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Modulatory Potentials of Flavonoid-Rich Extract of *Detarium* senegalense (FREDS) on Hematological indices and Lipid Metabolism in STZ-induced Diabetes in *Wistar* Rats

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Abstract

This study examined the effects of a flavonoid-rich extract of Detarium senegalense (FREDS) on haematological parameters and lipid profiles in Streptozotocin (STZ)-induced diabetic rats. A total of forty-two (42) rats were randomly assigned to seven groups. All groups, except the normal control, were administered 45 mg/kg body weight (b.w.) of STZ. The treatment groups included: diabetic control (normal saline), metformin (100 mg/kg b.w.), sildenafil (100 mg/kg b.w.), and three FREDS groups (50 mg/kg, 75 mg/kg, and 100 mg/kg b.w.). Diabetes induction resulted in a significant ($p<0.05$) increase in white blood cells (WBC; including neutrophils, lymphocytes, and basophils), serum total cholesterol, low-density lipoprotein (LDL), very-low-density lipoprotein (VLDL), triglycerides, along with a decrease in red blood cells (RBC; hematocrit, haemoglobin, mean cell haemoglobin, and mean cell haemoglobin concentration), platelet percentage, and high-density lipoprotein cholesterol (HDL-c). Treatment with FREDS significantly ($p<0.05$) reduced WBC, total cholesterol, LDL, VLDL, and triglycerides, while increasing RBC, platelet percentage, and HDL levels in a dose-dependent manner, with the most pronounced effects observed in the 100 mg/kg FREDS group compared to the normal control. These findings suggest that FREDS effectively improves both haematological parameters and lipid metabolism. This study indicates that Detarium senegalense flavonoid-rich extracts may serve as a promising therapeutic option for managing haematological abnormalities, hyperlipidemia, and related metabolic disorders in diabetes, potentially offering an alternative to conventional treatments.

Keywords: *Diabetes mellitus, Detarium senegalense, Streptozotocin, haematology hyperlipidemia*

INTRODUCTION

Millions of people worldwide suffer from diabetes mellitus, a metabolic disease that is becoming more common as a result of genetic predispositions and lifestyle choices (Ajiboye *et al*., 2024). In addition to hyperglycemia, diabetes frequently results in diabetic dyslipidemia, a complex of lipid abnormalities that is a major risk factor for cardiovascular disorders (Olana *et al*., 2019). Excessive production of free radicals and low levels of endogenous antioxidant molecules have been linked to the incidence of diabetes mellitus. Oxidative stress and its consequences, including lipid peroxidation, damage to cellular organelles (including red blood cells and sperm cells), and loss of pancreatic beta-cells, have been linked to this condition (Darenskaya *et al.,* 2021; Barati *et al*., 2020).

Untreated diabetes mellitus can lead to several problems, including retinopathy, neuropathy, nephropathy, dyslipidemia, and anaemia (Park *et al*., 2021). Lipid abnormalities caused by diabetes mellitus usually include increased small, dense low-density lipoprotein (LDL) particles, decreased levels of high-density lipoprotein (HDL) cholesterol, and higher triglycerides (Saleem *et al*., 2019). Since these lipid abnormalities increase the risk of atherosclerosis in diabetic individuals, managing them is

essential (LeRoith *et al.,* 2019). Haematological indices, such as haemoglobin (HB) concentration, hematocrit (HCT) levels, white blood cell counts (WBC), and red blood cell counts (RBC), are essential indicators for evaluating a person's general health and condition in diabetes. Frequently, these indices are changed, which can result in issues including anaemia and heightened vulnerability to infections (Andong *et al.,* 2021).

To avoid the aforementioned consequences, diabetes mellitus is currently primarily treated using synthetic medications like metformin. Restorative measures, however, are not substantially provided by the treatment (Ogunlana *et al*., 2021). As a result, focus has switched to the safer and more economical use of therapeutic herbs. The West African native plant *Detarium senegalense* has long been utilized for several medicinal benefits, including the ability to control hyperglycemia and enhance lipid metabolism (Salleh *et al*., 2021).

The medium-sized tree *Detarium senegalense* can reach a height of 40 meters. In Igboland, it is referred to as "Ofo," in Hausa, "Taura," and in Yoruba, "Ogbogbo" (Dossa *et al*., 2020). This leguminous tree, which belongs to the Fabaceae family and the Detarioideae subfamily, produces globular, nutrient-dense fruits (Ukwubile *et al*., 2017). Given that it provides a wealth of botanical anthelminthic medications utilized in traditional therapy, its therapeutic significance is innumerable. Ukwubile *et al.* (2017), claim that the bark infusion aids in the placenta's expulsion following birth. It is used to cure anaemia, wounds, skin problems, pneumonia, stomachaches, and digestive diseases, according to El-Kamali (2023). *Detarium senegalense* has antidiabetic properties (Olatunji *et al*., 2021). An isolate (zyloglucan) from the seeds of *Detarium senegalense* has been confirmed to reduce postprandial blood glucose and improve insulin concentrations in humans (Olatunji *et al*., 2021).

Numerous biological actions, including antiviral, anti-inflammatory, anti-cancer, and antioxidant properties, are linked to flavonoids (Kelechi *et al.,* 2022). Flavonoids are a possible therapeutic agent in the management of haematological and lipid problems caused by diabetes because of their demonstrated ability to alter red blood cells and lipid metabolisms, reduce oxidative stress, and ameliorate inflammatory responses (Oladeji *et al.,* 2022). Although flavonoids have shown encouraging effects on lipid profiles in animal models, few studies have explicitly looked at how flavonoids from *Detarium senegalense* affect the haematological and lipid abnormalities linked to diabetes. By examining the impact of flavonoid-rich extracts from *Detarium senegalense* on the lipid profile and haematological markers in rats with diabetes induced by streptozotocin (STZ), the current work seeks to close this gap.

MATERIALS AND METHODS

Chemicals

N-hexane, dichloromethane, (DCM), ethyl acetate (EAC), ethanol, silica gel, D-fructose, sodium citrate, sildenafil, citric acid and streptozotocin were purchased from Sigma-Aldrich (St-Louis, MO, USA). All other needed chemicals and reagents were of analytical grade.

Collection of plant materials and authentication

The leaves of *Detarium senegalense* were obtained from the Alumni Garden of Alex Ekwueme Federal University Ndufu Alike Ikwo, Ebonyi State. The leaves were identified and authenticated at the herbarium unit, Ebonyi State University, Abakaliki. A sample of the plant portion was deposited in the herbarium section (NRDS-423-2022) for future purposes.

Extraction of flavonoid-rich extract.

The leaves of *Detarium senegalense* were air-dried at room temperature. The air-dried leaves were ground to powder using an electric blender. About 30 g of the sample was dissolved in 600 mL of 10% H_2SO_4 in a small flask and was hydrolysed by heating on a water bath for 30 minutes at 100 ^oC. The mixture was placed on ice for 15 minutes to allow flavonoids aglycone precipitate, the cooled solution was filtered using Whatsmann filter paper (No.1). The residue was dissolved in 1.5 mL of warm 95% ethanol (45 ^oC) the resulting solution was filtered into 1000 mL volumetric flask which was made to mark with 95% ethanol. The filtrate collected was concentrated to dryness using a rotary evaporator and the resulting extract was stored in the fridge at 4 ^oC until needed, Oyinloye *et al*. (2022).

The flavonoid-rich extract of *Detarium senegalense* leaf was fractionated using Silica gel 230 mesh column chromatography to yield various fractions. Fractions with similar thin layer chromatographic (TLC) mobility profiles based on their retention factor were pooled together, and concentrated in a water bath at 40 ^oC. The obtained paste was stored in the fridge at 4 $^{\circ}C$ until needed. The extraction and TLC were done at the Biochemistry Programme, Department of Chemical Sciences, College of Sciences, Afe Babalola University, Ado Ekiti.

Ethical clearance

Ethical clearance (ABUADREC 887359 – IDRD2022/038) for the use of animals was obtained from the Research

Ethics Committee (REC) of the Institute of Drug Research and Development of Afe Babalola University Ado-Ekiti, Nigeria. The animal experimental protocols were followed in accordance with the recommendations of the REC. All animals received humane care.

Induction of Type 2 Diabetes Mellitus

Type 2 diabetes mellitus was induced in the experimental rats through intraperitoneal injection of 45 mg/kg body weight streptozotocin (STZ) dissolved in ice-cold 0.1 M citrate buffer (pH 4.5), after administration of 10% D-fructose in their drinking water for 7 days. Blood samples were taken by tail vein puncture and glucose levels were monitored using a test fine glucometer, type 2 diabetes mellitus was confirmed after 72 hours and animals with blood glucose levels ≥ 250 mg/dL were considered diabetic and were used for the study.

Animal Grouping

Forty-two (42) Male *Wistar* albino rats of 120–160 g were obtained from the ABUAD animal care facility and maintained under standard conditions at the Department of Biochemistry, College of Sciences, Afe Babalola University, Ado Ekiti. The rats were randomly shared into seven (7) groups containing six (6) rats each and were treated as follows:

Control: received distilled water.

STZ only: received 45 mg/kg b.w STZ

STZ + Met: received 45 mg/kg b.w STZ and 100 mg/kg b.w metformin.

STZ + SDF: received 45 mg/kg b.w STZ and 100 mg/kg b.w sildenafil.

STZ + FREDS 1: received 45 mg/kg b.w STZ and 50 mg/kg b.w FREDS.

STZ + FREDS 2: received 45 mg/kg b.w STZ and 75 mg/kg b.w FREDS.

STZ + FREDS 3: received 45 mg/kg b.w STZ and 100 mg/kg b.w FREDS.

(FREDS= Flavonoid-rich Extract of *Detarium senegalense*, STZ= Streptozotocin, Met: Metformin, SDF: Sildenafil, b.w: body weight).

Determination of Haematological Parameters:

Blood samples were collected from the venous sinus while the rat was under terminal anaesthesia. The neck was gently scruffed and the eye made to bulge. A capillary tube was inserted dorsally. Blood was allowed to flow by capillary action into the capillary tube. Haematological parameters were analysed using a haematology analyzer according to the methods of Chhabra (2018).

Determination of Lipid Parameters

Serum total cholesterol, triglycerides, VLDL, LDL and HDL cholesterols were determined by a direct method using an automatic analyzer (Bio-Majesty™ JCA-BM8000 series) according to the method of Tanaka *et al.* (2021).

Statistical Analysis

All analyses were done in triplicates and data were analysed using GraphPad prism software version 8.0.1. Data were expressed as mean ± standard deviation. Statistical comparisons were performed by one-way analysis of variance (ANOVA), followed by Tukey's multiple range post-hoc test.

RESULTS AND DISCUSSION

Detarium senegalense is a medium-sized tree that can grow up to 40 meters in height. Locally, it is known as "Ogbogbo" in Yoruba, "Ofo" in Igboland, and "Taura" in Hausa (Dossa *et al*., 2020). The seed and stem bark extracts have been reported to include alkaloids, flavonoids, tannins, phenols, and saponins (Dogara, 2022). As presented in Figure 1, the induction of diabetes in the experimental animals led to a decrease in red blood cell counts, hematocrits, haemoglobin, mean corpuscular haemoglobin and volume and red blood cell distribution width. On the administration of FREDS for 28 days, there was a major increase in the concentration and volume of red blood cells. However, the groups treated with low-dose FREDS do not have a significant increase in the red blood cell count compared to the normal control. Flavonoid-rich extracts of *Detarium senegalense* may be useful in treating haematological and lipid metabolism abnormalities caused by diabetes, as evidenced by the observed changes in red and white blood cell counts, platelet counts, and lipid metabolism following Streptozotocin-induced type 2 diabetes and treatment with the extract. Put together, the extracts at 100 mg/kg affected all the parameters positively. This supports the idea that FREDS can cause erythropoietin to be secreted, which in turn causes bone marrow stem cells to make red blood cells (Lodish *et al*., 2010).

In addition to the previously mentioned effects, red blood cell metabolism in diabetic individuals may be impacted by several risk factors, including inflammation, oxidative stress, and hyperglycemia, which can decrease membrane fluidity, increase aggregation, and decrease cell deformability. Thus, the total modification lowers the erythrocytes' survival rate, morphology, size, and physiological activities; ultimately, this influences the red blood cells' physiological functions (Abbas *et al*., 2023). The experimental animals' white blood cell counts, neutrophils, lymphocytes, basophils, and all other white cells that are neither lymphocytes nor granulocytes increased as a result of the diabetes induction, as shown in Figure 2. A significant ($p < 0.05$) drop in white blood cell concentration and percentage levels was observed

after 28 days of FREDS treatment. In contrast to the normal control group, the sildenafil-treated group could not significantly lower the white blood cell count ($p < 0.05$). The body's inflammatory response is reflected in these data. Although the quantity of neutrophils and lymphocytes may increase in diabetes, perhaps in response to the damage produced by hyperglycemia, their functioning is often compromised. They also play a role in oxidative stress, which can result in lung and cardiac conditions (Daryabor *et al.,* 2020). Diabetes damages T-cell responses and other lymphocyte functions, making diabetic patients more susceptible to infections and lowering immunological surveillance, which raises the risk of inflammation.

According to Daryabor *et al.* (2020), elevated monocytes in diabetics are linked to tissue damage and ongoing inflammation, which can result in complications including cardiovascular issues. Eosinophils and basophils, which are associated with allergic reactions, may potentially worsen the inflammatory condition in diabetes. Following 28 days of FREDS treatment, there was a significant drop in both the concentration and percentage levels of WBCs. The ability of FREDS to return WBC levels to nearly normal suggests that it lowered systemic inflammation, a major problem in the treatment of diabetes, by modulating the immune response in diabetic rats through its anti-inflammatory effect (Uhuo *et al*., 2023).

By reducing the overall WBC count, which includes neutrophils, lymphocytes, and MID cells, FREDS may mitigate the elevated immune response associated with chronic hyperglycemia. This may lessen the chance of complications from the disease since chronic inflammation is a major contributor to vascular damage, insulin resistance, and other comorbidities in diabetes. These findings align with the findings of other studies (Abbas *et al*., 2023; Ebrahim *et al*., 2022).

As shown in Figure 3, the experimental animals' blood platelet counts (PLT), and platelet distribution width (PDW) increased as a result of the diabetes induction. However, the concentration and percentage levels of blood platelets significantly ($p<0.05$) and decreased after 28 days of FREDS administration. Conversely, there was no discernible decrease in the groups treated with modest doses of FREDS when compared to the normal control. Diabetes can lead to platelet abnormalities, such as increased platelet aggregation, which raises the risk of cardiovascular diseases (Cakirca and Celik, 2019; Nwoke *et al*., 2023). The untreated diabetic group showed abnormal platelet counts and platelet indices, including elevated PDW, mean platelet volume (MPV), and platelet large cell ratio (PLCR). These changes are indicative of a higher proportion of larger and more reactive platelets, which are commonly observed in diabetes patients and are linked to an increased risk of thrombosis and vascular issues (Onuigwe *et al.,* 2024).

Furthermore, insulin insufficiency, insulin resistance, and hyperglycemia all contribute to the glycation of platelet proteins, which alters the shape and function of platelet indicators and hence impacts platelet reactivity (Beckman and Creager, 2016). Fortunately, platelet counts dropped and markers like MPV and PDW nearly recovered to normal when FREDS was given. This suggests that FREDS may have a role in controlling platelet reactivity and production. FREDS enhanced vascular health and decreased the incidence of thrombosis, a typical consequence of diabetes, by reducing platelet aggregation and oxidative stress on the vascular endothelium. As cardiovascular risks are closely associated with platelet reactivity and aberrant size distribution in diabetics, FREDS has shown the potential to be used as a supplement to diabetes treatment by lowering these platelet abnormalities and enhancing vascular health (Cakirca and Celik, 2019).

Figure 4: Triglycerides, total cholesterol, LDL cholesterol, and VLDL cholesterol increased whereas HDL cholesterol decreased in the experimental animal after diabetes was induced. When compared to the normal control, the 28-day administration of FREDS resulted in a significant rise in HDL cholesterol and a decrease in total cholesterol, triglycerides, LDL cholesterol, and VLDL cholesterol. According to the study's findings, giving diabetic rats an extract high in flavonoids from *Detarium senegalense* significantly improved their lipid profiles. In controlling dyslipidemia, a frequent consequence of diabetes, the extract significantly ($p<0.05$) decreased levels of very low-density lipoprotein (VLDL) cholesterol, low-density lipoprotein (LDL-c) cholesterol, total cholesterol, and triglycerides. These results are consistent with other research showing that flavonoids can decrease cholesterol by boosting the excretion of cholesterol and modifying lipid metabolism (Ali *et al.,* 2023; Yoon *et al*., 2021).

Given that HDL is essential for eliminating excess cholesterol from peripheral tissues and returning it to the liver for excretion, the results' improvement in HDL cholesterol levels points to an improvement in reverse cholesterol transport. Flavonoids are known to enhance antioxidant activity, reduce oxidative stress, and promote cardiovascular health in diabetes, so the bioactive compounds in *Detarium senegalense* may contribute to the increase in HDL levels (Song *et al*.,

2023). Furthermore, the results imply that *Detarium senegalense* may be a good substitute or supplemental treatment for diabetes patients' lipid abnormalities since it increases HDL-c levels and decreases important atherogenic lipoproteins including VLDL and LDL (Zhang *et al*., 2022).

According to several recent lines of evidence, the typical dyslipidemia seen in patients with type-2 diabetes which is characterized by elevated TGs, low HDL cholesterol, and a preponderance of small-dense LDL particles, may not only be a result of diabetes but also potentially lead to disruptions in glucose metabolism (Parhofer, 2015). In a related development, hypertriglyceridemia leads to elevated levels of free fatty acids (FFAs), which are thought to directly damage beta-cells and disrupt the molecular pathways linking insulin receptors to glucose transporters, thus promoting insulin resistance and beta-cell dysfunction (Erion *et al*., 2016). Moreover, hypertriglyceridemia and high FFAs can exacerbate inflammation, further impairing beta-cell function and increasing insulin resistance (Rachek *et al*., 2014). Additionally, reduced HDL-c levels may negatively affect glucose metabolism and contribute to low-grade inflammation, which can ultimately lead to the development of diabetes mellitus (Drew *et al*., 2012).

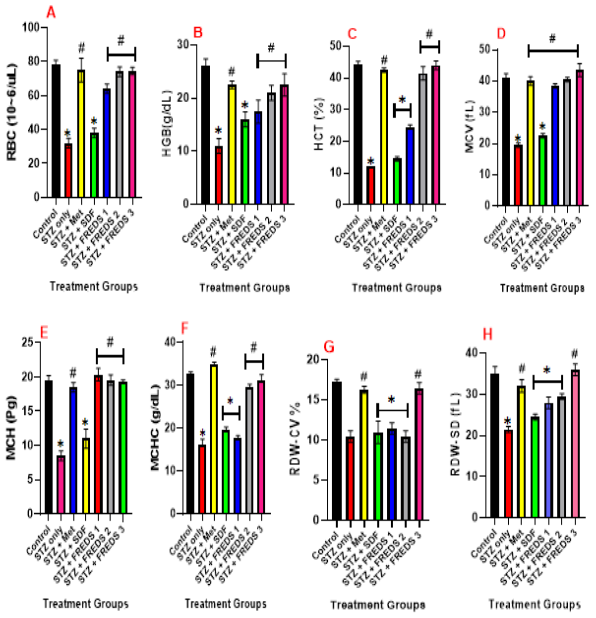

Figure 1. Effect of FREDS on the red blood cell count in STZ-induced type-2 Diabetes in albino rats

Data were expressed as Mean ± Standard Deviation. $p<0.05$, (n=6). * denotes values that are significantly different from the control. # denotes values that are not significantly different from the control. **A:** red blood cell count (RBC), **B:** haemoglobin (HGB), **C:** Hematocrit (HCT), **D:** mean cell volume (MCV), **E:** Mean cell haemoglobin (MCH), **F:** mean cell haemoglobin concentration (MCHC), **G:** red cell distribution width standard deviation (RDW-SD), and **H:** percentage concentration of red cell distribution width coefficient of variation (RDW-CV). **FREDS**= Flavonoids-Rich Extract of *Detarium Senegalense*, **STZ**= Streptozotocin. **Control:** received distilled water and animal feed only. **STZ only:** received 45 mg/kg b.w STZ, distilled water and animal feeds. **STZ + Met:** received 45 mg/kg b.w STZ and 100 mg/kg b.w metformin. **STZ + SDF:** received 45 mg/kg b.w STZ and 100 mg/kg b.w sildenafil **STZ + FREDS 1:** received 45 mg/kg b.w STZ and 50 mg/kg b.w FREDS. **STZ + FREDS 2:** received 45 mg/kg b.w STZ and 75 mg/kg b.w FREDS. **STZ + FREDS 3:** received 45 mg/kg b.w STZ and 100 mg/kg b.w FREDS.

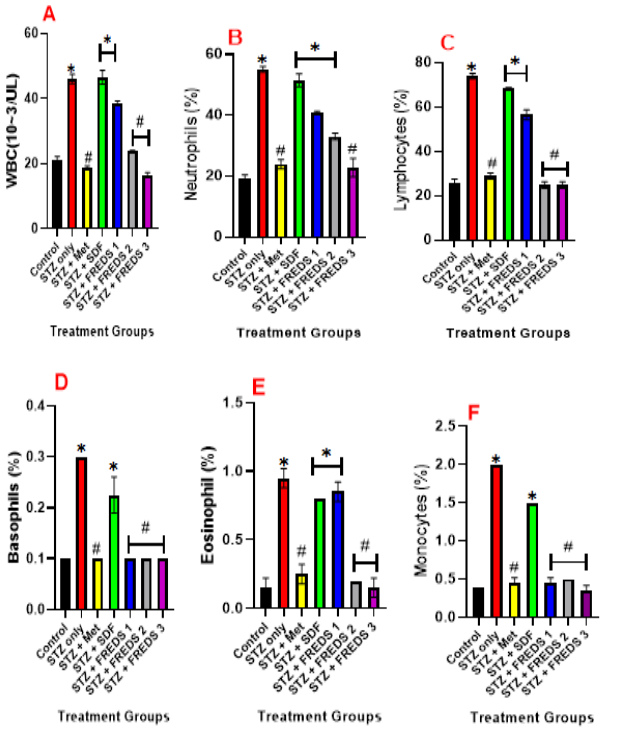

Figure 2. Effect of FREDS on the white blood cell count in STZ-induced type-2 Diabetes in albino rats

Data were expressed as Mean ± Standard Deviation. $p<0.05$, (n=6). * denotes values that are significantly different from the control. # denotes values that are not significantly different from the control. **FREDS**= Flavonoids-Rich Extract of *Detarium Senegalense*, **STZ**= Streptozotocin. **A:** white blood cell count, **B:** Neutrophils, **C** Lymphocytes, **D:** Basophils, **E:** Eosinophil, and **F:** Monocytes. **Control:** received distilled water and animal feed only. **STZ only:** received 45 mg/kg b.w STZ, distilled water and animal feeds. **STZ + Met:** received 45 mg/kg b.w STZ and 100 mg/kg b.w metformin. **STZ + SDF:** received 45 mg/kg b.w STZ and 100 mg/kg b.w sildenafil **STZ + FREDS 1:** received 45 mg/kg b.w STZ and 50 mg/kg b.w FREDS. **STZ + FREDS 2:** received

45 mg/kg b.w STZ and 75 mg/kg b.w FREDS. **STZ + FREDS 3:** received 45 mg/kg b.w STZ and 100 mg/kg b.w FREDS.

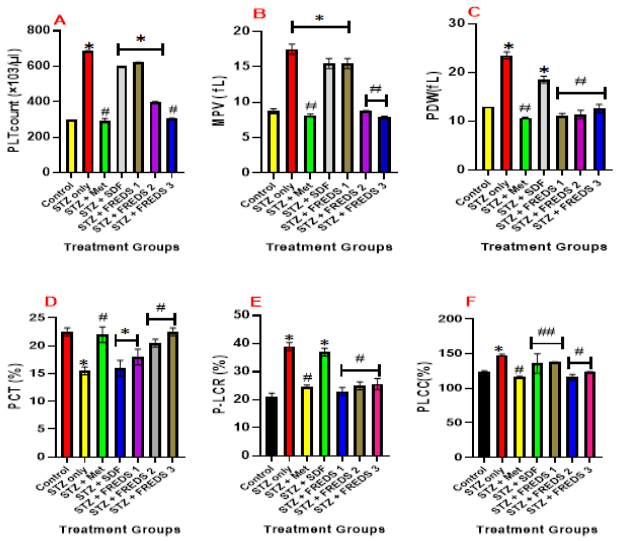

Figure 3. Effect of FREDS on the platelets count in STZ-induced type-2 Diabetes in albino rats

Data were expressed as Mean ± Standard Deviation. $p<0.05$, (n=6). * denotes values that are significantly different from the control. # denotes values that are not significantly different from the control. **FREDS**= Flavonoids-Rich Extract of *Detarium Senegalense*, **STZ**= Streptozotocin. **A:** platelet count (PLT).

B: Mean platelet volume (MPV), **C:** platelet distribution width (PDW), **D:** platelet crit (PCT) E**:** platelet large cell ratio (PLCR), and **F:** platelet large cell counts, (PLCC). **Control:** received distilled water and animal feed only. **STZ only:** received 45 mg/kg b.w STZ, distilled water and animal feeds. **STZ + Met:** received 45 mg/kg b.w STZ and 100 mg/kg b.w metformin. **STZ + SDF:** received 45 mg/kg b.w STZ and 100 mg/kg b.w sildenafil **STZ + FREDS 1:** received 45 mg/kg b.w STZ and 50 mg/kg b.w FREDS. **STZ + FREDS 2:** received 45 mg/kg b.w STZ and 75 mg/kg b.w FREDS. **STZ + FREDS 3:** received 45 mg/kg b.w STZ and 100 mg/kg b.w FREDS.

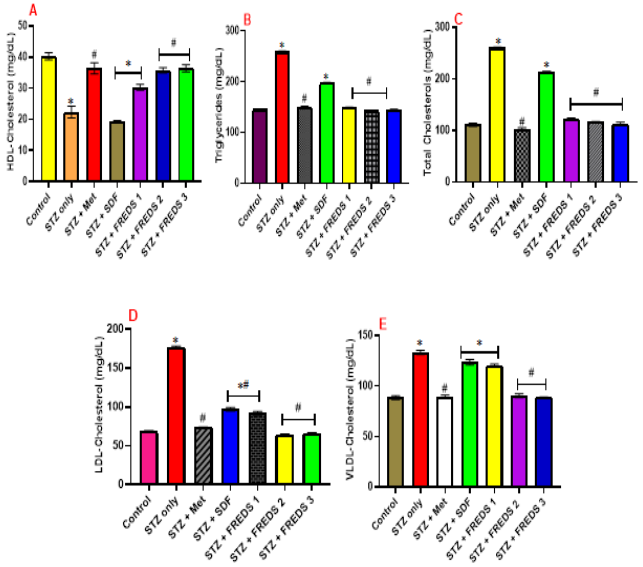

Figure 4. Effect of FREDS on lipid profiles in STZ-induced type-2 Diabetes in albino rats

Data were expressed as Mean ± Standard Deviation. $p<0.05$, (n=6). * denotes values that are significantly different from the control. # denotes values that are not significantly different from the control. **FREDS**= Flavonoids-Rich Extract of *Detarium Senegalense*, **STZ**= Streptozotocin, SDF= Sildenafil, Met= Metformin. **A:** HDL-cholesterol, **B:** Triglycerides, **C:** Total cholesterol, **D:** LDL- cholesterol, and **E:** VLDL- cholesterol. **Control:** received distilled water and animal feed only. **STZ only:** received 45 mg/kg b.w STZ, distilled water and animal feeds. **STZ + Met:** received 45 mg/kg b.w STZ and 100 mg/kg b.w metformin. **STZ + SDF:** received 45 mg/kg b.w STZ and 100 mg/kg b.w sildenafil **STZ + FREDS 1:** received 45 mg/kg b.w STZ and 50 mg/kg b.w FREDS. **STZ + FREDS 2:** received 45 mg/kg b.w STZ and 75 mg/kg b.w FREDS. **STZ + FREDS 3:** received 45 mg/kg b.w STZ and 100 mg/kg b.w FREDS.

CONCLUSION

FREDS exhibits both antidiabetic and antioxidant properties, which may be attributed to its high phytonutrient content. This may play a key role in reversing the impact of diabetes on haematological indices and lipid profiles. Taken together, the findings suggest that FREDS could serve as a safe alternative to traditional diabetes medications, helping to correct lipid metabolism imbalances and restore haematological abnormalities. Consequently, it may be recommended for the management of diabetes-related anemia, dyslipidemia, and associated complications.

Given our results, further studies with larger sample sizes and longer durations are necessary to confirm the persistence and reproducibility of the observed haematological and lipid metabolic changes. A more comprehensive understanding of FREDS' therapeutic potential could also be gained by examining its effects on additional relevant biochemical markers and organ functions. To translate these preclinical findings into practical applications, clinical studies involving human participants are crucial. Moreover, assessing potential side effects and optimizing dosing schedules will be key to ensuring that FREDS is a safe and effective supplementary treatment for lipid metabolism and hematological disorders linked to diabetes. This research paves the way for collaboration among researchers, pharmacologists, and healthcare professionals to further explore FREDS as a potential therapeutic agent for diabetes-related complications.

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