https://doi.org/10.48047/AFJBS.7.4.2025.1462-1492

African Journal of Biological Sciences

Journal homepage: http://www.afjbs.com

Research Paper Open Access

Hypoglycemic and antioxidant effects of the aqueous extract of *Suaeda mollis (Desf.) Delile* in Streptozotocin-induced diabetic rats.

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Volume 7, Issue 4,Apr 2025

Received: 15 Feb 2025

Accepted: 05 Mar 2025

Published: 05 Apr 2025

doi:10.48047/AFJBS.7.4.2025.1462-1492

Abstract

Diabetes is a metabolic disorder marked by chronic hyperglycemia and oxidative stress, leading to severe health complications. In search of alternative treatments, researchers are investigating medicinal plants with unstudied therapeutic potential, *Suaeda mollis* is one such plant that remains insufficiently explored. This study aimed to assess the antidiabetic and antioxidant properties of its aqueous leaf extract (AES) in both healthy and streptozotocin-induced diabetic rats. The study used the Fourier Transform Infrared Spectroscopy analysis (FTIR) to identify functional groups of phytochemicals, quantified polyphenols and flavonoids, and assessed antioxidant activity via DPPH, FRAP, and TAC assays. The hypoglycemic effect of AES was tested in STZ-induced diabetic Wistar rats over two weeks. Serum biochemical and hematological parameters were measured, and oxidative stress markers (MDA, SOD, CAT, GSH, GPx) in pancreatic homogenates and pancreatic histopathology changes were evaluated. FTIR analysis identified five functional groups in AES, which also exhibited high polyphenol and flavonoid contents and strong antioxidant activity. The extract significantly reduced blood glucose and enhanced antioxidant defenses in diabetic rats. However, it increased serum creatinine and pancreatic MDA levels. Histopathological analysis showed partial restoration of pancreatic islet structure. *Suaeda mollis* shows promising antidiabetic and antioxidant effects, but further research is needed to confirm its safety as a therapeutic agent.

Keywords: Antidiabetic- Antioxidants- FTIR- Oxidative stress- STZ- induced diabetes- *Suaeda mollis*.

Introduction

Diabetes mellitus (DM) is a devastating chronic and metabolic disorder characterized by persistent hyperglycemia resulting from defects in insulin or its action, which can lead to severe complications including cardiovascular disease, neuropathy, and nephropathy (Reddy, 2018).

Findings from the International Diabetes Federation 10th edition (IDF) confirmed that diabetes is one of the major health emergencies. It is estimated that 537 million people have diabetes, and this number is projected to reach 643 million by 2030 (IDF, 2021). As the global prevalence of diabetes continues to rise, there is an urgent need for effective therapeutic strategies that not only manage blood glucose levels but also mitigate the associated oxidative stress, a key factor in the progression of diabetic complications (Kooti et al., 2016). Oxidative stress occurs when there is an imbalance between reactive oxygen species (ROS) production and the body's antioxidant defenses. In the context of diabetes, elevated blood glucose levels can exacerbate oxidative stress, causing cellular damage and accelerating the development of diabetic-related issues (Gerber and Rutter, 2017; Salazar-García and Corona, 2021). Antioxidant mechanisms, therefore, play a crucial role in neutralizing ROS and protecting against oxidative damage, making them a vital component in the management of diabetes (Bhatti et al., 2022). Nutritional antioxidant derived from dietary sources have gained significant attention due to their potential to improve antidiabetic therapy (Krawczyk et al., 2023). For centuries, there has been growing interest in the use of natural products, particularly plant-based therapies, for managing diabetes and its complications through antihyperglycemic, antioxidant and anti-inflammatory mechanisms (Wasana et al., 2021). Many plants, traditionally used in folk medicine, have been found to possess potent antidiabetic and antioxidant properties. These natural remedies offer a promising alternative to synthetic drugs, which often come with undesirable side effects (Alam et al., 2022). Antioxidant plants, especially halophytes, provide a renewable source of bioactive compounds for food, cosmetics, and medicinal applications (Ksouri et al., 2012). Recent research indicates that these plants have multiple biological impacts due to their high concentrations of secondary metabolites, including polyphenols, which have shown potential in reducing oxidative stress (Hymery et al., 2021). *Suaeda mollis (Desf.) Delile*, a halophytic plant belonging to the Amaranthaceae family grown throughout arid and semi-arid range lands of Mediterranean basin, is one such plant that has garnered attention for its medicinal properties (Nedjimi, 2018). Traditionally used in various cultures for its purported health benefits, *S. mollis* has been reported to exhibit anti-inflammatory, anticancer, and antioxidant activities (Oueslati et al., 2023). The antidiabetic and antioxidant effects of *S. mollis* have not been fully explored *in vivo*, particularly in the context of diabetes induced by Streptozotocin (STZ), a compound commonly used to induce experimental diabetes in animal models. The primary objectives of this study were to identify the functional groups of the

bioactive compounds found in the aqueous extract of *S. mollis* (AES), quantify the polyphenol and flavonoid contents, and assess the antioxidant potential of the extract. Additionally, this research aimed to investigate the hypoglycemic effects of AES on STZ-induced diabetic rats, analyze oxidative stress markers in pancreatic homogenate and examine the histological changes of the pancreas, which provides a comprehensive insight to the therapeutic benefits of the extract for managing diabetes and oxidative stress.

Material and methods

Chemicals and reagents

All chemical products used in this study were purchased from Sigma-Aldrich Chemical Co. (St. Louis, MO, USA).

Plant material

Suaeda mollis (Desf.) Delile was collected in the Djellal area (34.92° N, 6.89° E; Khenchela-Algeria) and identified by Dr. Boughediri Larbi from the Department of Biology at Badji Mokhtar University, Annaba-Algeria, basing on the descriptions provided by (Ozenda, 1991). Only the leaves of the plant were utilized, they were cleaned and air-dried at room temperature in a shaded area to prevent degradation of bioactive compounds. Once fully dried, the leaves were ground into a fine powder using an electric grinder. The prepared powder was stored in an airtight container at room temperature until further use.

Preparation of the aqueous extract

The aqueous extract was prepared by adding 10 g of plant powder to 100 mL of distilled water, and putted on magnetic stirring for 24 hours. The mixture was then filtered to separate the micelle from the marc using Whatman cellulose filter papers. The filtrate was evaporated in an oven to obtain the dried extract, which was stored at 4°C in the dark for future use. For *in vivo* experiments, the extract was freshly prepared daily, with a concentration of 200 mg of the dried extract per 1 kg of rat body weight (BW), dissolved in 1 mL of water.

In vitro study

Fourier transform infrared resonance analysis (FTIR)

Functional groups in AES were detected using (FTIR; Agilent Cary 630, USA spectrometer). The measurements were performed between 25°C and 27°C and recorded from 400 to 4000 cm^{-1} with a spectral resolution of 4 cm^{-1}. This technique was used to determine the functional groups of the bioactive chemicals present in the extract, which was separated by its peak's wavenumbers. FTIR

transmittance spectrum was designed via Origin 2019b 64 Bit version, in which the spectrum was reprocessed using a baseline correction and smoothing to reduce the noise.

Determination of the total phenols content (TPC)

The polyphenols are determined using Folin-Ciocalteu reagent, according to the technique described by (Agbor et al., 2014). The absorbance is measured at 765 nm, and the total amounts of phenols are expressed in milligram of gallic acid equivalent per gram of extract's dry weight (mg GAE/g DW) based on a gallic acid standard curve.

Determination of the total flavonoids content (TFC)

Flavonoids were determined using the aluminium chloride colorimetric method (Pourmorad et al., 2006). The measurement of absorbance was carried out at 415 nm, and the flavonoids content is expressed in milligrams of quercetin equivalent per gram of extract's dry weight (mg QE/g DW) based on a quercetin standard curve.

Assessment of antioxidant activities

The antioxidant potential of AES was evaluated using the following spectrophotometric methods:

The Radical scavenging evaluation

To evaluate the scavenging ability of the 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical, the adopted approach was suggested by (Kabir et al., 2016). Quercetin has been used as a standard, and absorbance was measured at 517 nm. The result was shown as the amount of extract required to capture 50% of radicals (IC50 mg/mL).

The Ferric Reducing Antioxidant Power (FRAP) was measured using the technique described by (Yildirim et al., 2001). This method is based on the extract's ability to deliver an electron while converting ferric iron from ferric tripiridyl (Fe^{3+}) to a ferrous form (Fe^{2+}). When antioxidants are present in the extract, this reaction produces a detectible blue color at 700 nm. As a result, a high absorbance indicates that the extract possesses strong reducing potential. The result was presented as (EC50 µg/mL), which is the half-maximum effective concentration necessary to achieve a greater potency.

The Total antioxidant capacity (TAC)

The phosphomolybdenum assay is based on the reduction of molybdenum Mo (VI) present in the form of molybdate ions MoO_4^{2-} to molybdenum Mo (V) MoO^{2+} in the presence of the extract or an antioxidant agent. At an acidic medium, this reduction results in the creation of a greenish complex (phosphate/Mo (V)). The increase of this complex coloration in the presence of an

antioxidant is detected at 695 nm (Prieto et al., 1999). Ascorbic acid is used as a standard and the results obtained are expressed in milligram of ascorbic acid equivalent per gram of the extract's dry weight (mg AAE/g DW).

***In vivo* study**

Animals

Adult male Wistar rats, weighing 150 - 300g from Pasteur Institute in Algiers- Algeria were selected and housed under standard environmental conditions (24±1°C), with 12 h light and 12-h dark cycles. The rats had a free access to standard food pellets and water *ad libitum*. The Ethical Committee of the Directorate General for Scientific Research and Technological Development at Algerian Ministry PNR/SF 08/2012 approved all healthcare procedures.

Induction of experimental diabetes

Streptozotocin was injected intraperitoneal (IP) as a single dose of 60mg/kg to the rats after an overnight fasting. For this purpose, distilled water was used to dissolve STZ, the solution was freshly prepared to reach final concentration of 20 mg/mL just before use (Al-Hariri, 2012). After 1h, all the injected rats received glucose to avoid the hypoglycemic effect of STZ. After 3 days, only rats with a fasting glucose level of 2.5 g/l were selected for the group of diabetics.

Groups design

The study was conducted using 20 adult rats, which were divided into four groups, each containing five rats. The groups were formed based on the rats' body weight, ensuring that the animals in each group had similar weights:

Group 1 (Control group): Normal, healthy rats with no treatment, serving as the baseline for comparison.

Group 2 (STZ): The diabetic control, rats in this group were injected with STZ via a single IP dose (60mg/kg) to induce diabetes. The purpose of this group was to observe the influence of STZ on rats.

Group 3 (AES): Normal rats treated orally with (200 mg/kg) of AES, assessing the extract's effects on non-diabetic rats.

Group 4 (STZ+AES): Rats received STZ (60mg/kg) than treated orally with (200 mg/kg) of AES for two-weeks, evaluating the therapeutic effects of the extract on diabetes conditions.

The body weight of rats (BW) was recorded and blood glucose levels were measured by a reflective glucometer (Vital-Check, MM1200) in the 1^{st}, 3^{rd}, 5^{th}, 10^{th} and 15^{th} days of the experiment.

Blood collection

After two-weeks of the experiment, rats were fasted an overnight before being sacrificed by cervical decapitation to avoid animal stress, and the total blood was separated into tubes containing ethylenediaminetetraacetic acid (EDTA) as an anticoagulant, and tubes without EDTA. The tubes with EDTA were utilized for hematological analysis (counts of the White Blood Cells (WBC), Lymphocytes (LY), Monocytes (MO), Granulocytes (GR), Red Blood Cells (RBC), Hemoglobin (Hb), and Platelets (PLT), which were measured using an automated cell counter (ERMA INC-PCE 210; Japan). The tubes without anticoagulant were centrifuged at 3000 rpm for 15 minutes at 4°C. The resulting serum was then stored in the Eppendorf tubes at -20°C for biochemical analysis (the serum levels of creatinine, uric acid, albumin, total proteins, alanine aminotransferase (ALAT) and aspartate aminotransferase (ASAT), were estimated using an automated biochemical analyzer (VITROS® 5600 Integrated System, Quidel Ortho Corporation; USA).

Histology

Animals were dissected, the pancreas was quickly removed, carefully cleaned from fat, and weighted before being preserved in 10% formaldehyde. Pancreatic samples were rinsed, dehydrated with an increasing concentration of ethanol (70%, 95%, and 100%), and cleared in cyclohexane. After 12 h of paraffin impregnation in an incubator at 60C°, samples were then embedded in paraffin blocks. Subsequently, the blocks were sliced using a (Leitz 1512) rotary microtome (Marshall Scientific, Hampton, NH 03842, USA). After dewaxing and rehydration, the sections were stained with hematoxylin and eosin (Hould, 1984). The resulting slides were then observed under a light microscope (Leica Microsystems, DM 1000 LED) and the digital camera (Leica ICC50 HD) was used to take micro-photographs for histopathology study.

Determination of oxidative stress biomarkers

In order to prepare the pancreatic homogenate, the fresh pancreas samples were homogenized at a rate of 1:2 w/v in a Tris-Buffered Saline (TBS): 50 mm Tris, 150 mm NaCl, pH 7.4, and centrifuged (9000xg/15 minutes/4°C). The obtained supernatant was conserved at -20°C for the assessment of oxidative stress markers.

The glutathione (GSH): The assay was performed following the method developed by (Weckbecker and Cory, 1988). It is based on measuring the optical absorbance at 412 nm of the 2-nitro-5-mercapturic acid resulting from the reduction of 5,5-dithio-bis-2-nitrobenzoic acid (DTNB) by the (-SH) groups of glutathione.

The glutathione peroxidase (GPx): The enzymatic activity of GPx was assessed using the method of (Flohé and Günzler, 1984), which relies on the reduction of hydrogen peroxide (H_2O_2) in the presence of GSH. Optical densities were measured at 412 nm.

The superoxide dismutase (SOD): This assay was assessed using the nitro blue tetrazolium (NBT) method relies on the photo-reduction of the riboflavin/methionine complex, which generates superoxide anions (O^{2-}) (Beyer and Fridovich, 1987). The oxidation of NBT by O^{2-} is employed for detecting the presence of SOD. In an aerobic environment, the combination of riboflavin, methionine, and NBT results in a bluish coloration. The presence of SOD hinders the oxidation of NBT. The absorbances of the samples are measured at 560 nm.

The malondialdehyde (MDA): This assay was performed using the method of (Esterbauer et al., 1991). It is based on the condensation of MDA in an acidic and hot environment with thiobarbituric acid (TBA), resulting in the formation of a pink pigment. This chromogen can be measured at 530 nm.

Catalase (CAT): It was determined using the technique of (Aebi, 1984). Absorption was recorded at 240 nm every 15 seconds for 1 minute.

The Bradford test was used to determine pancreatic protein concentrations (He, 2011). Serum bovine albumin (BSA) was utilized as a standard.

Statistical analysis

The data is presented as (mean±SEM). Results were analyzed using one-way (Sidak test for multiple comparisons) or two-way (Tukey's post hoc test) analysis of variance (ANOVA) using GraphPad prism 8.0.2 (263) (Graph-Pad Inc., San-Diego, CA, USA). $p<0.05$ or less was considered statistically significant.

Results

Fourier transform infrared resonance analysis (FTIR)

The FTIR analysis of AES is illustrated in Figure 1. The results from the spectrum showed the presence of 5 elongation bands. The presence of a broad and strong rounded band at 3338.76 cm-1 was due to hydrogen bonding vibration of the hydroxyl (O-H) group. Alkyne (C≡CH) group is shown by the presence of a weak elongation band at 2109.21 cm-1. The intense elongation band in 1610.68 cm-1 indicated the (C=C) stretching vibration from the aromatic rings of phenols. (C-H) group bending vibration was assigned in 1360.25 cm-1. We noticed also an elongation with a

wavenumber of 1072.54 cm-1 which referred to (C-O) function group. At 491.31 cm-1 we observed a simple final band that could be associated with inorganic components.

Phytochemical compounds (TPC and TFC)

The extraction yield (%), TPC and TFC in AES are showed in Table 1. Using the method of maceration to obtain the dry water extract, we found that the percentage of extraction yield was 14.18 %. The assessment of the phenolic compounds and flavonoid concentrations revealed that TPC and TFC were (19.30 mg GAE/g DW and 80.66 mg QE/g DW respectively).

Anti-radical and antioxidant activities of AES

According to the estimation of in vitro antioxidant activity using the DPPH and FRAP scavenging methods, and TAC showed in the Table 2, our results revealed that the AES had a strong DPPH radical scavenging power of 0.39 mg/mL, an important ferric reduction ability of 434.65 µg/mL, and the TAC was assessed at 2.57 mg AAE/g DW.

Effect of treatment on blood glucose level

The effect of two-weeks treatment with AES on blood glucose levels is given in the Figure 2. After 48 hours of administering STZ (60 mg/kg), the blood glucose levels of (STZ+AES) rats group exhibited a statistically highly significant increase ($p<0.001$) compared to the control group. Similar results were observed on the (STZ) group during the entire experimental period. On the other hand, daily oral intake of AES in (STZ+AES) group induced a significant decrease ($p<0.01$) in the blood glucose level after 3 days of treatment compared to (STZ). It remained consistently decreased ($p<0.001$) started from the 5th day of the treatment until the end of the experiment.

Variation of body weight (BW) and pancreatic relative weight (PRW)

Body weight and pancreatic relative weight changes are illustrated in the Table 3. Concerning the change in BW during the experimental period, our results showed that the average BW of (STZ) group decreased significantly ($p<0.001$; -16.34%) in comparison to the control group. In the (STZ+AES) and (AES) groups, we observed a significant increase in BW ($p<0.001$; +6.20% and +18.11%, respectively). However, this increase was lower than that noticed in the control group (+46.18%). Whereas, the treatment with AES increased significantly ($p<0.001$) the BW in (STZ+AES) group compared to (STZ) group. Our data indicated a notable significant reduction ($p<0.05$) in the PRW for both groups the treated (STZ+AES) and untreated (STZ) diabetic rats compared to the (C) group. There were no significant changes observed on PRW of (AES) group.

Hematological study

The effects of STZ-induced diabetes and AES treatment on the complete blood count (CBC) is represented in the Table 4. Our results showed a significant decrease in the count of WBC ($p<0.05$) and LY ($p<0.001$), besides a statistically highly significant increase ($p<0.001$) of MO and RBC in (STZ) group compared to control. However, no significant differences have been noticed in the other hematological parameters (GR, Hb and PLT) in (STZ) group. The phytotherapy using the AES has increased GR level ($p<0.001$) but decreased significantly the levels of MO ($p<0.01$), Hb ($p<0.001$) and RBC ($p<0.05$). On the other hand, compared to control group, the daily oral intake of AES produced a significant decrease on LY ($p<0.001$) and PLT ($p<0.01$) in (STZ+AES) group. Moreover, in (AES) group we recorded a significant decrease on the level of LY ($p<0.05$) and an increase on the PLT number ($p<0.05$).

Biochemical parameters

Table 5 shows the effects of STZ induced diabetes and AES supplementation to biochemical compounds in the serum of diabetic and treated rats after two-weeks of treatment. Diabetic rats showed a significant increase on creatinine ($p<0.05$), uric acid ($p<0.05$), ASAT ($p<0.001$), ALAT ($p<0.01$), albumin ($p<0.001$) and total protein ($p<0.05$) compared to control rats. However, the treatment of diabetic rats with the AES has significantly decreased ($p<0.001$) ASAT, albumin, total protein, and ALAT ($p<0.01$) levels compared to (STZ) group. Comparing (STZ+AES) to control group, the assessment of a daily AES consumption exhibited a significant increase of creatinine ($p<0.001$) but a decrease on the total protein level ($p<0.01$). in (AES) group, we noticed that the plant's extract produced an increase on the level of albumin ($p<0.01$), and creatinine ($p<0.001$), however, it significantly decreased ($p<0.01$) the level of ASAT and total protein compared to control.

Oxidative stress parameters

The effects of STZ and AES on enzymatic antioxidants, reduced-GSH and MDA levels of pancreas homogenate are illustrated in Figure 3. In (STZ) group, there were a significant high levels of pancreatic antioxidant enzymes ($p<0.001$; GPx, SOD) and CAT ($p<0.05$). The same results were observed in the concentrations of GSH ($p<0.001$) and MDA ($p<0.01$) compared to the control group. On the other hand, it was noticed that the treatment in (STZ+AES) exhibited a significant decrease ($p<0.001$) of SOD and GPx levels. However, a highly statically significant increase was recorded on the level of MDA ($p<0.001$) compared to (STZ) group. in (AES) group, the oral administration of AES caused an obvious augmentation in MDA ($p<0.01$), GSH and CAT

(p<0.001) levels. Additionally, we observed a significant increase (p<0.001) on pancreatic CAT, GSH, MDA and SOD (p<0.05) levels in (STZ+ AES) group compared to control.

Histological study

Figure 4 presents photomicrographs highlighting the histological changes in the pancreas of the different experimental groups after two weeks of AES treatment in both normal and diabetic rats. In the control group (Figure 4. A), the pancreatic islets showed a typical histological architecture without any visible abnormalities. In contrast, (Figure 4. B) reveals that the pancreas of rats in the (STZ) group exhibited severe histopathological changes representing a degeneration and necrosis of pancreatic cells, with many cells showing pyknotic nuclei (indicated by red circles). The (Figure 4. C) demonstrates the pancreas of normal rats treated with AES, shows well-preserved pancreatic tissues with intact acinar cells and normal islet structure. Finally, (Figure 4. D) illustrates the pancreas from the (STZ+AES) group, showing a partial restoration of the Langerhans islets' normal structure with a slight hypertrophy and near-normal cellular composition (red arrow).

Discussion

Our research has focused on diabetes mellitus, which is one of the most frequent metabolic and endocrine disorders. We have investigated the hypoglycemic and antioxidant properties of AES in both, normal and diabetic rats. The application of traditional medicinal plants is proving to be the solution to the researches of scientists for the good management of diabetes. In order to identify the functional groups of the bioactive compound present in the plant and responsible of its possible effects, we used the Fourier-Transform Infrared spectroscopy as a potent and specific analytical technique. The result from the FTIR analysis spectrum revealed the existence of five peaks for various functional groups. Our results showed that AES contains a hydroxyl (O-H) group (broad signal at 3338.76 cm^{-1}) and aromatic carbons (C=C) which were noticed as a sharp elongation at 1610.68 cm^{-1}. These vibration signals are similar to those reported in the literature cited that these functional groups might come from phenolic compounds existed in this extract (Fatiqin et al., 2021; Mughal et al., 2024; Ramírez-Hernández et al., 2019). Moreover, AES also contained an alkyne (C≡CH) group (2109.21 cm^{-1}) and aldehyde (C-H) bending (1360.25 cm^{-1}). The band in 1072.54 cm^{-1} of (C-O) functional group, which is referred to aromatic ethers (acids and flavonoids likely flavanone) as reported by many authors (Hafizah et al., 2017; Noh et al., 2017). The final elongation band at 491.31 cm^{-1} showed the presence of some minerals as well as certain metal ions complexes. Using gamma-ray spectrometry, Nedjimi (2018), revealed that Suaeda mollis contains

a high quantity of calcium, potassium, cobalt, and sodium (Nedjimi, 2018), which at low concentrations could enhance the antioxidant potential and anti-inflammatory properties of the plants (Chouala et al., 2024; Kasote et al., 2015).

In our phytochemical study, we evaluated the % of the extraction yield and the amount of polyphenols and flavonoids in AES. We found an extraction yield percentage that was a fourfold higher (14.18%) compared to a prior study, which reported a low extraction yield ratio of 3.6% in the aqueous extract of *S. mollis* collected in Al Jouf area (Amin and Musa, 2016). The % of a plant yield could be influenced by the polarity of the solvent and the used extraction method, as mentioned by (El Mannoubi, 2023). Our findings suggests that the extraction yield may be influenced by several other factors, including the seasonal growth cycle and the maturity of the plant parts, as well as proper drying and storage conditions to prevent decomposition. Furthermore, a high phenolic compound continent (19.30 mg GAE/g DW) has been observed in AES. This data aligns with previous study indicating that the TPC was 24.51 mg GAE/g DW in the 80% acetonic extract of *S. mollis* collected in Tunisia (Oueslati et al., 2012). Whereas a low concentration of polyphenols (2.28 mg GAE/g DW) were reported in the aqueous extract of the same plant collected in Al Jouf area (Amin and Musa, 2016). In addition, we found also a high level of flavonoids concentration (80.66 mg QE/g DW) compared to other study (Amin and Musa, 2016) which obtained an TFC of 7.43 mg QE/g DW. These findings indicated that the plant's biotope as well as the mineral composition and physical properties of soil may greatly influence the variations of polyphenols and flavonoids rates through metabolic changes and transcriptional control, which in turn, affects the plant's stress tolerance and nutritional value (Heimler et al., 2017; Messaoudi et al., 2022).

A various assays have been used to assess the antioxidant potential of plants, often relying on spectrophotometric methods that either measure free radical scavenging or quantify the products of reactions involving either a single electron or hydrogen atom transfer (Christodoulou et al., 2022). In this study, the antioxidant activity of AES was assessed using the FRAP, DPPH, and TAC assays. The AES demonstrated strong scavenging activity against the DPPH radical (IC50 = 0.39 mg/mL), which is significantly higher than the values reported by Oueslati et al. (Tunisia) and Amin et al. (Al jouf area) for the same plant collected from different regions (IC50 = 2.5 µg/mL and 2.44 µg/mL, respectively), (Amin and Musa, 2016; Oueslati et al., 2012). These differences may be explained by variation in extraction methods, the used solvents, or the plant’s

growing conditions in different geographical locations. In the FRAP assay, the EC50 value for the ferric reducing ability of AES was 434.65 µg/mL, considerably higher than the EC50 of 130 µg/mL reported in prior research using an 80% acetonic extract (Oueslati et al., 2012). The lower FRAP activity of our aqueous extract could be attributed to its reduced ability to solubilize some potent antioxidant compounds, which are more effectively extracted by organic solvents like acetone. This aligns with findings from other studies on medicinal plants, which demonstrated that the antioxidant activity of plant extracts is heavily influenced by the polarity of the solvent and its capacity to extract various antioxidant substances (Lahmar et al., 2023; Tourabi et al., 2023). Furthermore, the TAC assay revealed a concentration of 2.57 mg AAE/g DW in the AES, which is lower than the value (23.29 mg AAE/g DW) observed in the acetonic extract from the aerial-parts of Tunisian *S. mollis* (Oueslati et al., 2012). This disparity may be due to differences in the quantities of secondary metabolites extracted by different solvents, the utilized specific parts of the plant, as well as environmental factors like soil composition and growing conditions.

In the current study, diabetes was induced in rats via a single IP injection of STZ at a dose of 60 mg/kg, which caused various symptoms commonly associated to diabetes, such as polyuria, polydipsia, and polyphagia. Moreover, the rats in (STZ) group exhibited a statistically highly significant increase in blood sugar level throughout the entire experimental period. Normally, elevated plasma glucose levels stimulate pancreatic β-cells to secrete insulin in order to maintain glucose homeostasis (H. Guo et al., 2023). Our findings confirmed that the STZ-induced diabetes protocol, in which STZ was dissolved in distilled water to reach a final concentration of 20mg/mL, led to an irreversible destruction of β-cells in the Langerhans's islets, consistent with previous reports (Al-Hariri, 2012; Noorafshan et al., 2004). The daily oral intake of AES for two weeks did not show an obvious hypoglycemic effect in normal rats. However, AES significantly lowered the elevated blood glucose levels in the (STZ+AES) group compared to the (STZ). These outcomes demonstrated that *S. mollis* has a hypoglycemic effect in diabetic rats. Plants are natural antioxidants and potent sources of phytotherapy, mainly because they contain antidiabetic compounds (flavonoids, phenols, tannins, and alkaloids), which improve pancreatic function by either increasing insulin secretion or decreasing glucose absorption in the gut (Kooti et al., 2016) Previous phytochemical findings from AES, have established that *S. mollis* leaves possessed a range of secondary compounds, with a significant presence of polyphenols and flavonoids. These bioactive compounds improve pancreatic tissue efficiency by stimulating insulin secretion,

increasing glucose uptake in peripheral tissues such as adipose and muscles, or inhibiting hepatic gluconeogenesis (Jeeva S and Anlin Sheebha Y, 2014). To our knowledge, this is the first study to report the significant antidiabetic effect of *S. mollis* and its antioxidant properties in vivo, using an STZ-induced diabetic rat model.

In the present study, STZ-induced diabetes caused a considerable loss in body weight of rats in (STZ) group compared to control, which remained decreased despite the polyphagia until the end of the experimental period. Previous studies found a significant loss of body weight in STZ-induced diabetic rats due to uncontrolled glucose levels. Also, Muscle atrophy attributed to the catabolism of amino acids in muscle tissue, degradation of fat from adipose tissues, and degeneration of structural proteins, which are known to be a major contributor to body weight loss (Bencheikh et al., 2020; Eluehike and Onoagbe, 2018; Tebboub and Kechrid, 2021). Furthermore, the excessive food intake has not led to weight gain as a result of insulin deficiency, because the destruction of pancreatic cells has considerably reduced the insulin levels (Akhtar et al., 2023). Which has rendered the body cells unable to use glucose as an energy source, prompting compensatory utilization of muscle proteins and fats from adipose tissues for energy production (Riyahi et al., 2016; Singh et al., 2022). On the other hand, treatment with AES significantly inhibited weight loss in the (STZ+AES) group compared to the diabetic group. This result may be attributed to the potential of this plant to reduce insulin resistance and enhance anti-inflammatory effects. Similar results found that some plants (*Holarrhena pubescens*, *Spondias mombin* and *Cichorium intybus*) can increase body weight in diabetic rats via there antihyperglycemic effect by reducing the blood sugar level and improving insulin sensitivity in cells (Akhtar et al., 2023; Eluehike and Onoagbe, 2018; Saravanamuttu and Sudarsanam, 2012). Body weight gain indicates that the anabolic effects have taken precedence over the catabolic ones (Al-Attar and Alsalmi, 2019). Contrary, some antidiabetic plants such as *Bauhinia holophylla* has decreased the body weight of diabetic animals, possibly due to its toxic effect (Pinheiro et al., 2017). The results from relative weight of pancreas in this investigation showed a significant decrease in PRW of treated (STZ+AES) and non-treated diabetic rats compared to control, in accordance with many previous studies (Alsharif et al., 2023; Eluehike and Onoagbe, 2018; Shawky et al., 2020). They confirmed that β-cells in the pancreatic islets of Langerhans die after STZ-injection, suggesting that the decrease in pancreatic relative weight is related to the degradation and atrophy of the islets, as found later in our histological study. However, a study found that the PRW remained unchanged,

as the pancreatic weight appeared to decrease proportionally with the overall reduction in body weight, rather than being directly influenced by the diabetic condition. (Muhammed Zafar and Syed Naeem-ul-Hassan Naqvi, 2010). Whereas, oral administration of AES showed no significant effect of PRW in (AES) group.

It has been reported that various hematological parameters could be a useful indicator in assessing the harmful effects of drugs as well as medicinal plants, which may also vary during diabetes (Mahmoud, 2013). In this study, we found that STZ administration significantly reduced the WBC and LY while increased the level of MO and RBC. These results are in consonance with findings by earlier researches (Fagbohun et al., 2020; Rehman et al., 2023). The increased monocytes level might be due to high blood sugar level, which prompted the bone marrow to generate more monocyte progenitor cells, leading to monocytosis (Kanter et al., 2020). Additionally, the decrease in LY and WBC counts can be attributed to the body's stress response following the injection of STZ (Helal et al., 2005). Prolonged hyperglycemia can lead to an increase in RBC level and cause damage to the cytoskeleton of the RBC's membrane due to oxidative stress. This damage leads to a low-grade inflammation that is linked to many complications of diabetes (Simmons, 2010; Williams et al., 2023). However, following to AES administration in (STZ+AES) group, the number of RBC and MO were appreciably reduced to near normal, besides an abnormal decrease in PLT and Hb levels but an increase in the number of GR. In contrast, the aqueous extract of stem bark of the antidiabetic plant *Afzelia Africana* has increased LY, MO and PLT in diabetic rats (Oyedemi et al., 2011). Other studies showed that some antidiabetic plants can lead to reduced Hb and PLT level as a compensatory mechanism of antioxidant and anti-inflammatory effects of the plants (Esmail Al-Snafi et al., 2019; Yilmaz, 2020). Besides, in some contexts, the reduction in blood glucose level may correlate with lower hemoglobin levels particularly in the plants influence RBC production or its survival (Esmail Al-Snafi et al., 2019). The aqueous extract of *S. mollis* might normalize the RBC level by using vital nutrients of the plant, which support blood cell formation (hematopoiesis), protect the red cells from oxidative stress damage, and maintain their integrity and function (Cherrada et al., 2024). The significant increase in GR and the decrease in MO levels could be as result of the plant's potential to prevent diabetes complications and treat the inflammations and damages caused by STZ induction.

Impaired kidney function and increased protein catabolism are associated with higher creatinine and uric acid concentrations, while albumin and total protein levels can be influenced by changes

in protein synthesis and muscle loss caused by diabetes. In this study, STZ-induced diabetic rats showed an increased levels of: creatinine, uric acid, ASAT, ALAT, albumin, and total protein which indicated a renal dysfunction and metabolic disturbances in the liver. Studies have shown that the effects of diabetes on renal function, liver damage, as well as total metabolism, are significantly affected by these biochemical markers in diabetic models (Alq and Hussein, 2021; Ghanbari et al., 2015; L. Guo et al., 2021). It was notable that the treatment with AES reduced the hepatic markers ASAT and ALAT to normal besides albumin and total protein levels but increased the level of creatinine (to diabetic and normal rats) which is considered as a sign of renal failure or nephrotoxicity caused by the plant's extract. These outcomes concorded with those reported that the *Talinum triangulare* flavonoids extract and *Nigella sativa* oil were effective in reducing the increased serum uric acid and liver enzymes in STZ-induced diabetic rats (Al-Logmani and Zari, 2011; Oluba et al., 2019). Creatinine is a waste product of muscle metabolism that is filtered by the kidneys. When kidney function is impaired due to nephrotoxicity, creatinine accumulates in the blood, resulting in elevated serum creatinine levels (Kim and Moon, 2012). Some plants, such as *Aristolochia* and *Rhubarb,* have been associated with nephrotoxicity and may contribute to increased creatinine levels due to kidney damage (Pearson et al., 2022), which aligns with our findings.

Hyperglycemia promotes the generation ROS, leading to oxidative stress, which plays a major role in the pathogenesis of diabetes, particularly in STZ-induced models. Besides, it contributes to the complications linked to diabetes (Bhatti et al., 2022). In the current study, increased activities of SOD, GPx, CAT, GSH and MDA have been observed in the pancreatic homogenate of (STZ) group. Persistent hyperglycemia in diabetes leads to elevated production of oxygen free radicals, resulting in lipid peroxidation, which generates MDA and increases membrane fluidity and permeability. Antioxidant enzymes such as CAT, GPx, and SOD play crucial roles in protecting cells from oxidative damage (Kakkar et al., 1995). Kakkar et al. (1995) noted that, heightened GPx activity in diabetes may prevent SOD inactivation caused by excessive H_2O_2, thereby increasing SOD activity and providing further protection to CAT and GPx from inactivation by O_2 anion. Ultimately, this sequence of events would enhance both CAT and GPx activity (Kakkar et al., 1995) . The rise in CAT activity is attributed to increased generation of H_2O_2, as reduced insulin levels enhance fatty acyl CoA oxidase activity, which triggers the oxidation of fatty acids and H_2O_2 production (Kakkar et al., 1995). Studies have indicated that catalase plays a role in detoxification

by facilitating the decomposition of H_2O_2 into H_2O and O_2, thereby providing protective effects against oxidative damage (Bhatti et al., 2022; De duve and Baudhun, 1966). Additionally, elevated glucose levels contribute to increased oxidative stress in pancreatic β-cells. The overexpression of GPx boosts its activity and shields Langerhans's islets from harmful effects including the accumulation of H_2O_2 and lipid hydroperoxides by facilitating their breakdown with GSH as a co-substrate (Salazar-García and Corona, 2021). Higher levels of GSH may safeguard cellular proteins from oxidation via GSH redox cycle to neutralize reactive oxygen species generated by STZ induced diabetes (Soliman et al., 2015). Furthermore, GSH is recognized for its ability to neutralize hydrogen and lipid peroxides (Bhatti et al., 2022). On the other hand, administration of AES significantly restored the normal pancreatic SOD and GPx levels, but it also increased the level of MDA in the pancreas of the (STZ+AES) group more than in the (AES) group. Additionally, we noticed an elevation in GSH and CAT levels compared to control group. This could be due to the presence of effective phytochemicals in the aqueous extract of Suaeda mollis leaves. Researchers suggested that the bioactive compounds such as polyphenols, flavonoids and terpenoids present in antidiabetic plants could lower reactive oxygen species, boost the antioxidant enzymes activities and improve insulin sensitivity (Alam et al., 2022; Krawczyk et al., 2023). When MDA presents at elevated levels, it enhances glucose-stimulated insulin secretion in pancreatic islets by upregulating the expression of key genes like glucokinase, glucose transporter 2 (GLUT 2) and pancreatic duodenal homebox 1 (PDX1) (Wang et al., 2014). Researchers have indicated that following to STZ exposure, GLUT2 improves β-cell survival, while STZ reduces GLUT2 expression, impairing glucose-stimulated insulin secretion and leading to β-cell dysfunction. Although some β-cells may survive the initial STZ injury, their reduced functionality due to lower GLUT2 levels creates a negative feedback loop, worsening hyperglycemia and lowering β-cell activity (Hahn et al., 2020; Hosokawa et al., 2001). Moreover, MDA affects the intracellular ATP/ADP ratio and cytosolic calcium levels, which are essential for insulin secretion (Wang et al., 2014). A previous study proposed that malondialdehyde (MDA), a marker of oxidative stress and lipid peroxidation, serves as a possible therapeutic target for preserving pancreatic β--cell function, playing a role in diabetes-related complications (Angie et al., 2024). We hypothesize that although the two-week AES supplementation did not fully counteract the antioxidant imbalance and cellular damage induced by STZ, a prolonged study could potentially restore this balance. Additionally, the increased MDA concentration in the pancreas may contribute

to lowering glucose levels by enhancing insulin secretion from the surviving β-cells and promoting glucose uptake through the upregulation of GLUT 2 expression.

The results of histological study showed altered pathological changes in pancreas as a result of STZ injection. We observed a reduced β--cell mass, pyknotic nuclei, potential islets atrophy and increased fibrous tissue in (STZ) group compared to control group. This alteration contributed to impaired insulin production and glucose metabolism, characteristics of diabetes. These findings are similar with those observed by Indu et al. (2019) where diabetes was induced in rats by STZ and nicotinamide (Indu et al., 2019). Another study in Egypt also reported a shrunken in the islets of Langerhans, β-cells, generative and necrotic changes (Barakat et al., 2020). Whereas, our data showed that treating the diabetic rats with AES has restored the Langerhans islet's structure nearly to normal, but we observed a slight hypertrophy. The same results were found when using the Watermelon peels (20%) as a treatment to STZ induced diabetic rats (Rezq, 2017). Islet hypertrophy can occur in response to various physiological and metabolic changes, such as increased insulin secretion during hyperglycemia. This enlargement may result from β-cell proliferation (Simeone et al., 2006). Additionally, in diabetic states, islet hypertrophy may develop as a compensatory mechanism to maintain insulin production despite cellular stress or damage (Nugent et al., 2008).

Conclusion

Based on our research, the use of the aqueous extract from *S. mollis* leaves as a natural supplement for two-weeks in Wistar rats, enhance the antioxidant defense system in diabetic rats due to its high content of phytochemical compounds like flavonoids and polyphenols and showed positive effects on improving STZ-induced hyperglycemia. This extract appears to decrease the blood glucose level and improve the survival and function of insulin-secreting pancreatic β-cells. However, our findings indicate that AES may elevate the level of creatinine in the bloodstream, suggesting possible nephrotoxicity. This study deserves to be conducted over a longer period to confirm the plant's effect on the studied parameters. Further investigation is necessary to identify and characterize the active compounds responsible for these effects, indicating its potential as a valuable addition to diabetes management approaches.

Acknowledgments

We thank the entire group of the "Laboratory of Biochemical and Environmental Toxicology" Faculty of Sciences, BADJI Mokhtar University, Annaba, Algeria. This study was supported by the Algerian Ministry of Higher Education and Scientific Research, Government of the Algerian Republic in Algeria.

Conflict of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

Data availability statement

The data is available in the manuscript. Additional data or information will be available on request.

Funding statement

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author Contributions

Abrazi Yamina performed the experiments, conducted the visualization and analysis of data, writing – review and editing and Writing – original draft. Boufermes Radia contributed in writing – review and editing, supervision and conceptualized the study. Kadi Assia and Messarah Mahfoud managed the project administration, ensuring smooth coordination and progress. Chiheb Nadia provided essential resources and support for the phytochemical study. Houicha Haroun performed the FTIR analysis.

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Table 1. Extraction yield, total phenols and flavonoid contents in the aqueous extract of Suaeda mollis leaves.

Parameters	Values
Extraction yield (%)	14.18
Total phenols (mg GAE/g DW)	19.30±1.32
Flavonoids (mg QE/g DW)	80.66±1.34

Values are presented as mean±SEM (n=3). g DW: Gram of extract's dry weight, GAE: Gallic acid equivalent, QE: Quercetin equivalent.

Table 2. Antioxidant activities of the aqueous extract of Suaeda mollis leaves.

Parameters	Values
50% scavenging on DPPH radical (mg/mL)	0.39±0.05
FRAP test (EC50) (µg/mL)	434.65±0.09
Total antioxidant capacity (mg AAE/g DW)	2.57±0.28

Values are presented as mean±SEM (n=3).

Table 3. The effects of the aqueous extract of *S. mollis* leaves in body weight and relative pancreatic weight on normal and diabetic rats after two-weeks of treatment.

Parameters	Control	(STZ) (60mg/kg.BW)	(AES) (200mg/kg.BW)	(STZ+AES)
Initial body weight (g)	151.2±2.84	212±5.05	228.4±3.48	227±4.98
Final body weight (g)	220.6±1.61	176±7.45	269.8±3.99	241±5.42
Body weight change (%)	+46.18±4.35	-16.34±5.12$^{(c)}$	+18.11±1.53$^{(c)}$	+6.20±2.74$^{(f, c)}$
Relative weight (mg/100g BW)	0.48±0.02	0.29±0.04$^{(a)}$	0.44±0.02	0.26±0.03$^{(a)}$

Values are given as mean ±SEM for groups of 5 animals each. (C): the normal control group; (STZ): the diabetic rats; (AES): the normal rats + (200mg/kg) of AES; (STZ+AES): the diabetic rats + (200mg/kg) of AES. Significant difference: (a) $p<0.05$, (c) $p<0.001$ when compared to the control. (f) $p<0.001$ when compared to (STZ).

able 4. Effects of diabetes and AES supplementation on hematological parameters of control and treated (normal and diabetic) rats after two-weeks of treatment.

Parameters	Control	(STZ) (60mg/kg.BW)	(AES) (200mg/kg.BW)	(STZ+AES)
WBC (10^3 /µL)	8.48±1.21	6.38±0.91$^{(a)}$	7.18±0.75	7.12±0.76
LY (× 10^3 /µL)	6.62±0.52	3.94±0.82$^{(c)}$	5.21±0.91$^{(a)}$	4.0±0.78$^{(c)}$
MO (× 10^3 /µL)	0.66±0.23	1.14±0.46$^{(c)}$	0.59±0.33	0.8±0.31$^{(e)}$
GR (× 10^3 /µL)	1.22±0.52	1.26±0.55	1.96±0.76	5.38±0.85$^{(f, c)}$
RBC (× 10^6 /µL)	5.41±1.01	7.422±1.05$^{(c)}$	7.73±1.22	8.75±1.41$^{(a)}$
Hb (g/dL)	11.96±1.41	13.14±1.52	11.8±1.09	4.87±0.59$^{(f, c)}$
PLT (× 10^3 /µL)	368.8±8.68	293.2±7.74	506.4±9.57$^{(a)}$	204.2±3.99$^{(b)}$

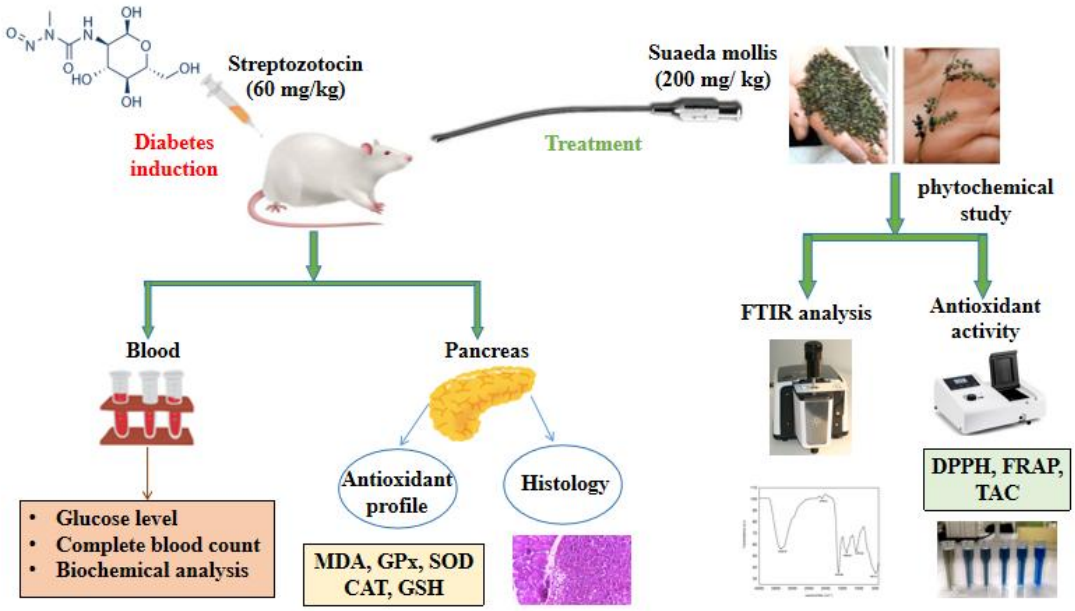
Values are presented as mean±SEM (n=5). White blood Cells (WBC); Lymphocytes (LY); Monocytes (MO); Granulocytes (GR); Red Blood Cells (RBC); Platelet (PLT); Hemoglobin (Hb). Letters in each column indicate significant differences as follows: (a) $p<0.05$, (b) $p<0.01$, (c) $p<0.001$ when compared to control. (e) $p<0.01$, (f) $p<0.001$ when compared to (STZ).

Table 5. The effects of AES supplementation on biochemical parameters in serum of normal and diabetic rats after two-weeks of treatment.

Parameters	Control	(STZ) (60mg/kg.BW)	(AES) (200mg/kg.BW)	(STZ+AES)
Creatinine (µmol/l)	22.4±1.4	43.8±3.08$^{(a)}$	65.8±3.61$^{(c)}$	67.6±3.51$^{(c)}$
Uric acid (µmol/l)	101.8±3.7	148.4±5.98$^{(a)}$	81.2±4.07	111.8±2.7
ASAT (U/L)	69.6±3.4	186±3.13$^{(c)}$	70.6±3.97	85.8±3.05$^{(f)}$
ALAT (U/L)	72.8±3	147±6.5$^{(b)}$	63.6±2.82	78.2±5.40$^{(e)}$
ALB (G/L)	30±1.73	39.4± 1.79$^{(c)}$	36.4±1.55$^{(b)}$	31±1.25$^{(f)}$
Prt tot (mg/ml)	101.8±3.67	145±5.90$^{(a)}$	54.46±2.71$^{(b)}$	52.83±2.80$^{(f, b)}$

Values are presented as mean±SEM (n=5 animals/group), ASAT: Aspartate aminotransferase; ALAT: Alanine aminotransferase; ALB: Albumin; Prt tot: Total protein. Letters in each column indicate significant differences as follows: (a) $p<0.05$, (b) $p<0.01$, (c) $p<0.001$ when compared to control. (e) $p<0.01$, (f) $p<0.001$ when compared to (STZ).

Graphical abstract



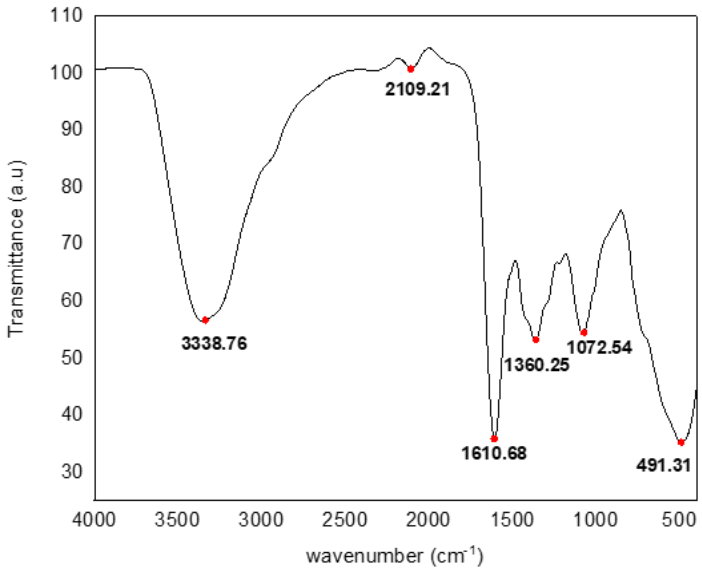


Figure 1. *FTIR spectra showing 5 bands of the bioactive compounds present in the aqueous extract of S. mollis leaves.*

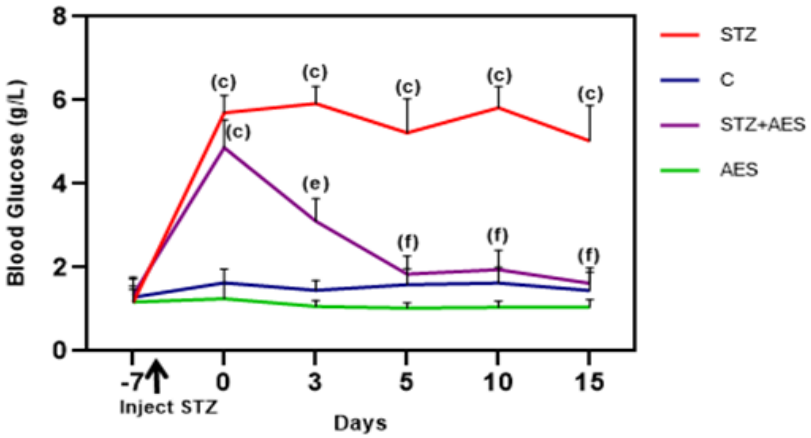


Figure 2. *Variations of blood glucose levels of control (C), Diabetic (STZ), Diabetic treated with aqueous extract of S. mollis (STZ + AES) and Normal treated with (200 mg/kg) of the aqueous extract of S. mollis (AES), before and after IP injection with STZ, during two-weeks of treatment. Note that diabetic rats started to show a relatively stable level of hyperglycemia approximately 48h after injection with STZ. Data are shown as mean±SEM. Letters in each point indicate significant differences as follows: (c) p<0.001 when compared to control. (e) p<0.01, (f) p<0.001 when compared to (STZ).*

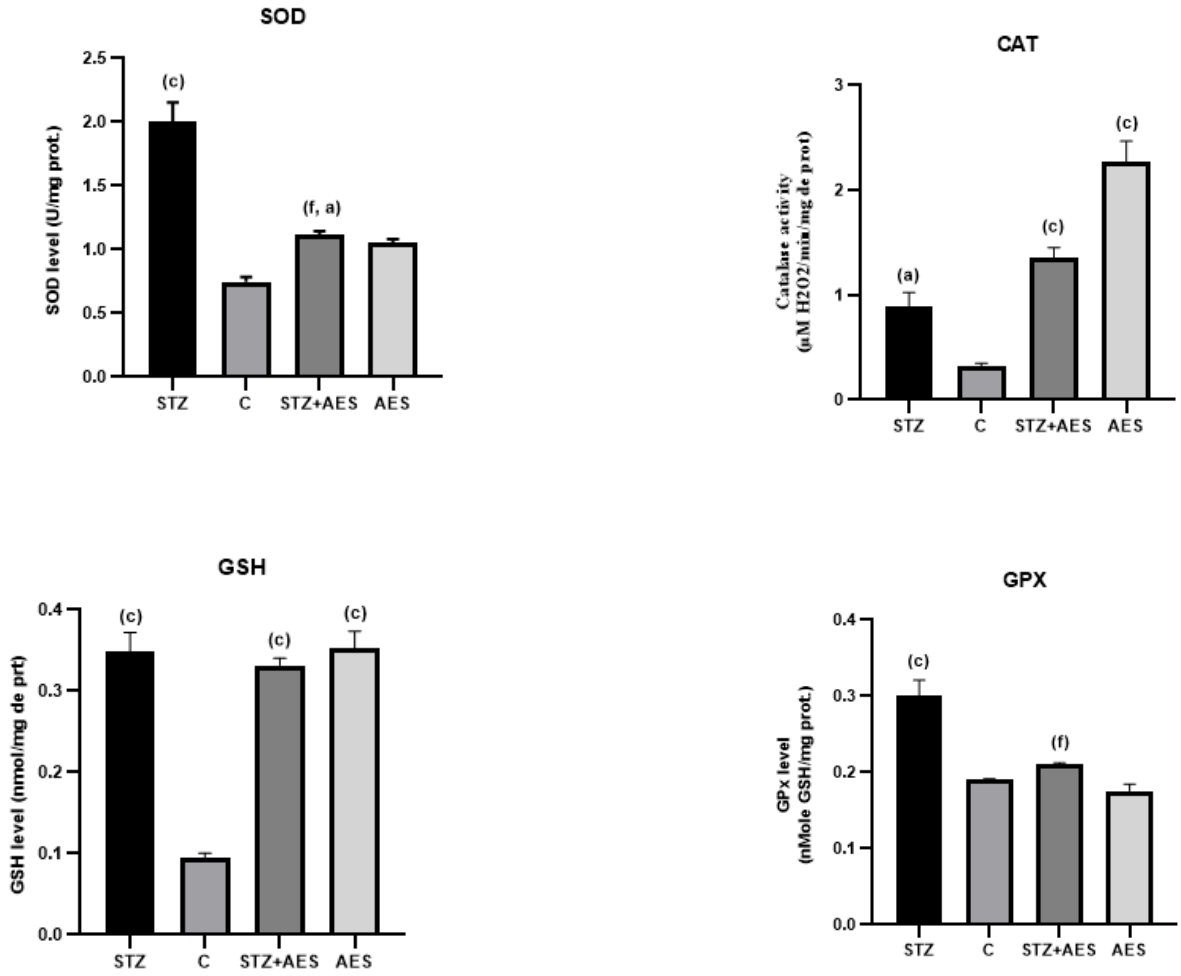
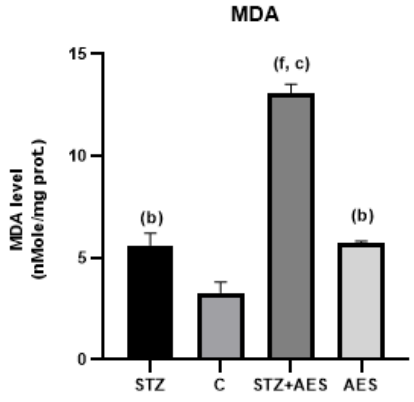


Figure 3. *Effects of STZ-induced diabetes and AES supplementation on oxidative stress*



biomarkers (the enzymatic and non-enzymatic antioxidants) in pancreas tissues of rats. Superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), reduced glutathione (GSH), and malondialdehyde (MDA) are represented as mean±SEM (n=5). (a) p<0.05, (b) p<0.01, (c) p<0.001 when compared to control. (d) p<0.05, (e) p<0.01, (f) p<0.001 when compared to (STZ).

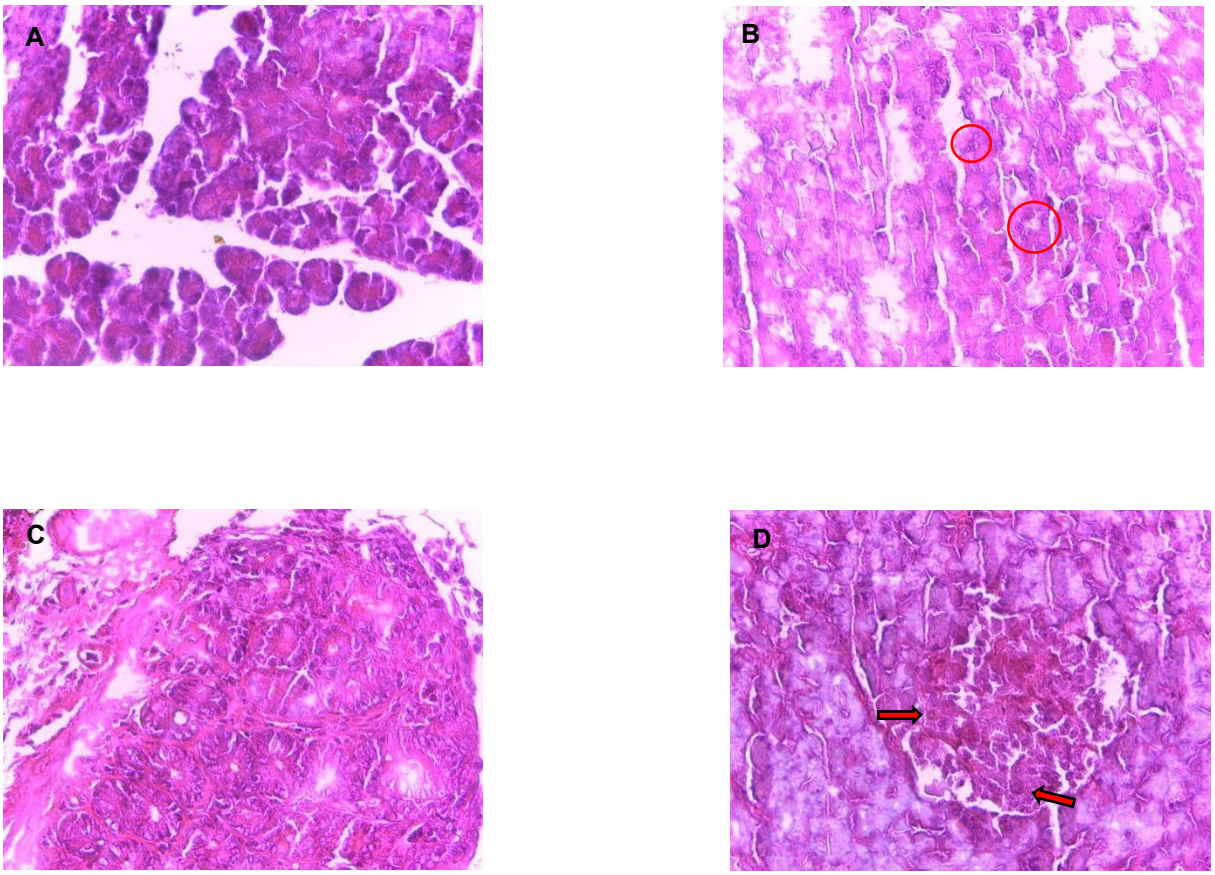


Figure 4. *Photomicrographs (A–D) demonstrates the histological sections of the pancreas tissues of different groups stained by hematoxylin and eosin [Magnification 40X]. A: control (C), B: Diabetic (STZ), C: Normal treated rats (AES) with (200 mg/kg) of the aqueous extract of S. mollis, D: Diabetic treated rats (STZ+AES) with the aqueous extract of S. mollis. Red cercles: pyknotic nuclei, red arrows: hypertrophy of islets.*