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Evaluation of In Vivo and In Silico Antidiabetic Effects of *Erythrina senegalensis* (Fabaceae) Hydroethanolic Stem Bark Extract on Rats

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ABSTRACT

Aim: The present study aimed to evaluate the effects of *Erythrina senegalensis* hydroethanolic extract on diabetes.

Methods: Six groups of five rats each were used for oral glucose, maltose, and starch tolerance tests. These groups consisted of distilled water, glibenclamide (5 mg/kg) or acarbose (400 mg/kg), and the extract (50, 100, 200, and 400 mg/kg). Diabetes was induced by streptozotocin (55 mg/kg) in 25 Wistar rats, confirmed one week later, and the groups were treated *per os* as follows: distilled water, insulin, and the extract (100, 200, and 300 mg/kg) for 4 weeks. Hemodynamic parameters were recorded, after which animals were sacrificed, and blood was collected for serum biochemical parameter assays and pancreas was taken for histological examination. In silico study of some compounds identified from *E. senegalensis* and downloaded from the PubChem database was performed using Molegro Virtual Docker software on HMG-CoA reductase, NADPH oxidase, and human liver glycogen phosphorylase obtained from the PDB database.

Results: *E. senegalensis* was able to prevent the increase in glycemia and accelerate its decrease. Streptozotocin significantly increased ($p < 0.001$) glycemia and serum creatinine, uric acid, triglycerides, total cholesterol, LDL cholesterol, bilirubin, transaminase activity ($p < 0.01$), and blood pressure and significantly decreased ($p < 0.001$) HDL-C, proteins, and pancreatic islet in diabetic animals compared to normal animals. The extract improved all the above cited parameters in diabetic rats. In silico, the compounds inhibited HMG-CoA reductase, NADPH oxidase, and human liver glycogen phosphorylase.

Conclusion: The extract might exert its antidiabetic effects through its hypoglycemic, antihyperglycemic, hypolipidemic, and antioxidant properties.

1 | Introduction

Though being the less prevalent form of diabetes mellitus, Type 1 diabetes is the most severe in terms of symptoms and complications. In fact, in 2021, an estimated 8.1 million new cases were identified, with 18% occurring in individuals younger than 20 years. Furthermore, more than 35,000 previously undiagnosed patients presenting with complications succumbed within 12 months following

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diagnosis. Epidemiological projections indicate a substantial increase in disease burden, with the number of cases expected to rise to between 15.5 and 17.4 million by the year 2040 [1]. In fact, diabetes mellitus is a chronic metabolic impairment characterized by high blood sugar due to an impairment in the production or the action of insulin. Type 1 diabetes is classified as autoimmune disease; the associated hyperglycemia might be due to low insulin secretion because of the immune attack of pancreatic beta cells. The chronic hyperglycemia in turn will result in many complications (nephropathies, retinopathies, neuropathies and the increase of cardiovascular risk factors). The common treatment of Type 1 diabetes so far remains the exogenic insulin substitution therapy. Nonetheless some researches are being carried out to personalize the treatment and even to prevent the disease [2]. The application of such results however would not be affordable for the common people. According to Bommer et al. [3], the cost of the present treatment of Type 1 diabetes was estimated at USD 1.3 trillion in 2017. The substantial economic burden associated with the management of diabetes mellitus has driven increased interest in the identification and implementation of alternative strategies within primary health care. Of course, many medicinal plant extracts have proven to be effective in the treatment of Type 1 diabetes and in the prevention of its complications [4–6]. In addition to the medication, a good and balanced diet accompanied with physical exercise are also required in the management of diabetes [7]. *Erythrina senegalensis* is a Fabaceae used in Cameroon by the local population to solve their metabolic problems, and its antidiabetic activity has already been demonstrated in Type 2 diabetes [8]. Empirically, the plant is used to treat fevers (including malaria), pain, inflammation, infections, and certain nervous disorders such as insomnia [8, 9]. The plant has also proved to have beneficial effects on the cardiovascular system [9, 10] with hypoglycemic activity [11]. The above reported effect may be related to the presence of several compounds including senegalensein, erysenegalensein E, erysenegalensein D, Warangalone, erythrisenegalone, 6,8-diprenylgenistein, erysenegalensein O, and erysenegalensein N as revealed by LCMS [8]. Knowing that Type 1 and Type 2 diabetes have neither the same etiology nor the same treatment, though a common problem (hyperglycemia), it was also of interest to find out if *E. senegalensis* could also be effective in Type 1 diabetes and prevent some of its complications. The present study was then carried out to evaluate the effect of the hydroethanolic extract of the stem bark of *E. senegalensis* on a streptozotocin-induced model of Type 1 diabetes in Wistar rats.

2 | Materials and Methods

2.1 | Chemicals

All the chemicals and reagents were purchased from Sigma-Aldrich Co., Germany and were of analytical grade. The commercial diagnostic kits (LABKIT, Spain) were purchased for some biochemical assays.

2.2 | Plant Material and Extract Preparation

The stem bark, fresh leaves, and flowers were harvested at Bangangte, west region of Cameroon, and identified at the National Herbarium with the voucher number N° 13752 SRF Cam. The barks were then shadow dried and grounded. The powder (400 g) was soaked in 3 L of hydroethanolic (70:30) mixture for 48 h and then filtered with the Whatman paper No. 3. After concentration under reduced pressure and evaporation in an oven (45°C), 42 g of extract was obtained from the filtrate, yielding 10.50%.

2.3 | Animals and Ethics Statement

Animals used were albino Wistar rats, aged between 8 and 10 weeks, weighing 160–180 g for the oral glucose tolerant tests (OGTTS), and 10–12 weeks, weighing 190–250 g for the antidiabetic test. The animals were reared in the animal house of the Laboratory of Animal Physiology of the Faculty of Sciences of the University of Yaoundé 1 under normal day/night cycle and temperature. Animals had free access to tap water for drinking and standard rats' pellets as food. Animals were cared according to the European Community guideline on animal's laboratory use and care (CEE Council 86/609), adopted by the Cameroon Institutional National Ethics Committee, Ministry of Scientific Research and Innovation (reference: FWA-IRD 00001954).

2.4 | Effects of *E. senegalensis* on the Blood Glucose of Normal Rats

2.4.1 | Follow-Up Glycemic Test

The follow-up glycemic test was carried out on the normal rats after 12 h of water-free fasting. Thirty healthy rats were selected and divided into 6 groups of 5 rats each. One group (normal control) was given distilled water (10 mL/kg), while another group (positive control) was receiving glibenclamide (5 g/kg; reference drug, hypoglycemic sulfonylurea). The last four groups were receiving the plant extract at the doses of 50, 100, 200 and 400 mg/kg, respectively. The glycemia of each animal was measured before the administration of any substance and then 1, 2, 3, 4 and 5 h after administration using glycemia test strips and a glucometer (ACCU-CHEK Active).

2.4.2 | OGTTs

Three OGTTs were performed on the normal rats after 12 h of overnight water-free fasting, namely, with glucose (OGTT), maltose (OMTT), and starch (OSTT). Thirty healthy male rats were used for each of the three tests. The animals were divided into 6 groups of five rats each and treated as follows: the first group (normal control) received distilled water (1 mL/kg); the second group (positive control) received glibenclamide (5 g/kg for OGTT) or acarbose (400 mg/kg for OMTT and OSTT), and the last four groups (test groups) received the plant extract (50, 100, 200, and 400 mg/kg, respectively). Thirty minutes after the administration of the treatments, hyperglycemia was induced using glucose (5 g/kg), maltose (5 g/kg), or starch (3 g/kg), respectively, according to the test. Blood glucose levels were measured on an empty stomach (30 min before treatment), just after hyperglycemia induction (0 min), and then 30, 60,120, and 180 min after hyperglycemia induction using glycemia test strips and a glucometer (ACCU-CHEK Active).

2.5 | Evaluation of the Effects of Hydroethanolic Extract of *E. senegalensis* on Type 1 Diabetes and Some of Its Complications

2.5.1 | Induction of Type 1 Diabetes and Animal Grouping and Treatment

Sixty healthy male rats were used, among which 7 received a saline solution (1 mL/kg) and the others received

streptozotocin (55 mg/kg via intravenous injection after 12 h of overnight water-free fasting. Before the injection and 7 days after, glycemia was measured according to the previously described method. On the 7th day, animals with blood glucose ≥ 300 mg/kg were considered Type 1 diabetics and were divided into 5 groups of 5 animals each and maintained for one additional week to allow for the complications. The group of rats which received the injection of saline was maintained as normal control group and was given distilled water. The diabetic groups were treated as follows: one group received distilled water (Type 1 diabetic: T1D), another group received insulin (2 UI: Ins 2), and the last three groups received the plant extract (50, 100, and 300 mg/kg, respectively). This treatment lasted 4 more weeks and the glycemia and body weight were measured at the end of each week using glycemia test strips and a glucometer (ACCU-CHEK Active). Then, at the end of the treatment, blood glucose was also evaluated using commercial diagnostic kits (LABKIT, Spain).

2.5.2 | Hemodynamic Parameter Recording

At the end of the 4 weeks of treatment, blood pressure and heartbeat were recorded as described by Bilanda et al. [8]. Briefly, rats were anesthetized, using an intraperitoneal injection of 15% urethane (1.5 g/kg). The arterial blood pressure was then registered by the direct method through the carotid artery via a cannula connected to a pressure transducer coupled with a hemodynamic recorder, Biopac Student Lab (MP35), and a computer. The recorder also registered the heartbeat.

2.5.3 | Animal Sacrifice and Sample Preparation

At the end of hemodynamic parameter recording, animals were sacrificed while still under anesthesia. Blood was collected in dry labelled *Eppendorf* tubes, left for 30 min, and then centrifuged at 3000 rpm, 4°C for 15 min. The supernatant was collected in other labelled *Eppendorf* tubes and kept at −20°C for biochemical parameter assays. After blood collection, the pancreas was removed, weighed, and put in 10% buffered formaldehyde for histology procedure.

2.5.4 | Biochemical Parameter Assays

Total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG) were evaluated in the serum using commercial diagnostic kits (LABKIT, Spain), and atherogenic index (AI) was calculated [12]. Transaminases, blood glucose, creatinine, uric acid, and bilirubin were evaluated using the same diagnostic kits as mentioned above. Proteins were assayed [13] using the biuret method. Serum insulin was assessed using a rat insulin ELISA commercial kit (Crystal Chem, Europe).

2.5.5 | Histology and Histomorphometry of Pancreas Islets

After one week of fixation in the 10% buffered formaldehyde, the pancreas was trimmed and dehydrated, and then it followed a normal histological routine. The resulting slides were hematoxylin–eosin-stained and examined using a light microscope. The images were snapped using a computer with MiniSee software and analyzed.

2.6 | In Silico Molecular Docking Assessment

2.6.1 | Ligand and Protein Identification

Compounds isolated and identified from *E. senegalensis* stem bark such as senegalensein (ID: 124035), erysenegalensein E (ID: 15478903), erysenegalensein D (ID: 25256865), warangalone (ID: 5379679), erythrisenegalone (ID: 15224381), 6,8-diprenylgenistein (ID: 480783), erysenegalene O (ID: 49768587), erysenegalene N (ID: 49768588), glibenclamide (ID: 3488), simvastatin (ID: 54454), and vitamin C (ID: 54670067) were obtained from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/) in the form of 3D image SDF files and were primarily used for docking to three enzymes. The structures of target enzymes such as HMG-CoA reductase (ID: 1HW9), human NADPH oxidase (ID: 7U8G), and human liver glycogen phosphorylase (ID: 1EM6) were downloaded from the RCSB Protein Data Bank (PDB) in PDB file format (https://www.rcsb.org/) [14].

2.6.2 | Molecular Docking

The ligand–protein interaction was analyzed using Molegro Virtual Docker software. The molecular docking method was used to predict the interactions that occur between two or more molecules and the strength of the docking score, as well as the type of binding that occurs. The principle of docking is to attach a ligand to the active site of a receptor or enzyme. After this interaction, the docking results were saved in PDB format and the binding affinity data were transferred to Microsoft Excel. The binding energies (Kcal/mol) between the ligand and the different active sites of each enzyme were obtained and used to evaluate the affinity between the ligand and the enzyme [15, 16].

2.6.3 | 2D and 3D Docking Result Visualization

These interactions were visualized using Discovery Studio v.2016 software to obtain 2D and 3D images showing the bonds and distances between molecules.

2.7 | Statistical Analysis

Results were expressed as mean ± standard error of the mean (SEM). Statistical analysis was performed using one-way analysis of variance (ANOVA) followed by Tukey's multiple comparison post hoc test using GraphPad Prism 8.0.1 software. The differences were considered significant at $p < 0.05$.

3 | Results

3.1 | Effects of Hydroethanolic Extract of *Erythrina senegalensis* Stem Bark on the Blood Glucose of Normal Rats

The effects of hydroethanolic extract of *E. senegalensis* on the glycemia of the normal rats are summarized in Figures 1(a), 1(b), 1(c), and 1(d). In the normal rats following a 12 h water-free fasting (Figure 1(a)), the hydroethanolic extract of *E. senegalensis* at all the doses used gradually reduced initial glycemia, more effectively than distilled water, but less than glibenclamide. Four hours after administration, the glycemia of the groups which received the plant extract was reduced by 36.5% (50 mg/kg), 31.6% (100 mg/kg), 32.6% (200 mg/kg), and 26.8% (400 mg/kg), respectively. While the glycemia of the distilled water group and

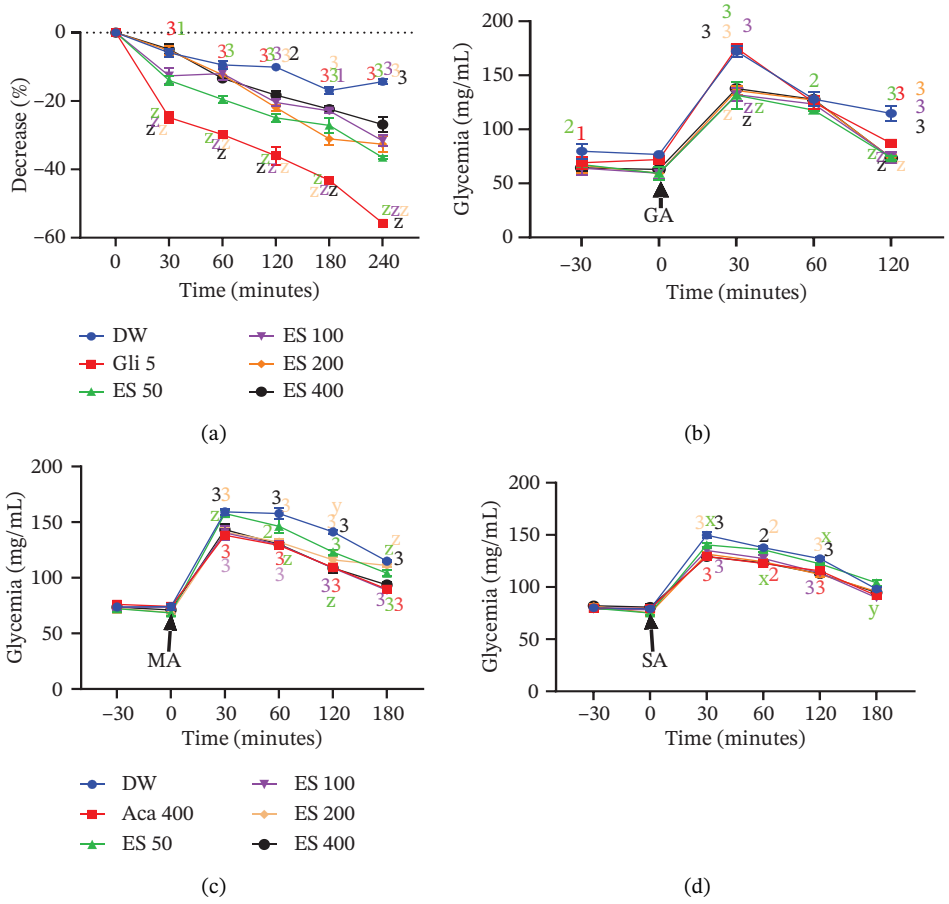


FIGURE 1 | Effects of hydroethanolic extract of *Erythrina senegalensis* on the blood glucose of normal rats. Glycemia follow-up (a), OGTT (b), OMTT (c), and OSTT (d). Each point represents mean ± SEM; $n = 5$; $^{1}p < 0.05$, $^{2}p < 0.01$, $^{3}p < 0.001$: significant differences compared to the rats receiving distilled water; $^{x}p < 0.05$, $^{y}p < 0.01$, $^{z}p < 0.001$: significant differences compared to the rats receiving reference treatment. DW: rats receiving distilled water (10 mL/kg); GA: glucose administration; MA: maltose administration; SA: starch administration; Gli 5: rats receiving glibenclamide (5 mg/kg); Aca400: rats receiving acarbose (400 mg/kg); ES 50, ES 100, ES 200, and ES 400: rats receiving *Erythrina senegalensis* extract at doses of 50, 100, 200, and 400 mg/kg, respectively.

the glibenclamide group was reduced by 14.3% and 55.7% compared to their glycemia before administration.

Figure 1(b) summarizes the effects of hydroethanolic extract of *E. senegalensis* on the blood glucose changes during OGTT. It is observed that the extract reduced the peak glycemia induced by the administration of glucose (5 mg/kg). That reduction was 23.59% (50 mg/kg), 23.28% (100 mg/kg), 21.10% (200 mg/kg) and 20.06% (400 mg/kg), while glibenclamide did not affect that hyperglycemic peak compared to the group treated with distilled water. Following the peak (30 min after the administration of glucose), a gradual reduction in the glycemia in all the groups was observed. At the end of the test (120 min after glucose administration), the glycemia levels of all the groups treated with the plant extract were almost back to their initial values recorded before the glucose administration, while those in the groups treated with distilled water or glibenclamide were still higher than the initial values. The reduction in the extract-treated groups was 35.69% (50 mg/kg), 35.46% (100 mg/kg), 35.75% (200 mg/kg), and 36.04% (400 mg/kg), respectively, while glibenclamide showed a reduction of 11.62% compared to the group treated with distilled water.

Figure 1(c) represents the results of effects of plant extract on the OMTT. It is revealed that, as with the OGTT, the administration of maltose (5 mg/kg) led to a glycemic peak after 30 min, which persisted until 60 min in the group treated with distilled water. Pre-treatment with the plant extract or acarbose significantly prevented the hyperglycemic peak induced by maltose. The reduction was 10.99% (100 mg/kg), 10.61% (200 mg/kg), and 9.22% (400 mg/kg), respectively. Then, a gradual reduction in glycemia was observed in all the pre-treated grouped until the end of the test (180 min). The reduction induced with the extract at the end of the test (180 min) was 10.15% (50 mg/kg), 23.40% (100 mg/kg), and 17.92% (400 mg/kg), respectively. Pre-treatment with acarbose (400 mg/kg) showed a similar effect to the extract at a dose of 100 mg/kg.

Figure 1(d) summarizes the effects of hydroethanolic extract of *E. senegalensis* on the blood glucose changes during OSTT. It is noticed that the extract has reduced the peak of glycemia induced by the administration of starch (3 mg/kg) after 30 min. This decrease was 9.85% ($p < 0.001$), 12.19% ($p < 0.001$), and 13.86% ($p < 0.001$) at doses of 100, 200, and 400 mg/kg, respectively, and 13.58% ($p < 0.001$) with acarbose, compared to the group of

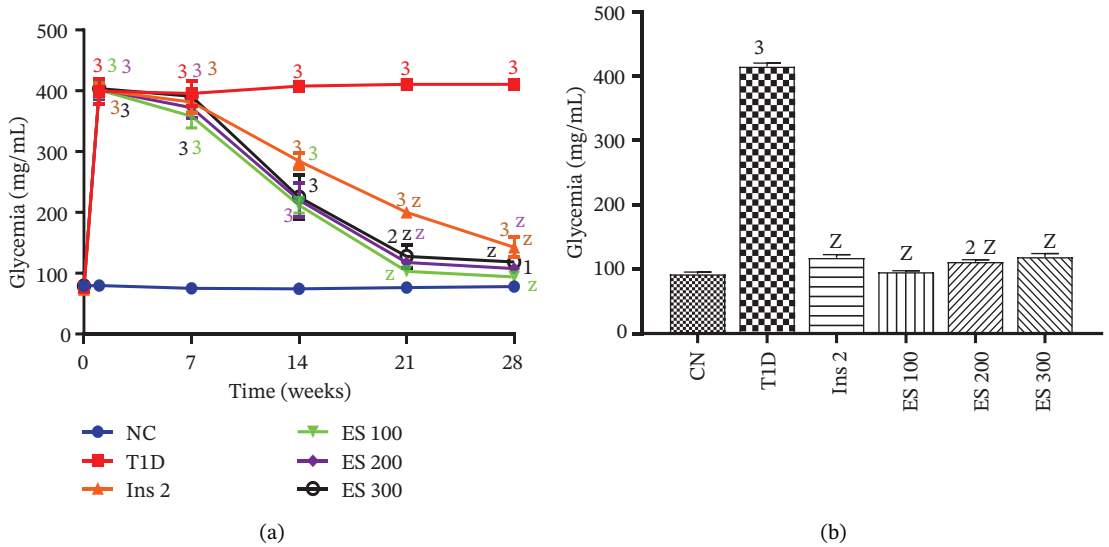


FIGURE 2 | Effects of hydroethanolic extract of *E. senegalensis* on blood glucose levels in Type 1 diabetic rats at the end of each week measured using test strips (a) and at the end of the experiment using diagnostic kits (b). Each point and bar represent mean ± SEM; $n = 5$; $^{2}p < 0.01$, $^{3}p < 0.001$: significant difference compared to the normal rats, $^{z}p < 0.001$: significant difference compared to the diabetic rats. NC: normal control rats; T1D: Type 1 diabetic rats; Ins 2: diabetic rats receiving insulin at 2 UI; ES 100, ES 200, and ES 300: diabetic rats receiving *Erythrina senegalensis* extract at doses of 100, 200, and 300 mg/kg, respectively.

animals receiving distilled water. After the hyperglycemic peak, a gradual drop in glycemia was observed in all the groups until 180 min, at which point levels were almost the same in all the groups and very close to the baseline values.

3.2 | Effects of Hydroethanolic Extract of *E. senegalensis* on Blood Glucose Levels in Diabetic Rats

The effects of hydroethanolic extracts of *E. senegalensis* on Type 1 diabetes rats during the 4 weeks of treatment are summarized in Figure 2. The results show that blood glucose levels in untreated diabetic rats remained significantly higher ($p < 0.001$) compared to those in the control group. The ethanolic extract of *E. senegalensis* at all doses (100, 200, and 300 mg/kg) significantly and gradually dropped the glycemia of the Type 1 diabetic rats, throughout the 4 weeks of treatment. At the end of treatment, the glycemia reduction was 77.18% (100 mg/kg), 73.72% (200 mg/kg), and 71.29% (300 mg/kg), respectively, while the insulin group showed a reduction of 65.21%, all compared to the Type 1 diabetic group (Figure 2(a)). These results are confirmed by spectrophotometric measurement of blood glucose levels (Figure 2(b)). At the end of treatment, blood glucose levels were reduced by 76.94% (100 mg/kg), 73.17% (200 mg/kg), 71.35% (300 mg/kg), and 71.60% (insulin), respectively, compared to the Type 1 diabetic group.

3.3 | Effects of Hydroethanolic Extract of *Erythrina senegalensis* on Insulin Levels in Diabetic Rats

The effects of hydroethanolic extract of *E. senegalensis* on insulin levels of Type 1 diabetes rats during the 4 weeks of treatment are summarized in Figure 3. It was observed that the insulin levels of untreated diabetic rats were significantly ($p < 0.001$) lower compared to the normal group, with a 3.33-fold reduction. The ethanolic extract of *E. senegalensis* at all doses (100, 200, and 300 mg/kg) significantly and dose dependently increased the insulin levels of the Type 1 diabetic rats. Compared to untreated diabetic rats, there was a 2.31, 2.44, and 2.75-fold increase in insulin levels of rats treated at the respective doses of 100, 200, and 300 mg/kg of *E. senegalensis* extract.

3.4 | Effects of Hydroethanolic Extract of *Erythrina senegalensis* Stem Bark on Type 1 Diabetic Rats' Pancreas

Figures 4(a) and 4(b) show the effects of the extract on pancreatic islet architecture and area. Compared to normal

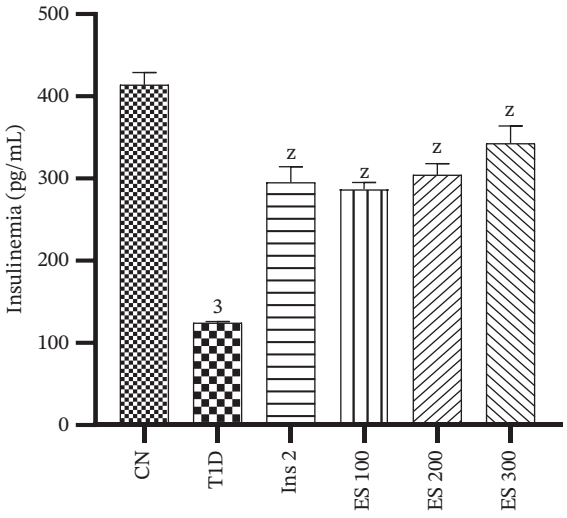


FIGURE 3 | Effects of hydroethanolic extract of *E. senegalensis* stem bark on insulin levels of Type 1 diabetic rats at the end of the experimentation. Each bar represents mean ± SEM; $n = 5$; $^{3}p < 0.001$: significant difference compared to the normal rats, $^{z}p < 0.001$: significant difference compared to the diabetic untreated rats. NC: normal control rats; T1D: Type 1 diabetic rats; Ins 2: diabetic rats receiving insulin at 2 UI; ES 100, ES 200, and ES 300: diabetic rats receiving *Erythrina senegalensis* extract at doses of 100, 200, and 300 mg/kg, respectively.

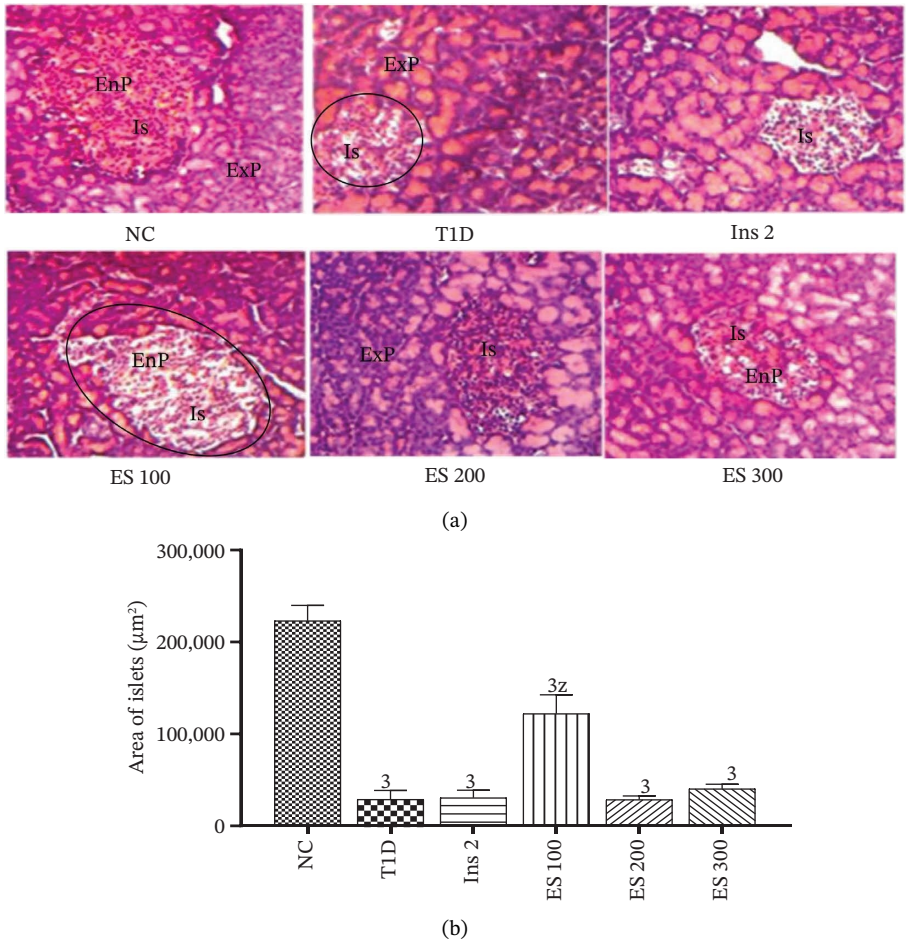


FIGURE 4 | Effects of hydroethanolic extract of *Erythrina senegalensis* stem bark on pancreatic structure (a) and islet area (b) (hematoxylin–eosin, 200X). Each bar represents mean ± SEM; $n = 5$; $^{3}p < 0.001$: significant difference compared to the normal rats; $^{z}p < 0.001$: significant difference compared to the diabetic rats. Is = islets of Langerhans; EnP = endocrine pancreas; ExP = exocrine pancreas. NC: normal control rats; T1D: Type 1 diabetic rats; Ins 2: diabetic rats receiving insulin at 2 UI; ES100, ES 200, and ES 300: diabetic rats receiving *Erythrina senegalensis* extract at doses of 100, 200, and 300 mg/kg, respectively.

animals, diabetic animals showed a significant decrease in pancreatic islet size and area ($p < 0.001$) of 87.06%. The 100 mg/kg extract alone significantly ($p < 0.001$) increased pancreatic islet area and size by 77.92% compared to diabetic rats. However, the cells were denser in the pancreas treated with the 200 mg/kg extract.

3.5 | Effects of the Hydroethanolic Extract of *E. senegalensis* on Some Complications of Type 1 Diabetic Rats

3.5.1 | Effects on the Hemodynamic Parameters

The effects of *E. senegalensis* on systolic (SBP), diastolic (DBP), and mean (MBP) blood pressure and heart rate (HR) are summarized in Table 1. It is shown that Type 1 diabetes has significantly increased all the above parameters. The increase was 26.55% (SPB), 84.51% (DBP), 56.41% (MBP), and 22.19% (HR), respectively, compared to the normal control group. The treatment with the extract (100, 200, and 300 mg/kg) or insulin significantly reduced those parameters compared to the Type 1 diabetes group. The reduction was 17.48%, 20.28%, 15.38%, and 18.18% for SBP, 30.35%, 25.36%, 21.43%, and 17,59% for DBP, 26.47%, 23.19%, 18.93%, and 17.21% for MBP, and lastly 23.11%, 17.45%, 21.93%, and 19.10% for HR, respectively, compared to the Type 1 diabetes group.

3.5.2 | Effects on the Lipid Profile of Type 1 Diabetic Rats

The table represents the effects of *E. senegalensis* hydroethanolic extract on the lipid profile of Type 1 diabetic rats. Type 1 diabetes induced an increase in TC (119.81%), LDL cholesterol (LDL-C) (804.76%), TG (62.86%), and AI (274.37%) and a drop in HDL-C (40.98%) compared to the normal control. Compared to the Type 1 diabetic group, the treatment with the extract (100 mg/kg) during 28 days led to a significant decrease in TC (55%), TG (54.8%), LDL-C (76%), and AI (70.11%) and an increase in HDL-C (62.69%). At the dose of 200 mg/kg, the plant extract reduced the TC (43.8%), TG (43%), LDL-C (71.4%), AI (57.76%), and the HDL-C (87.3%) significantly. When given at 300 mg/kg, the plant extract reduced the TC (53.3%), TG (21.4%), LDL-C (75.87%), and AI (61.77%). Compared to the group with Type 1 diabetes, insulin treatment resulted in a reduction in serum TC (49.22%), TG (32.98%), LDL-C (80.87%), and AI (67.61%) levels, as well as an increase in HDL-C (58.33%) levels.

TABLE 1 | Effects of hydroethanolic extract of *Erythrina senegalensis* stem bark on blood pressure and heart rate of Type 1 diabetic rats.

Parameters	NC	T1D	Ins 2	ES 100	ES 200	ES 300
SBP (mmHg)	113.0 ± 3.7	143.0 ± 3.9^{2}	117.0 ± 1.0^{y}	118.0 ± 1.7^{y}	114.0 ± 2.4^{y}	121.0 ± 0.3^{y}
DPB (mmHg)	60.7 ± 3.5	112.0 ± 3.5^{3}	92.3 ± 1.6^{3z}	78.0 ± 3.3^{3z}	83.6 ± 2.6^{3z}	88.0 ± 0.4^{3z}
MBP (mmHg)	78.0 ± 3.5	122.0 ± 3.6^{3}	101.0 ± 1.3^{3z}	89.7 ± 1.8^{1z}	93.7 ± 2.4^{3z}	98.9 ± 0.3^{3z}
HR (beat/min)	347.0 ± 13.4	424.0 ± 6.4^{3}	343.0 ± 4.8^{z}	326.0 ± 4.1^{z}	350.0 ± 4.7^{z}	331.0 ± 0.8^{z}

Note: Each value represents mean ± SEM; $n = 5$; $^{1}p < 0.05$, $^{2}p < 0.01$, $^{3}p < 0.001$: significant differences compared to the normal rats. $^{y}p < 0.01$, $^{z}p < 0.001$: significant differences compared to the diabetic rats. beats/min: beats per minute. NC: normal control rats receiving distilled water; DW: diabetic rats receiving distilled water; Ins 2: diabetic rats receiving insulin; ES100, ES 200, and ES300: diabetic rats receiving *Erythrina senegalensis* extract at doses of 100, 200, and 300 mg/kg, respectively. Abbreviations: DBP, diastolic blood pressure; HR, heart rate; MBP, mean blood pressure; SBP, systolic blood pressure.

3.5.3 | Effects on Some Liver and Kidney Function Marker Parameters

The table summarizes the effects of hydroethanolic extract of *E. senegalensis* on some liver and kidney function marker parameters. As observed in the table, Type 1 diabetes for 6 weeks without treatment led to a significant increase in serum creatinine (72.60%), uric acid (208.36%), bilirubin (84.66%), and ASAT (124.21%) and ALAT (134.08%) activity and a drop (49.43%) in proteins. Compared to the Type 1 diabetic group, the treatment with the extract (100, 200, and 300 mg/kg) led to a significant decrease ($p < 0.001$) in ALAT activity of 60.20%, 47.27%, and 57.47% respectively. A significant ($p < 0.001$) drop in uric acid, respectively, 58.19%, 62.93%, and 58.42% and a significant ($p < 0.001$) decrease of 51.82%, 44.28% and 50.32% were also noticed. Also, bilirubin was significantly ($p < 0.001$) decreased (84.15%, 85.59%, and 72.54%, respectively) and proteins were significantly ($p < 0.001$) increased (96.47%, 86.40%, and 77.60%, respectively). Only at the dose of 100 mg/kg that the activity of ASAT was significantly ($p < 0.01$) decreased (58.45%) with the plant extract's treatment. The treatment with insulin led to a significant decrease in ALAT end ASAT activities, uric acid, and creatinine levels and an increase in protein level, respectively, of 59.04%, 50.27%, 48.02%, 0.38%, and 92.70% compared to the Type 1 diabetic group.

3.6 | Docking Analysis

Table 2 summarizes the binding energies; Tables 3, 4, and 5 summarize the 2D and 3D structures of the ligands and enzymes of interest, and Table 6 summarizes the amino acids involved in the ligand–enzyme binding interaction of the compounds senegalensein, erysenegalensein E, erysenegalensein D, warangalone, erythrisenegalone, 6,8-diprenylgenistein, erysenegalensein O, erysenegalensein N, glibenclamide, simvastatin, and vitamin C in enzymes such as HMG-CoA, NADPH oxidase, and human hepatic glycogen phosphorylase, respectively. The results show that, in addition to binding to the same amino acids as the positive control, the compounds derived from *E. senegalensis* interact in silico with the various enzymes, binding to other active sites of these enzymes. This strong affinity between the enzymes and the compounds of *E. senegalensis* explains the low binding energies obtained during the ligand–protein interaction.

4 | Discussion

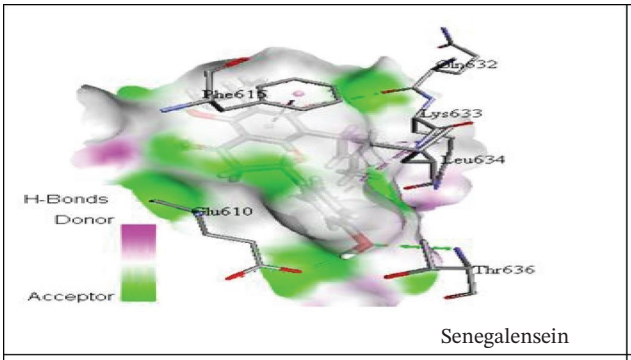
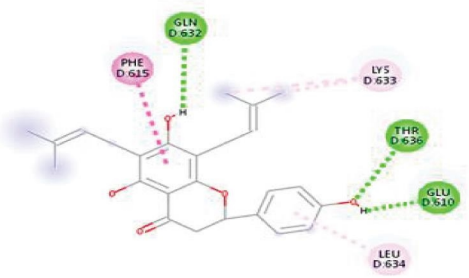
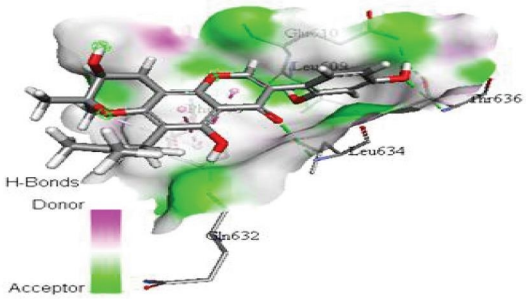
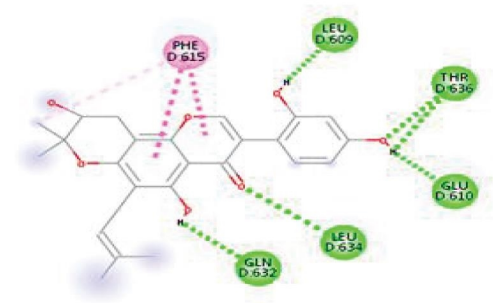
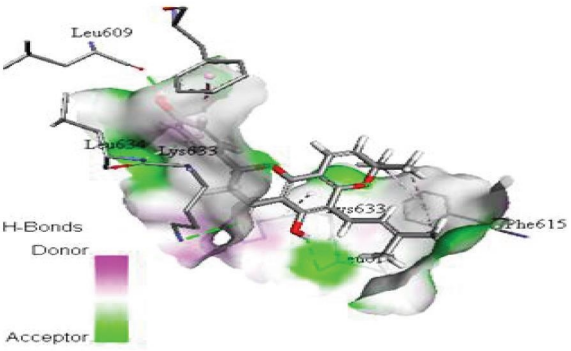
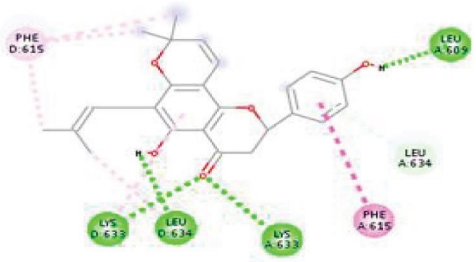
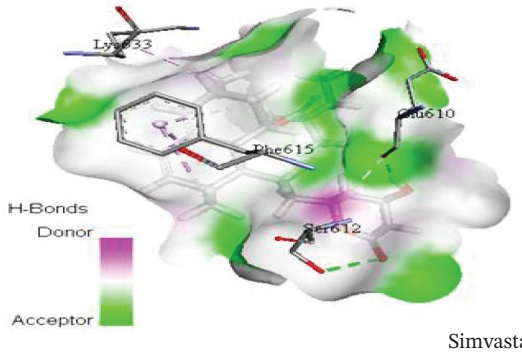
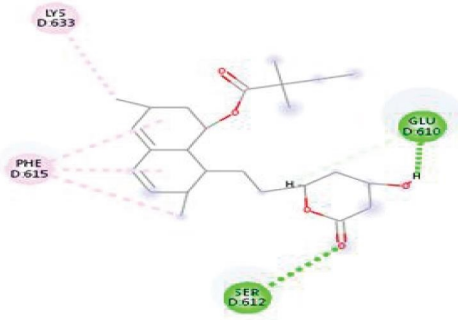
The aim of the present study was to evaluate the effects of hydroethanolic extract of *Erythrina senegalensis* stem bark on Type 1 diabetes and some of its complications in rats. The high blood glucose level obtained in the Type 1 diabetic group at the end of induction was a sign that the animals were diabetic. Streptozotocin is known to selectively destroy pancreatic islet beta cells by various mechanisms, including their ferroptosis [13, 17]. Pancreatic beta cell death can in turn lead to a reduction in islet size and density, as confirmed by histology and histomorphometry of the pancreas observed in Type 1 diabetic rats (Figure 4). The persistent hyperglycemia in these animals can

TABLE 2 | Ligand–protein binding energy of some *Erythrina senegalensis* compounds.

Ligands	Energy (Kcal/moL)		
	HMG-CoA reductase	NOX2	HLG phosphorylase
Senegalensein	−35.96	−48.65	−44.54
Erysenegalensein E	−40.45	−41.58	−47.72
Erysenegalensein D	−42.67	−35.04	−46.89
Warangalone	−37.72	−36.98	−49.63
Erythrisenegalone	−37.72	−48.12	−45.30
6,8-Diprenylgenistein	−36.63	−44.52	−46.23
Erysenegalensein O	−39.64	−38.21	−40.67
Erysenegalensein N	−41.11	−48.01	−47.68
Glibenclamide	−38.62	−56.05	−44.54
Simvastatin	−34.48	/	−40.63
Vitamin C	/	−24.51	/

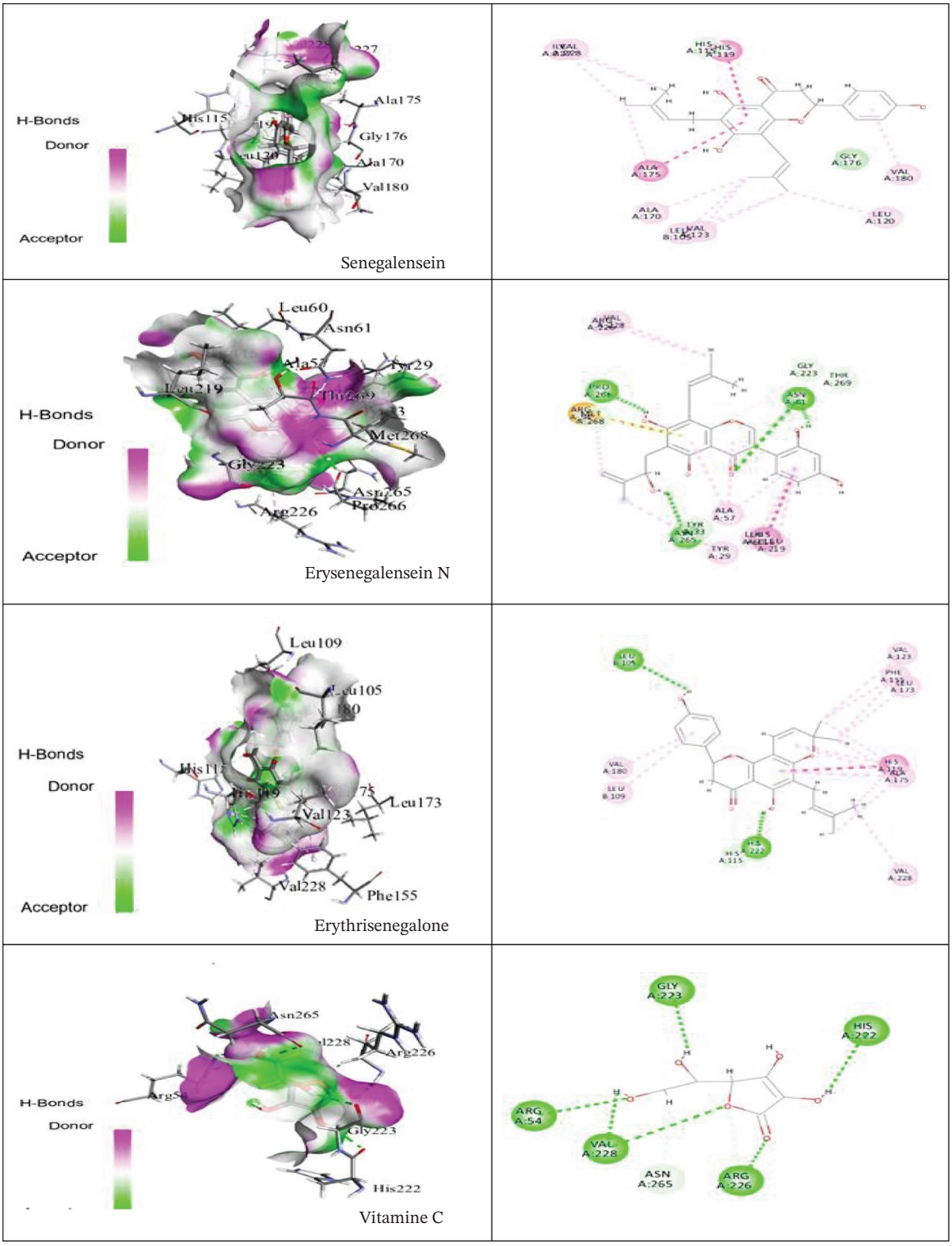
Note: HMG-CoA reductase: 3-hydroxy-3-methylglutaryl-coenzyme A reductase; HLG phosphorylase: human liver glycogen phosphorylase.

TABLE 3 | 2D and 3D interactions of compounds with the human HMG-CoA reductase enzyme.

 Senegalensein	
 Erysenegalensein O	
 Erythrisenegalone	
 Simvastatin	

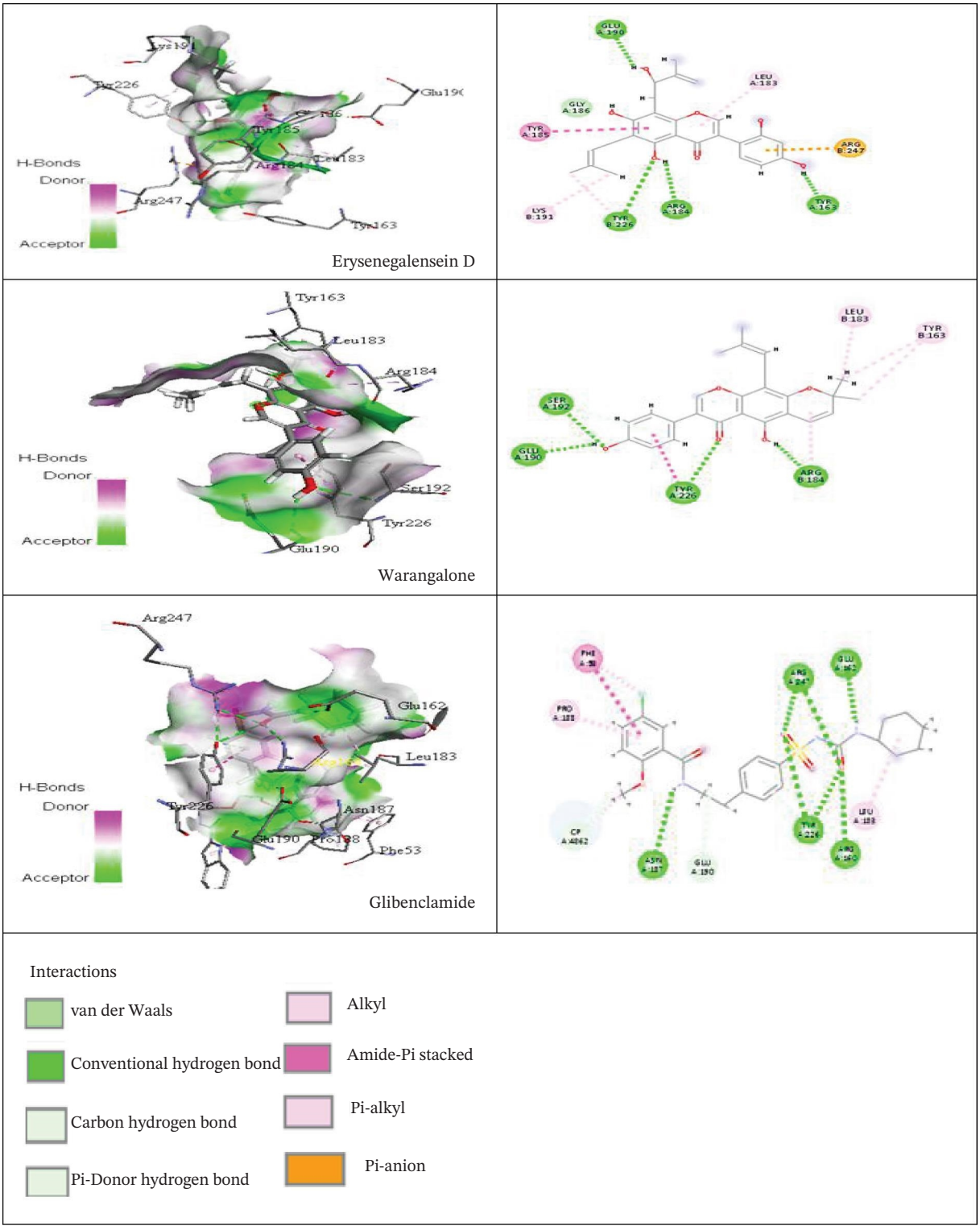
then be explained by this destruction of pancreatic beta cells [14]. Since these cells are the only ones that produce insulin, the only hormone involved in the use of blood glucose by the cells of the body, it is understandable that their reduction should lead to an increase in blood glucose levels [17]. Blood glucose regulation in groups treated with the plant extract or insulin confirms the hypoglycemic activity of *E. senegalensis* (Figure 2). In the long term, the extract could also promote pancreatic β-cell hypertrophy. Assuming that all animals are initially diabetic and therefore have damaged pancreases, the improvement in insulin

TABLE 4 | 2D and 3D interactions of compounds with the human NADPH oxidase (NOX2) enzyme.



level and in islet size would be the result of cell regeneration. The extract may also have an insulin-like effect, since the islets of the 200 and 300 mg/kg test groups did not increase in size compared to the diabetic and insulin-treated groups. Taken together, all of these actions of the hydroethanolic extract of *E. senegalensis* stem bark would explain the observed reductions in blood glucose levels. These effects may be due to the presence of certain bioactive compounds in the extract. Indeed, phytochemistry has shown that the hydroethanolic extract of *E. senegalensis* contains saponins, alkaloids, phenolics, and flavonoids which antihypertensive and antidiabetic effects have been demonstrated [11]. It is also interesting to notice that the lowest dose of the extract used had a greater effect than glibenclamide and insulin on blood glucose levels. This would suggest that the 100 mg/kg dose of the

TABLE 5 | 2D and 3D interactions of compounds with the human liver glycogen phosphorylase enzyme.



extract would have resulted in the proliferation and/or hypertrophy of pancreatic β-cells, which would also justify the greater efficacy of this dose. The effect of the extract on blood glucose levels was confirmed in oral hyperglycemia tests with glucose, maltose, and starch. In fact, the peak blood glucose levels observed after administration of these different sugars were inhibited by the extract at different doses (Figure 1). This inhibition was greater for starch and then maltose than for glucose. It can then be suggested that the extract may affect the activity of enzymes involved in the hydrolysis of polyoses [18, 19]. The accelerated decrease in blood glucose levels observed from the first hour after the administration of the different sugars could confirm an indirect effect on the stimulation of insulin secretion and/or action. It could also be thought that the extract

TABLE 6 | Amino acids involved in conventional ligand–enzyme binding.

Ligands	Interactions	HMG-CoA reductase	NOX2	Human liver glycogen phosphorylase
Senegalensein	CarHB		HIF115	/
	ConHB	GLN632, THR636, GLU610	/	ARG160, TYR226, CP4862
Erysenegalensein E	CarHB	LEU634, LUS633, LYS633	THR116	—
	ConHB	LEU634, LEU609, LYS633	/	ASN187, GLU190, THR38
Erysenegalensein D	CarHB	/	GLY223, HIS222	/
	ConHB	LEU609, LEU634, GLN632, GLU610, THR636	TYR33, PRO266, ARG54, ASN617	GLU190, ARG184, TYR226, TYR 168
Warangalone	CarHB	LEU609	HIS222	/
	ConHB	GLU610, THR636, LEU634, GLN632	SER112, THR183	ARG184, TYR226, GLU190, SER192
Erythrisenegalone	CarHB	LEU634	HIS115	/
	ConHB	LEU634, LYS633, LYS633, LEU609	LEU105, HIS222	ARG160, TYR163, GLU273, ARG184
6,8-Diprenylgenistein	CarHB	/	/	PRO188, TYR226
	ConHB	LYS633, LEU609	/	SER192, LEU183
Erysenegalensein O	CarHB	/	/	TYR226, GLU190
	ConHB	GLN632, LEU634, GLU610, THR636, LEU609	HIS119	LEU183, GLU190, ARG160, GLU162
Erysenegalensein N	CarHB	GLN632	MET268, GLY223, THR269, TYR33	—
	ConHB	GLN632, LEU634, GLU610, THR636	PRO266, ASN61, ASN265	TYR226, GLU273, TYR163
Glibenclamide	CarHB	LEU609	ARG226, PRO266, HIS22	GLU190, CP4862
	ConHB	GLN632, LEU634	ARG54	ASN187, TYR226, ARG160, ARG247, GLU162
Simvastatin	CarHB	/	/	ASN187
	ConHB	SER612, GLU610	/	ARG160, GLU190
Vitamin C	CarHB	/	ASN265	ARG184
	ConHB	/	GLY223, ARG54, ARG226, VAL228, HIS222	TYR163, GLU162

Note: CarHB: carbon–hydrogen bond; ConHB: conventional hydrogen bond; NOX2: human NADPH oxidase.

TABLE 7 | Effects of hydroethanolic extract of *Erythrina senegalensis* stem bark on the lipid profile of Type 1 diabetic rats.

Parameters	NC	T1D	Ins 2	ES 100	ES 200	ES 300
TC (mg/mL)	64.6 ± 3.1	142.0 ± 8.2^{3}	72.1 ± 4.3^{z}	63.9 ± 2.2^{z}	79.8 ± 2.2^{z}	66.2 ± 3.5^{z}
HDL-C (mg/mL)	42.7 ± 1.9	25.2 ± 0.9^{3}	39.9 ± 2.1^{z}	41.0 ± 1.7^{z}	47.2 ± 0.2^{z}	31.2 ± 0.3^{3}
TG (mg/mL)	70.0 ± 2.2	114.0 ± 2.1^{3}	76.4 ± 0.4^{z}	51.5 ± 7.3^{1z}	64.9 ± 4.6^{z}	89.6 ± 3.9^{1y}
LDL-C (mg/mL)	12.6 ± 4.5	114.0 ± 1.2^{3z}	21.8 ± 2.2^{z}	27.3 ± 5.6^{z}	32.6 ± 5.5^{1z}	27.5 ± 5.3^{z}
AI	1.6 ± 0.1	5.9 ± 0.5^{3}	1.9 ± 0.1^{z}	1.7 ± 0.1^{z}	2.5 ± 0.2^{z}	02.3 ± 0.4^{z}

Note: Each value represents mean ± SEM; $n = 5$; $^{1}p < 0.05$, $^{3}p < 0.001$: significant differences compared to the normal controls. $^{y}p < 0.01$, $^{z}p < 0.001$: significant differences compared to the diabetic controls. TG = triglycerides; Ins 2: diabetic rats receiving insulin; ES100, ES 200, and ES 300: diabetic rats receiving *Erythrina senegalensis* extract at doses of 100, 200, and 300 mg/kg, respectively.
Abbreviations: AI, atherogenic index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol.

mimics the action of insulin on target cells. In addition, the bioactive compounds in *E. senegalensis* may also inhibit human liver glycogen phosphorylase, which is responsible for raising blood glucose levels by breaking down liver glycogen into glucose [20]. In fact, in silico results show that both the extract compounds and simvastatin bind to the active sites of this enzyme, thereby blocking its function and reducing hyperglycemia [20]. This binding also reflects the ability of *E. senegalensis* compounds to competitively inhibit the activity of human liver glycogen phosphorylase, making this pathway a candidate for *E. senegalensis* diabetes therapy. The maintenance of high blood glucose levels in diabetics eventually leads to damage to the endothelium of blood vessels, resulting in elevated blood pressure, which, if persistent, leads to arterial hypertension [21]. Thus, diabetes disrupts endothelial function, which can no longer maintain vascular homeostasis [21]. This hypothesis was confirmed in the present study by an increase in the systolic blood pressure of diabetics at the end of the experimental period, which was over 140 mmHg (Table 1). The prevention of elevated blood pressure by the extract could be attributed to its protective effects on the cardiovascular system [9, 22]. It could also be related to the previously demonstrated effect of the plant on blood glucose levels [11]. A disturbance in lipid metabolism characterized by an increase in TG, TC, and LDL-C and a decrease in HDL-C is one of the hallmarks of metabolic diseases [5, 23, 24]. This characteristic dyslipidemia was observed in diabetic rats in the present study (Table 7). Such observations have also been made by several authors inducing metabolic diseases [5, 23, 24]. In fact, dyslipidemia is closely associated with diabetes in both rats and humans, especially when diabetes is associated with hypertension [24]. In the present study, the coexistence of the two pathologies would aggravate complications on the lipid metabolism, cardiovascular system, and kidneys [25, 26]. The extract at all doses succeeded in improving the lipid profile of diabetics, with better effects than insulin for some parameters. It could therefore be assumed that the improvement of the lipid profile is a way by which the extract prevents the complications of diabetes on the cardiovascular system. In fact, the activation of HMG-CoA reductase in diabetics is responsible for hyperlipidemia through increased cholesterol biosynthesis [27]. By inhibiting the activity of this enzyme, as observed in silico, *E. senegalensis* reduces cholesterol biosynthesis, thereby improving the lipid profile. Several authors have attributed the prevention of hypertension to the improvement of the lipid profile, independent of the model [5, 23, 24]. Diabetes, like several other chronic diseases, leads to alterations in liver and kidney functions. In the present study, markers of the functions of these two organs were found to be impaired in diabetic rats (Table 8). The maintenance of high blood glucose levels in diabetics results in the formation of protein glycation, which alters the physiology of certain organs [28]. Altered liver and kidney functions are evidenced by increased serum creatinine, uric acid, and bilirubin levels and serum transaminase activity. According to several authors, such an increase is associated with liver and kidney damage [5, 22, 26]. Oxidative stress plays an important role in the dysfunction of these organs. The high expression of NADPH oxidase in diabetics is responsible for the production of reactive oxygen species, which are highly potent in peroxidising the membranes of these organs, hence the observed dysfunction [29]. The reduction of these markers by the extract suggests that the damage caused by chronic hyperglycemia and free radicals to these two organs has been reduced by the plant extract. In addition to its hypoglycemic

TABLE 8 | Effects of hydroethanolic extract of *E. senegalensis* stem bark on some liver and kidney function marker parameters in Type 1 diabetic rats.

Parameters	NC	T1D	Ins 2	ES 100	ES 200	ES 300
CREA (mg/dL)	0.7 ± 0.0	1.3 ± 0.0^{3}	0.7 ± 0.0^{z}	0.6 ± 0.1^{z}	0.7 ± 0.1^{z}	0.6 ± 0.1^{z}
UA (mg/dL)	2.9 ± 0.2	8.8 ± 0.7^{3}	4.6 ± 0.4^{z}	3.7 ± 0.3^{z}	3.3 ± 0.3^{z}	3.7 ± 0.4^{z}
ASAT (U/L)	66.9 ± 4.5	150.0 ± 3.8^{3}	74.6 ± 3.1^{z}	59.7 ± 4.4^{z}	79.1 ± 5.3^{z}	63.8 ± 1.5^{z}
ALAT (U/L)	5.8 ± 0.4	13.6 ± 3.1^{2}	5.6 ± 1.0	5.6 ± 0.6^{y}	8.9 ± 0.4	9.1 ± 0.4
TBILI (mg/dL)	0.1 ± 0.0	1.2 ± 0.0^{3}	0.2 ± 0.0^{z}	0.2 ± 0.0^{z}	0.2 ± 0.0^{z}	0.3 ± 0.1^{2z}
PROT (mg/dL)	1.6 ± 0.0	0.8 ± 0.0^{3}	1.5 ± 0.0^{z}	1.6 ± 0.1^{z}	1.5 ± 0.1^{z}	1.4 ± 0.0^{z}

Note: Each value represents mean ± SEM; $n = 5$; $^{2}p < 0.01$, $^{3}p < 0.001$: significant differences compared to the normal controls. $^{y}p < 0.01$, $^{z}p < 0.001$: significant differences compared to the diabetic controls. TBILI: total bilirubin; CREA: creatinine; NC: normal rats receiving distilled water; T1D: Type 1 diabetes rats receiving distilled water; Ins 2: diabetic rats receiving insulin; ES100, ES 200, and ES 300: diabetic rats receiving *Erythrina senegalensis* extract at doses of 100, 200, and 300 mg/kg, respectively.
Abbreviation: UA, uric acid.

effects, *E. senegalensis*, through the presence of bioactive compounds, is also able to inhibit NADPH oxidase activity, as demonstrated in silico, thus protecting the liver and kidneys from the action of free radicals [28, 29].

5 | Conclusion

The aim of this study was to evaluate the effects of hydroethanolic extract of *Erythrina senegalensis* stem bark on a streptozotocin-induced Type 1 diabetes model in rats. The results showed that the extract, particularly at 100 mg/kg, was able to stimulate the regeneration/hypertrophy of pancreatic β cells. At all doses, the extract increased insulin secretion and subsequently reduced blood glucose levels in diabetic rats. The plant extract also improved hemodynamic parameters and liver and kidney functions. The action of the extract is thought to involve a direct effect on blood glucose levels and/or an insulin-like action. By regulating blood glucose levels, HMG-CoA reductase activity, and hepatic glycogen phosphorylase in diabetic patients, the extract may protect them from metabolic disorders leading to dyslipidemia. The extract's regulation of blood sugar levels and NADPH oxidase activity also prevents diabetics with developing hypertension and hepatic, renal, and cardiovascular disorders. These results obtained from the hydroethanolic extract of *E. senegalensis* justify its empirical use in the treatment of diabetes and its complications.

Author Contributions

Ronald Bidingha A. Goufani: methodology, software, in silico study, and writing–original draft; Myriam Kana: methodology, data analysis, and writing–original draft; Barnabé Nkono Ya Nkono: design and supervision,; Danielle Claude Bilanda: design, supervision, data analysis, and writing–original draft; Marie-Claire Tchamadeu: design and data analysis; Pascal Emmanuel Owona: histology; Yannick Carlos Tcheutchoua and Léonard Tédong: histology; Marcelle Bejoutance Djami: biochemical parameter assay; Paul Désiré Djomeni Dzeufiet: supervision, design, data analysis, and writing–original draft.

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The authors have nothing to report.

Ethics Statement

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data are available on request from the corresponding author.

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