heart of the animals after administering anesthesia and performing an abdominal incision using a heparin syringe. The collected blood was then subjected to centrifugation (AG22331 Eppendorf, Germany) at 3,000 rpm for 15 min to isolate the plasma. In order to assess the extent of liver damage, the plasma samples were analyzed for blood glucose, GGT, ALT, AST, ALP, and urea levels [33].

In order to measure the level of tissue injury resulting from the blood collection, the liver was isolated and then partitioned into different segments according to stereological research. To ensure preservation, the liver was placed in a 10% formalin solution and transferred to the pathology lab. After being fixed, the separated liver went through distinct tissue processing steps, such as dehydration and embedding in paraffin, leading to the formation of a paraffin mold. Microtome was used to obtain 5 µm sections from the cast, which were then stained with hematoxylin and eosin. The tissue damage degree was evaluated by a pathologist. Stereological indicators were employed to compare the changes in tissue volume and the extent of damage in both the tissue and vessel regions among the various groups [33].

2.5 *In vitro* study

2,2-diphenyl-1-picrylhydrazyl (DPPH) is commonly employed to assess the antioxidant activity of different compounds because of its high sensitivity and simplicity. This method relies on the hydrogen absorption by the DPPH, resulting in a color change to yellow. Consequently, there is a reduction in absorption at 517 nm. The DPPH absorption is highest at 517 nm. About 2 mg of DPPH powder was dissolved in ethanol

(30 mL) to prepare the working solution. In order to assess the extent of free radical inhibition by NPs, varying concentrations of NPs (1–1,000 µg/mL) were prepared using the serial dilution method in microtubes. Subsequently, 1 mL of DPPH solution was introduced into each microtube. The IC_{50} index was employed to assess the free radicals inhibition, representing the substance concentration that hinders 50% of DPPH. The calculation is determined through the relationship provided [34–41]:

$$\text{Inhibition (\%)} = \frac{\text{Sample A}}{\text{Control A}} \times 100.$$

2.6 Statistical analysis

The synthesized NPs' biological parameters were calculated and significant differences were checked using SPSS-22 software and one-way ANOVA.

3 Results and discussion

3.1 Characterization of FeNPs

The mixture of *A. repens* and $FeCl_3 \cdot 6H_2O$ was provided and incubated for 3 h. During the reaction, the color of the solution changed to black, thus verifying the photosynthesis taking place in the creation of FeNPs. The change in color was observed as a result of the surface plasmon resonance activity indicated by the nanoparticles [42,43]. The previous study mirrored our data regarding the solution's color visual alteration [44]. An absorption peak at 291 nm was observed in the FeNPs, which was associated with the metal free electrons excitation during the NPs formation, known as surface plasmon resonance (Figure 1). The recent spectra reveal valuable insights into the colloidal FeNPs characteristics and development. An absorption peak in 280–300 nm serves as an AgNPs distinctive attribute [42–44].

Figure 2 displays the FeNPs FT-IR spectrum. The existence of peaks at wavenumbers 454 and 687 cm^{-1} confirms

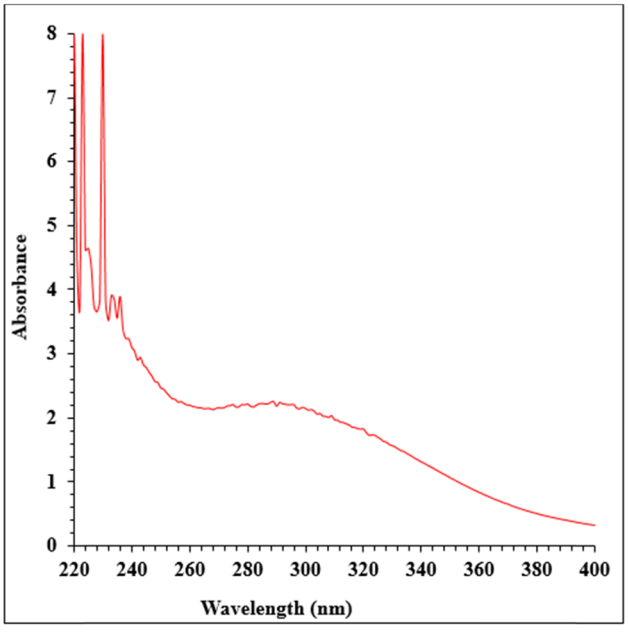

Figure 1: UV-Vis analysis of FeNPs.

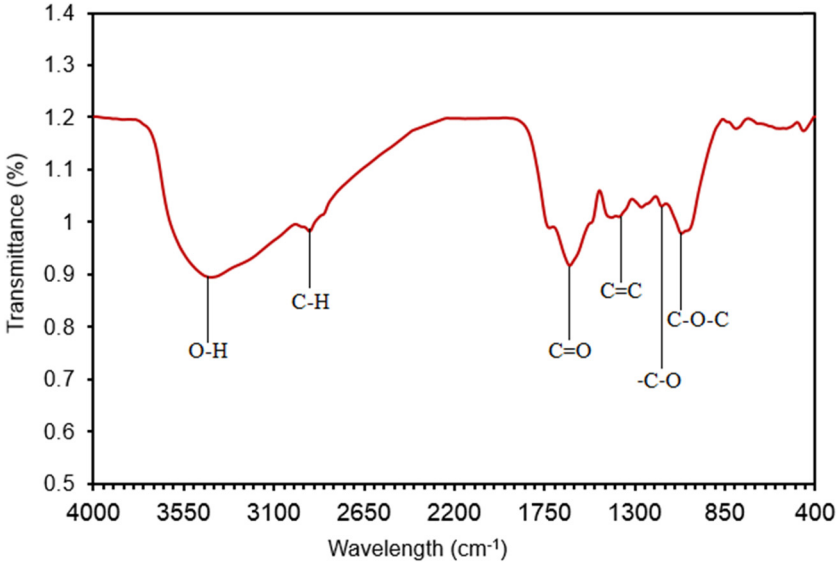

Figure 2: FT-IR analysis of FeNPs.

the formation of FeNPs. These peaks correspond to the bending vibration of Fe–O. Other research groups have also reported similar peaks with slight variations in the wavenumber for green-mediated FeNPs [42–44]. The various peaks observed in the spectrum can be associated with the distinct organic compounds' functional groups found in the plant extract. These compounds are known to be connected to the FeNPs surface. Previous studies have reported the presence of secondary metabolites like triterpenes, flavonoid, and phenolic in the plant extracts [42–44]. The C–H and O–H bonds are responsible for the peaks observed at 2,921 and 3,429 cm^{-1}, respectively. The peaks ranging from 1,401 to 1,624 cm^{-1} indicate the stretching of C═C and C═O bonds. Moreover, the peaks reported at 1,072 and 1,163 cm^{-1} are indicative of the stretching of C–O–C and –C–O bonds.

The FeNPs morphology was evaluated using the FE-SEM method. Figure 3 illustrates the FeNPs FE-SEM images, revealing their spherical structure and an average particle size of 48.23 nm. Moreover, the NPs exhibit aggregation. In our comprehensive analysis, the size range of 11.0–98.79 nm was documented for the biosynthesis of FeNPs, employing extract as the capping agent [45–48].

The FeNPs elemental analysis was assessed through the implementation of EDX, which yielded qualitative results. Figure 4 displays the EDX diagram of FeNPs, showcasing the outcomes of the analysis. The obtained findings confirmed the presence of iron, as indicated by the peaks observed at 7.13 keV for FeLβ, 6.44 keV for FeKα, and 0.71 keV for FeLα.

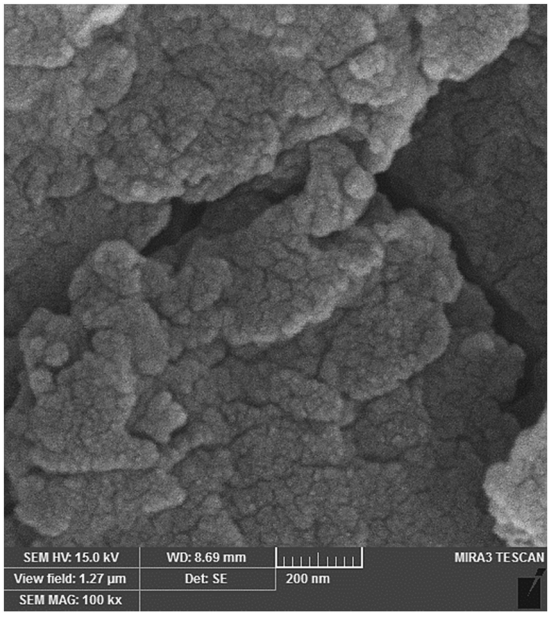

Figure 3: FE-SEM image of FeNPs.

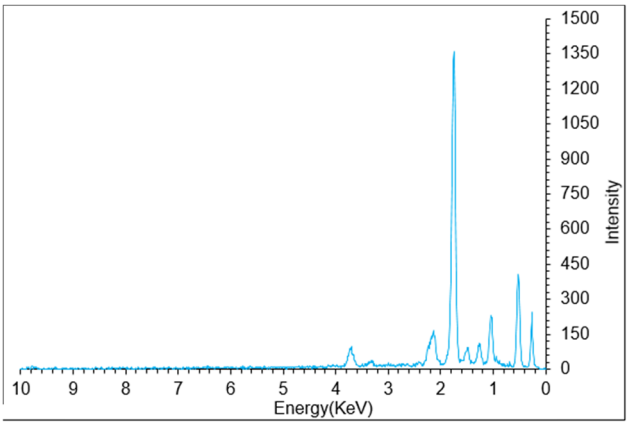

Figure 4: EDX analysis of FeNPs.

Additionally, the analysis revealed the existence of oxygen (OLα: 0.52 keV) and carbon (CLα: 0.28 keV) within the FeNPs. Other research groups have confirmed the detection of iron based on the signal [49]. The connection between plant extract organic compounds and FeNPs has been validated by the carbon and oxygen presence.

3.2 Anti-diabetic effects of FeNPs

Gestational diabetes is a condition characterized by impaired glucose tolerance that arises or is identified for the first time during pregnancy. Despite improvements in medical and obstetric care, the presence of gestational diabetes typically increases the complications likelihood for both the fetus and mother after and before pregnancy [50–53]. Maternal complications associated with diabetes encompass high blood pressure, excessive amniotic fluid, preterm delivery, and infectious complications [51–53]. Children born to mothers with gestational diabetes have been found to have obesity, overweight, kidney disease, insulin resistance, type 2 diabetes, and high blood pressure, according to research studies. In terms of epidemiology, gestational diabetes is frequently linked to type 2 diabetes [51,52]. The application of nanotechnology in diabetes research has paved the way for the creation of innovative methods for measuring glucose levels and administering insulin. These advancements have the potential to greatly enhance the quality of life for individuals living with diabetes [54,55]. NPs have been offered as potential carriers for insulin, enabling peptide delivery through more user-friendly methods such as oral or nasal routes, eliminating the requirement for injections [54]. The inclusion of nanoscale elements often enhances the sensitivity and temporal response of glucose sensors, resulting in the development of sensors that enable continuous glucose monitoring in

living organisms [55]. Recent studies have explored the use of different types of NPs, such as drug nanosuspensions, nanoemulsions, niosomes, liposomes, dendrimers, micelles, and polymeric and lipid NPs, as a means to enhance the delivery of oral hypoglycemic medications in comparison to traditional treatments [54,55].

Figure 5 demonstrates the impact of FeNPs on fasting blood sugar (FBS) in diabetic animals. Administering FeNPs to STZ-diabetic rats at both doses lead to a significant reduction ($p \leq 0.05$) in FBS levels, similar to the effects observed with glibenclamide treatment.

There was a notable distinction ($p \leq 0.05$) seen between the two doses of FeNPs after 10 and 20 days. Furthermore, the impact of the FeNPs was most pronounced on Day 20. However, there were no considerable differences ($p \leq 0.05$) found between FeNPs-120 and glibenclamide in terms of FBS levels.

The toxicity induced by STZ lead to a considerable increase ($p \leq 0.05$) in GGT, ALT, AST, and ALP levels. However, both doses of FeNPs were able to significantly ($p \leq 0.05$) decrease the elevated levels of above parameters. There were no significant variances ($p \leq 0.05$) detected in the aforementioned parameters between glibenclamide and FeNPs-120 (Figure 6).

Figure 7 illustrates the data regarding the mean absolute volume of the liver. The liver volume was significantly improved ($p \leq 0.05$) with the administration of FeNPs at both doses, compared to the untreated animals. But, there were no significant differences ($p \leq 0.05$) seen in the liver volume between the FeNPs-120 and glibenclamide treatments.

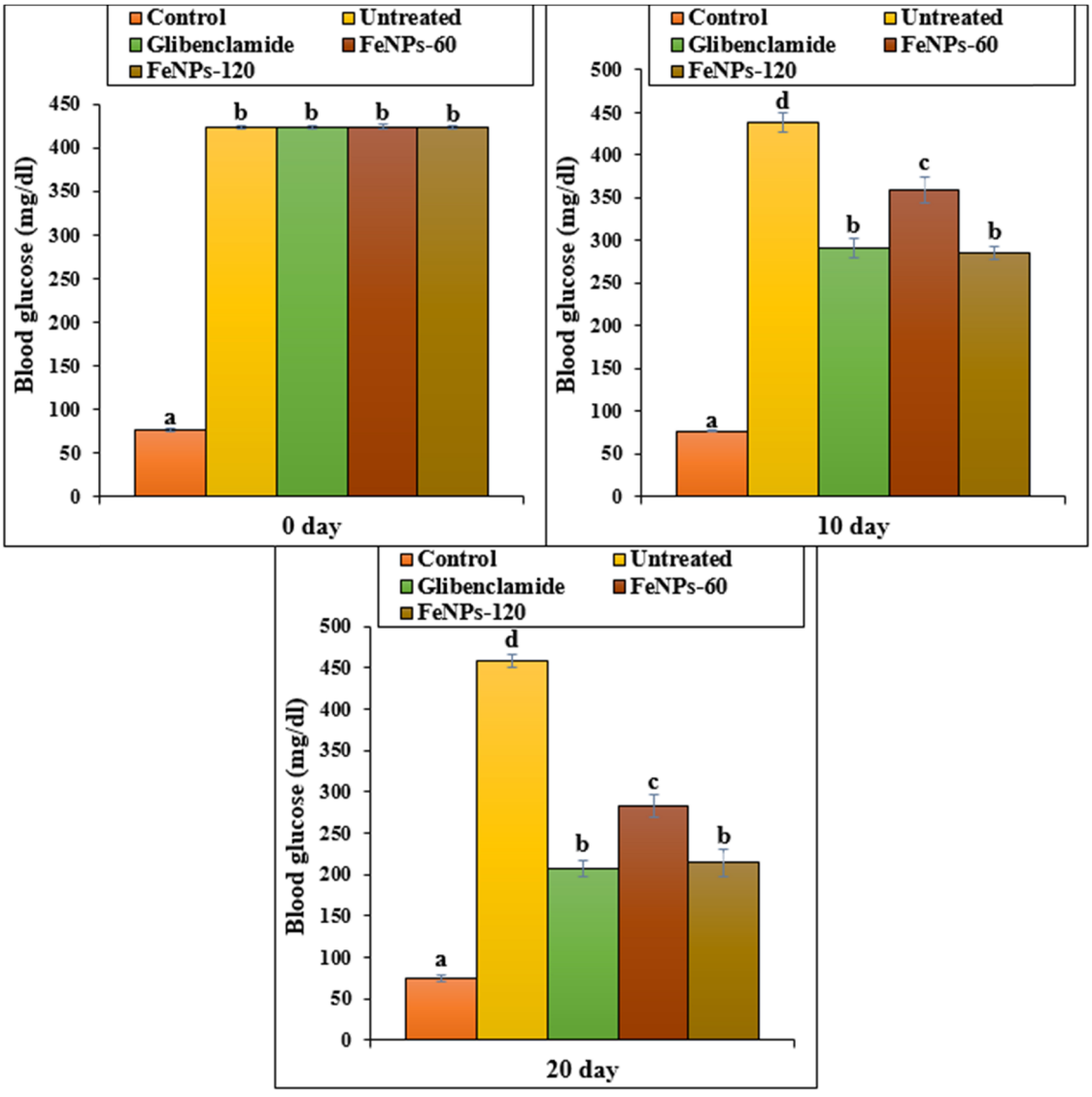

Figure 5: Blood glucose levels on 0, 10, and 20 days in treated animals.

The untreated diabetic rats showed a notable increase ($p \leq 0.05$) in the volumes of liver sub-compartments when compared to the control rats (Figures 8–10). However, the administration of FeNPs at both doses was able to significantly ($p \leq 0.05$) decrease the liver structures volume. There were no considerable variances ($p \leq 0.05$) detected in the aforementioned parameters between glibenclamide and FeNPs-120.

The inhibitory effects of FeNPs at various concentrations are illustrated as inhibition (%) in Figure 11. The IC_{50} value for FeNPs in combating DPPH free radicals was found to be 84 µg/mL, respectively, as shown in Figure 11.

It is theorized that nanomaterials may pose a higher toxicity risk as compared to micro-compounds, attributed to their elevated surface potential and activity for cellular penetration and accumulation [10–13]. Experimental results have shown that oxidative stress can significantly contribute to the cytotoxic effects of NPs on human carcinoma cells [12–14]. Consuming a significant amount of compounds and NPs that contain them through oral ingestion typically results in harm to the digestive system. Prolonged consumption of NPs (high concentration) can result in conditions such as pancreatic failure, anemia, and a reduction in dense lipids within the body [14–16]. Based on the findings from the pancreas and liver histopathological analyses, it is apparent that the NPs concentration produced through biological means, although possessing anti-diabetic efficacies, did not exhibit any notable toxic effects on either pancreas or liver tissues. Nevertheless, non-biological NPs synthesized within the liver tissue exhibit harmful properties, in contrast to biological NPs. However, no adverse tissue reactions were detected in the pancreas following NP treatment. Hence, the results of this investigation demonstrated that the artificially produced NPs exhibited

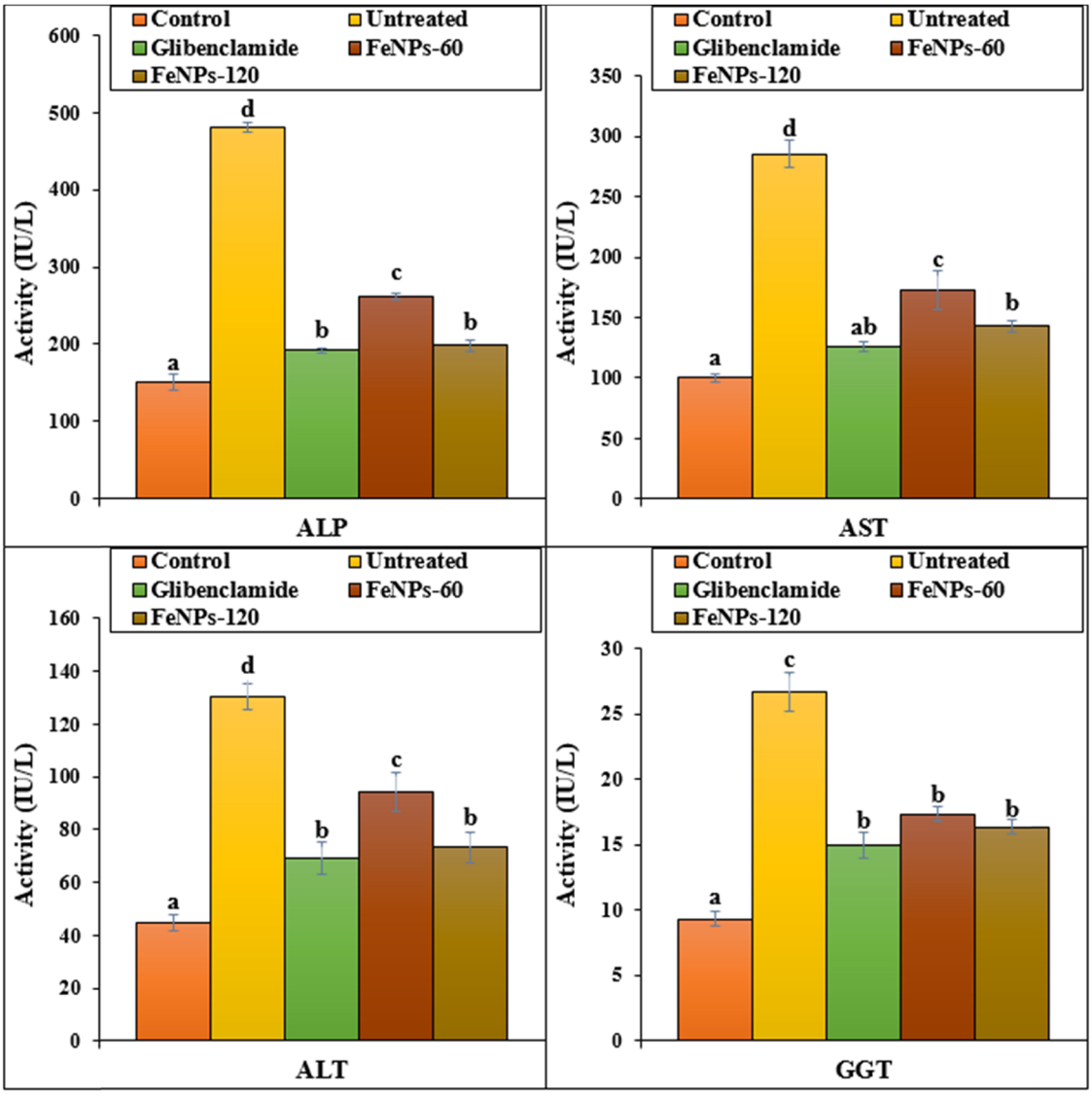

Figure 6: ALP, AST, ALT, and GGT levels in treated animals.

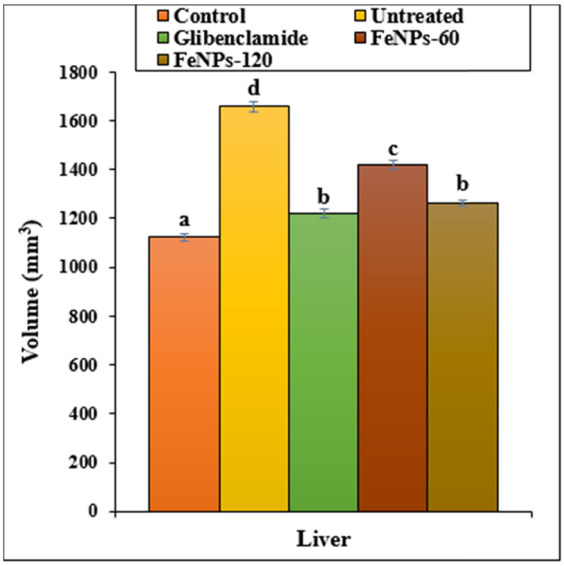

Figure 7: Volume of liver in treated animals.

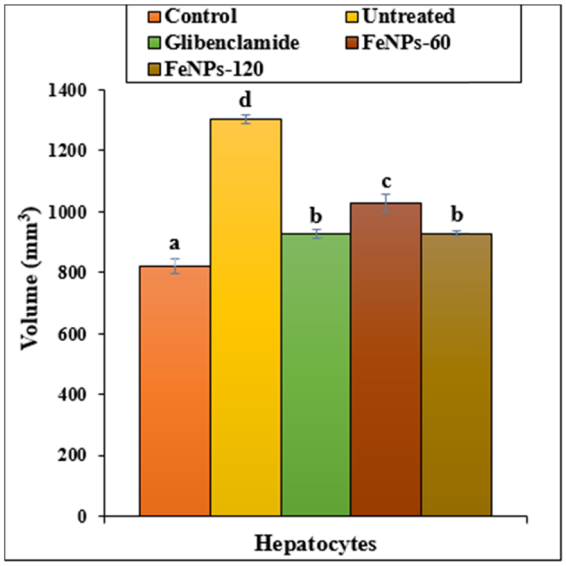

Figure 8: Volume of hepatocytes in treated animals.

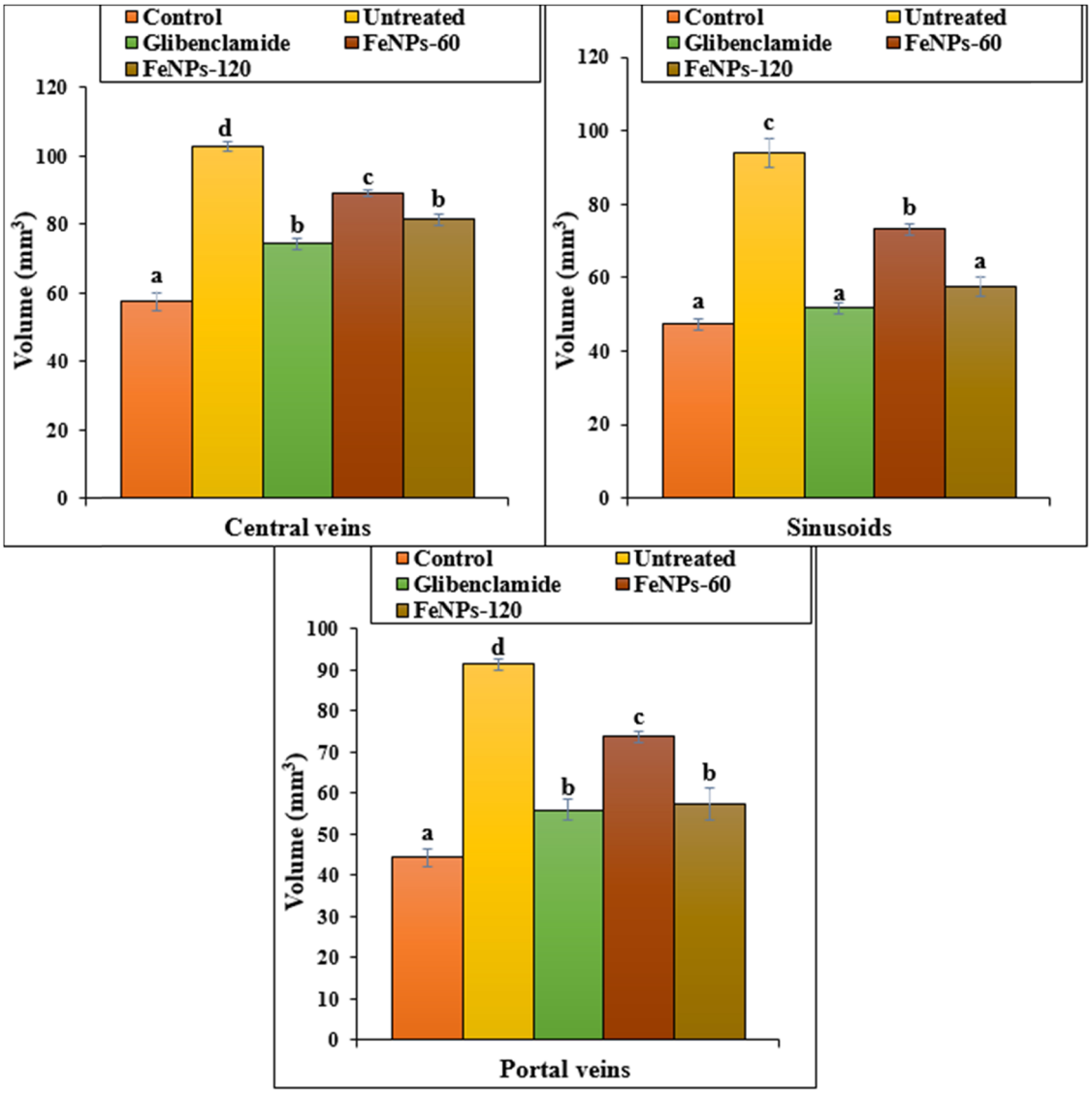

Figure 9: Volume of portal veins, sinusoids, and central veins in treated animals.

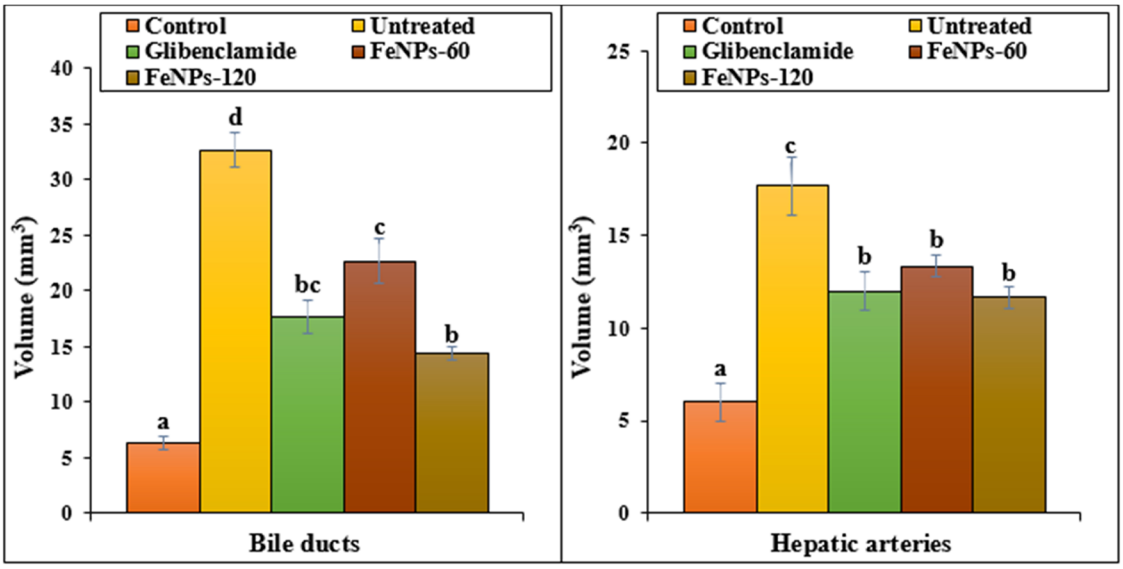

Figure 10: Volume of hepatic arteries and bile ducts in treated animals.

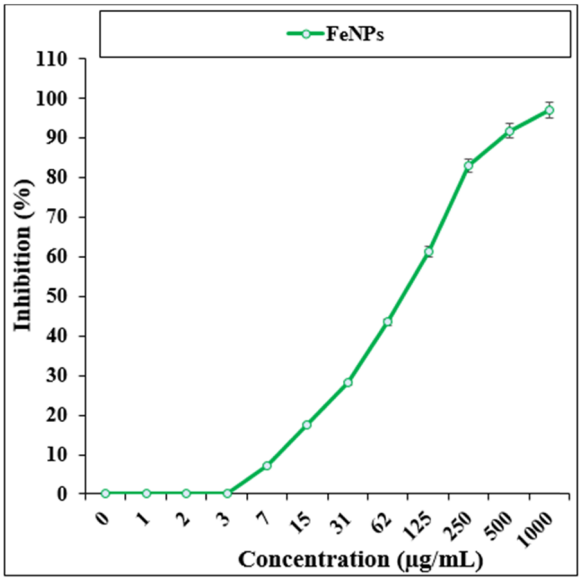

Figure 11: Antioxidant properties of FeNPs against DPPH.

favorable outcomes in safeguarding the liver and pancreas tissues in diabetic rats. Given the expanding scope of clinical research on the utilization of medicinal plant extracts, numerous plants with distinctive anti-diabetic properties have been employed. Recent advancements have shown that medicinal plants containing antioxidant and anti-inflammatory efficacies have the potential to alleviate complications arising from liver and pancreas diseases [10–13]. A novel approach that has gained traction involves enhancing the efficacy of these compounds in biological tissues through metal nanomaterials synthesis using plant-derived active ingredients [15–19]. Various research studies have demonstrated the protective properties of medicinal plants containing diverse flavonoid, anthocyanin, and phenolic compounds on various organs including the kidney, pancreas, and liver [46–49]. Furthermore, investigations into the effects of different NPs on the human body have revealed that their small size and ability to easily penetrate cells have led to significant harm in the examined studies [44–46]. In contrast to the findings suggesting harmful impacts of NPs on living tissues, this study did not observe any notable tissue effects. The outcome of this research suggests that even at low concentrations, NPs do not disrupt the body tissues functioning [13–17] through drug delivery. Regulating the frequency and dosage of NPs can lead to notable therapeutic outcomes and minimize the potential side effects. Since glibenclamide has some side effects such as arthralgia, intense hunger, heart disease, anorexia, dark urine, confusion, psychomotor agitation, yellow eyes and skin, hematemesis, skin redness or mild rash, hypoglycemia, dizziness, difficulty with swallowing, difficulty with moving, fatigue or weakness, headache, blurred vision, abdominal pain, heartburn, fast heartbeat, diarrhea, nausea, chills, and anxiety, the recent NPs may be used as a novel therapeutic drug with low side effects for the treatment of gestational diabetes after conducting clinical trial studies in humans [56].

4 Conclusion

The present investigation entails an environmentally friendly technique for the *in situ* FeNPs immobilization facilitated by

plant extract, devoid of the utilization of any hazardous capping and reducing agents. The characterization of the physicochemical, morphology, and structure properties was conducted. The DPPH free radical scavenging assay confirms the antioxidant properties of FeNPs. The IC_{50} value of FeNPs for inhibiting the DPPH free radicals was 84 µg/mL. The findings from the *in vivo* study suggest that both doses of FeNPs demonstrated notable antihyperglycemic effects comparable to those seen in diabetic mice treated with glibenclamide. The data of this research suggest that the biological nanoparticles produced using plant extract demonstrated a notable impact on regulating blood glucose levels in diabetic rats, while showing no adverse effects on the pancreas and liver tissues. Additionally, improvements were observed in stereological, histopathological, and biochemical parameters, indicating potential value in the treatment of diabetes. Through further research and identifying the most effective concentration of biological nanoparticles, significant progress has been made in managing and treating a range of illnesses.

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Conflict of interest: Authors state no conflict of interest.

Ethical approval: The conducted research is not related to either human or animals use.

Data availability statement: The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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