Oxidative Stress, Hyperglycemia, Hyperlipidemia, and Hemostasis Impairment as Risk Factors for Diabetes in Rats: Investigating the Therapeutic Potential of Samwa (*Cleome droserifolia*)

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ABSTRACT

The current study aimed to investigate the potential efficacy of Samwa (*Cleome droserifolia*) ethanolic extract of as a hypoglycemic, hypolipidemic, and antioxidant agent, as well as its role in enhancing hemostatic effects in alloxan-induced diabetic rats, a model for type II diabetes. A total of 36 rats were allocated into two main groups: the first group (Group 1, 6 rats), serving as the normal control, was maintained on a basal diet (BD), while the second group (30 rats) was used for the induction of type 2 diabetes and further subdivided into five equal subgroups. These subgroups were as follows: {Group 2: Diabetic rats fed solely on BD (positive control). Groups 3–6: Diabetic rats fed on BD and administered Samwa ethanolic extract (SEE) at doses of 100, 200, 300, and 400 mg/kg body weight per day, respectively, for 28 days}. Induction of diabetes with alloxan caused a significant increase ($p \leq 0.05$) in serum glucose, triglycerides, total cholesterol, LDL-c, malondialdehyde (MDA), hydrogen peroxide (H_2O_2), and leptin levels, with respective increases of 236.12%, 100.00%, 44.44%, 34.69%, 60.06%, 69.20%, and 67.40% compared to the normal control group. In contrast, HDL-c, paraoxonase, and arylesterase activities decreased by 42.65%, 51.04%, and 34.52%, respectively. Additionally, hemostatic parameters, including bleeding and clotting times, were prolonged at multiple time points (7, 14, 21, and 28 days). Treatment with SEE for 28 days significantly ameliorated these parameters in a dose-dependent manner. Improvements included reductions in glucose, lipid profiles, oxidative stress markers, and normalization of hemostatic parameters. These findings suggest that SEE has therapeutic potential in managing type 2 diabetes and its associated complications. Consequently, the incorporation of SEE into pharmacological formulations is recommended for individuals with type 2 diabetes.

Keywords: Liver functions, leptin, insulin, malonaldehyde, paraoxonase, arylesterase, bleeding and clotting times.

INTRODUCTION

Diabetes is a metabolic disorder characterized by impaired carbohydrate metabolism due to the body's diminished ability to produce or respond to insulin, leading to hyperglycemia (Wolf and Dean, 1987). This condition prevents the transport of glucose from the bloodstream into cells, resulting in elevated blood glucose levels. According to the International Diabetes Federation (IDF, 2021), diabetes caused an estimated 1.62 million deaths worldwide in 2021, ranking as the eighth leading cause of death. Approximately 10.5% of the global adult population (ages 20–79) is affected, with projections indicating that by 2045, 1 in 8 adults (783 million) will have diabetes.

While diabetes is a significant global health concern, its complications primarily arise from chronic conditions associated with the disease rather than its direct effects. These complications include peripheral arterial disease, coronary heart disease, retinal, renal vascular disease, and neurological disorders. Research has shown that severe manifestations of diabetes, such as ketoacidosis, neuropathy, cardiomyopathy, atherosclerosis, nephropathy, and immunomodulation, contribute to these complications (Jacob *et al.,* 1992; Takeda *et al.,* 2014; Shah *et al.,* 2019; Elsemelawy *et al.,* 2021 and Elhassaneen *et al.,* 2022a, 2024a).

Oxidative stress, induced by the overproduction of reactive oxygen species (ROS), plays a critical role in the pathogenesis of diabetes and its associated complications. ROS can damage cellular components, including proteins, lipids, and nucleic acids (Elhassaneen, 1996, 2004; Andallu & Varadacharyulu, 2003 and Mahran & Elhassaneen, 2023). This damage impairs cellular functions, causes oxidative damage to membranes (including cell membranes, mitochondria, lysosomes, and vessel walls), and increases susceptibility to lipid peroxidation (Esterbauer *et al.,* 1992; Elhassaneen *et al.,* 1996, 2022a and Elhassaneen & Abd Elhady, 2014). Consequently, oxidative stress and lipid peroxidation are significant contributors to the development of complications such as cardiovascular disease (CVD) and atherosclerosis in diabetes (Martín-

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Gallán *et al.,* 2003; Mishra & Singh, 2013 and Elhassaneen *et al.,* 2021 a,b,c).

Under normal physiological conditions, cells have robust antioxidant defense mechanisms to counteract ROS. These mechanisms include non-enzymatic and enzymatic components. Among the enzymatic elements, Paraoxonase-1 (PON1) plays a pivotal role. Also known as serum paraoxonase and arylesterase 1 (ARE), PON1 is a calcium-dependent enzyme synthesized in the liver and secreted into the bloodstream, where it binds to high-density lipoprotein (HDL). PON1 exhibits esterase and paraoxonase activity and protects against lipid peroxidation, thereby its functions as a hydrolase with a broad spectrum of substrates, which includes lipid peroxides. Also, PON-1 acts as a calcium-dependent arydialkylphosphatase that is synthesized in the liver and subsequently secreted into the bloodstream, where it binds to high-density lipoprotein (HDL), thus providing substantial atheroprotection (Mackness & Mackness, 2013 and Kumar *et al.,* 2020). The PON1 gene is stimulated by Peroxisome Proliferator-Activated Receptor Gamma (PPAR-γ), which enhances the synthesis and release of paraoxonase 1 enzyme from the liver, thereby mitigating atherosclerosis (Khateeb *et al.,* 2010). In human serum, nearly all endogenous serum PON activity is associated with HDL (Aviram and Vaya, 2013). The prevention of atherosclerosis by PON1 may be attributed to its lipid-modifying characteristics, antioxidant properties, anti-inflammatory effects, anti-apoptotic actions, anti-thrombotic capabilities, and anti-adhesion functions (Grzegorzewska *et al.,* 2021). Multiple studies have demonstrated that the levels and/or activity of PON and ARE enzymes are diminished in conditions of elevated oxidative stress, such as dyslipidemia, coronary artery disease, and diabetes (Boemi *et al.,* 2001; Gbandjaba *et al.,* 2012 and Aboraya *et al.,* 2022). Additionally, in diabetes mellitus, oxidative stress is primarily attributed to an increased generation of oxygen free radicals coupled with a marked decline in antioxidant defenses (Laaksonen *et al.,* 2000). Therefore, current studies suggest that intervention using antioxidants can protect PON1 from inactivation and/or reduction arising from oxidative stress, thus increasing the potential ameliorative effects against diabetes and related complications.

On the other hand, it is reviewed that in diabetic patients, CVD continues to be the primary cause of morbidity and mortality, with approximately 80% of patients succumbing to cardiovascular complications (Kaur *et al.,* 2018). Research indicates that hemostasis plays a role in the development of vascular complications associated with this metabolic disorder (Preston, 1982; Carr, 2001 and Aboraya *et al.,* 2022). Hemostasis is defined as the process of preventing and stopping bleeding by maintaining blood within a damaged blood vessel. The hemostatic process involves three major steps: vasoconstriction, the temporary blockage of a hole in a damaged blood vessel by a platelet plug, and blood coagulation (Boon, 1993). The hemostatic system consists of five major components: platelets, coagulation factors, coagulation inhibitors, fibrinolysis, and blood vessels (Lewis and Decie, 2002). Many studies have shown that most of the complications of DM, including Hyperglycemia, oxidative stress, and insulin resistance are related to the hemostatic system (Aboraya *et al.,* 2022). Hyperglycemia has been linked to the hemostatic system, as it has been observed to induce platelet-vascular activation and post-prandial coagulation activation (Kluft, 1994). Insulin resistance and deficiency have been shown to lead to platelet dysfunction, or hemostasis (Schneider, 2009). Given hemostasis' critical role in preserving bodily functions, the exploration of compounds that facilitate this process is of medical significance.

The aim of diabetes treatment is to get blood glucose levels down to normal in order to promote overall health and reduce the evolution and worsening of the disease's long-term consequences. Several decades ago, many therapies including insulin and various synthetic anti-diabetic agents/drugs were available but almost all of them can produce multiple side effects. Hypoglycemia, or excessively low blood glucose levels, is the most frequent adverse effect linked to anti-diabetic medications. It primarily affects elderly people with compromised liver or kidney function and is also not recommended in some healthy conditions like pregnancy (Murad *et al.,* 2009). Therefore, it is necessary to discover alternative therapies to manage this health problem. Numerous herbal plants are thought to be effective ways to prevent and/or manipulate diabetes and its complications (Scartezzini & Speroni, 2000; Aboraya *et al.,* 2022 and Elhassaneen *et al.,* 2022b, 2023). In the current study, Samwa (*Cleome droserifolia*), Family *Cleomaceae* is selected. It is grown in different regions including Egypt, Libya, Saudi Arabia, Palestine, Syria, and other arid and semi-arid areas (Moustafa *et al.,* 2019). Perhaps the Bedouin inhabitants of these areas use this herb to treat many diseases such as stomachache, abdominal and rheumatic pains, inflammations, skin allergies, open wounds and liver disorders (Abdel-Kader *et al.,* 2009 and Ezzat & Abdel Motaal, 2012). Also, different Samwa extracts have been used as hepatoprotective, hypoglycemic, antihistaminic, relaxant, tranquilizing, anticarcinogenic, antiparasitic, antioxidant, and antimicrobial agents (Mikhail, 2000, Ezzat & Abdel Motaal, 2012; Abdel Motaal *et al.,* 2014; Maksoud *et al.,* 2020; Elhassaneen *et al.,* 2024a). All of these biological impacts are

connected to the different classes of active secondary metabolites that occur naturally in Samwa including polyphenols, terpenes, flavonoids, glucosinolates, anthocyanin and alkaloids (Moustafa & Mahmoud, 2023 and Elhassaneen *et al.*, 2024a). According to our knowledge, studies related to explaining the potential mechanisms underlying the therapeutic effects of Samwa extracts against diabetes complications are still limited. Therefore, the present study sought to investigate the potential activities of an ethanolic extract of the Samwa (*Cleome droserifolia*) as a hypoglycemia, hypolipidemic and antioxidant substance as well as haemostatic effects enhancer in alloxan-induced diabetic rats as a model for type II diabetes.

MATERIALS AND METHODS

Materials

Samwa

Samwa **[***Cleome droserifolia* (Forssk.) Del.], ariel plant parts, were obtained from the desert lands adjacent to the city of Bir al-Abd City, North Sinai Governorate, Egypt, in December, 2023. The collected plant parts were verified by the Staff of the Faculty of Environmental Agricultural Sci., El-Arish Univ., El-Arish City, North Sinai Gov., Eg.

Chemicals, Instruments and Kits

Sigma-Aldrich in St. Louis, MO supplied alloxan and thiobarbituric acid (TBA). All other chemicals (Except as otherwise stated), casein, vitamins and salts mixtures, buffers, reagents and solvents of analytical grade were obtained from El-Ghomhorya Company of Trading Drugs, Chemicals, and Medical Instruments, El-Amiryia, Cairo, Eg. UV-visible spectrophotometer (UV-160A; Shimadzu Corporation, Kyoto, Japan) and Microplate Reader, (Manualslib, BioTek ELx808, USA), were used for all biochemical analyses. Kit's assays for glucose and malondialdehyde (MDA) were purchased from BIODIAGNOSTIC, Dokki, Giza, Eg. Triglycerides (TGs), Total cholesterol (TC), HDL-Cholesterol and LDL-Cholesterol were purchased from El-Nasr Pharmaceutical Chemicals, Cairo, Eg., and hydrogen peroxide (H_2O_2) from Elabscience, Houston, TX, USA.

Methods

Preparation of Samwa extract

Aerial parts samples from Samwa were manually sorted to remove foreign bodies and then washed with running water to remove the dust. The cleaned parts were dried in a hot air oven (Horizontal Forced Air Drier, Proctor and Schwartz Inc., Philadelphia, PA) at 40°C for 48 h and ground using high-speed mixers (El Araby Co., Benha, Egypt) to a fine powder and then sieved through a 0.25 mm sieve. The resulting powder was kept in polyethylene bags and stored in a refrigerator at 4°C for use in biological experiments. The resulting Samwa powder was used to prepare the ethanolic extract (SEE) according to the method reported by Gharib *et al.* (2022) with few modifications. In brief, 50g of dried Samwa powder was extracted with 500 ml of hydro-ethanolic (80%, 80 mL ethanol and 20 mL water) on an orbital shaker (Unimax 1010, Heidolph Instruments GmbH & Co. KG, Germany) at 55 ºC for 5 h. The extract was filtered on a Buchner funnel using filter paper, Whatman No. 5. A rotary evaporator under reduced pressure (Laborata 4000; Heidolph Instruments GmbH & Co. KG, Germany) at 40ºC was used to evaporate the residual solvent and the resulting extract was stored at 4ºC for the biological experiments.

Biological experimental

Ethical Considerations

The Ethical Considerations were approved by the Scientific Research Ethics Committee, Faculty of Home Economics, Menoufia Univ., Egypt. Approval # 05-SREC-12-2023.

Animals

Rats, albino adult males (137±8.35 g/each), got them from Station of Helwan, Ministry of Health and Population, Helwan, Cairo, Egypt.

Animal maintenance

The tests used mature male albino (Sprague Dawley) rats with an average body weight of 135±7.67g. Individual rats were housed in wire cages in a room with a temperature of 25±2.5°C and typical healthy circumstances. They were fed a basal diet (BD) for one week before beginning the experiment to allow for acclimatization.

Basal/standard diet

The basal diet (BD) is prepared by Reeves *et al.* (1993). As follows: (69.5%) corn starch, (10%) protein, (10%) corn oil, (5%) cellulose, (4%) mineral mixture, (1%) vitamin mixture, (0.3%) methionine, and (0.2%) choline chloride. Vitamin and salt mixture components are developed based on the same reference.

Induction of type-2 diabetic mellitus (T2D)

A diabetic state was established in normal healthy rats via subcutaneous injection of freshly made alloxan monohydrate in saline at a dose of 150 mg/kg body weight (Sheriff *et al.*, 2019). After 72 hours of injection of alloxan, fast blood glucose (FBG) was determined using a drop of blood drawn from the tail vein and subjected to a strip of glucometer (Abbott Glucometer Medicines Products, USA). Rats with FBG > 11mmol/L (198 mg/dl) were deemed to be diabetics and used for the study (Elhassaneen *et al.*, 2024a).

Experimental design

All biological studies followed the National Research Council's Institute of Laboratory Animal Resources and Commission on Life Sciences Rules (NRC, 1996). Thirty-six rats were divided into two groups: the usual control group (Group 1, 6 rats) was still fed on the BD, while the other main group (30 rats) was utilized for T2D induction and was evenly grouped into five equal sub-groups as follows: group (2), model control, fed on BD only as a positive control (diabetic rats) and groups (3-6) fed on BD and treated with CEE by a concentration 100, 200, 300 and 400 mg/kg body weight per a day, respectively. SEE was administrated to the animals by an intragastric tube for 28 days. The concentrations of SEE selected for the present study according to several previous studies (El-Khawaga *et al.*, 2010; El-Komy *et al.*, 2017; Elhassaneen *et al.*, 2023 and Elhassaneen *et al.*, 2024a). All of these groups mentioned were housed in one cage for 28 days.

Biological evaluation

Body weight gain (BWG, %), food intake (FI), and food efficiency ratio (FER) were recorded daily, and body weight was recorded weekly during the 28-day experimental period. BWG, FI, and FER were calculated according to Chapman *et al.* (1959) using the following equations: BWG (%) = (Final weight– Initial weight)/ Initial weight×100, FER = (Grams gain in body weight/Grams feed intake) both (g/28day).

Blood sampling

At the end of the experiment (28 days), rats were deprived of food overnight and sacrificed by decapitation. Blood samples were collected using the abdominal aorta. According to Drury and Wallington (1980), to clot blood samples, they are placed in a water bath (35°C) for 28 min. before being centrifuged for 10 minutes at 3000 rpm to separate the serum. The serum was carefully aspirated, transferred to a clean cuvette tube, and frozen at -20°C for future biochemical evaluation.

Blood Plasma Biochemical Attributes

a. Serum glucose, insulin and leptin

For measuring serum glucose the colorimetric method described by Tietz (1976) was used. Insulin was determined using the colorimetric detection method mentioned by Mirsalari and Elhami (2020). Leptin was assayed by Human Leptin ELISA Kit [Colorimetric], One-Step Assay, NPP2011ZP220, manufactured by Creative Biolabs neuroS, Shirley, NY, USA.

b. Liver functions

Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) activity were evaluated in serum utilizing the modified kinetic method of Tietz (1976), whilst alkaline phosphatase (ALP) activity was assessed using the modified kinetic method of Vassault *et al.* (1999).

c. Serum lipids profile

Total cholesterol (TC), triglycerides (TGs), HDL-Cholesterol and LDL-cholesterol were determined in serum similarly to the method of Ahmadi *et al.* (2008); Fossati & Prenape (1982); Lopes-Virella *et al.* (1977) and Richmod (1973), respectively.

d. Redox Status Indicator

Malondialdehyde (MDA) was assayed using the colorimetric approach given by Buege and Aust (1978) based on the reaction of thiobarbituric acid (TBA) with MDA. Serum hydrogen peroxide (H_2O_2) level was determined with the aid of a colorimetric assay kit (Elabscience, Houston, TX, USA). Paraoxonase activity was assayed in serum such as described by Eckerson *et al.* (1983) by using paraoxon as the substrate and expressed in U/L (1mmol *p*-nitrophenol generated per minute under the following conditions: the rate of hydrolysis of paraoxon was measured by monitoring the increase in absorbance at 412 nm at 25^0C). Arylesterase activity was assayed in serum such as described by Haagen and Brock (1992) by using phenylacetate as the substrate and expressed in kU/L (1mmol phenol generated per minute under the following conditions: the reaction mixture contained 1.0 mM phenylacetate and 0.9 mM calcium chloride in 9.0mM Tris-HCl buffer, pH 8.0).

e. Hemostatic effects

Bleeding time

Bleeding time (BT) in animals was assayed such as described by Ochei and Kolhatkar (2000). In brief, the tail of each animal was cleaned with ethanol spirit and kept from the perforated spaces of each cage. To measure bleeding time (BT), the tail tip was severed using a disposable lancet. Bleeding was timed using a stopwatch, starting immediately. The filter paper was used to absorb blood every 15 seconds. BT was recorded as the time when bleeding ceased, determined by the absence of blood on the filter paper. BT was calculated by multiplying the number of 15-second intervals by 60 seconds per minute.

Clotting time

Clotting time (CT) was determined using a modified method of Cole (1987). Briefly, the animal's tail was cleaned with ethanol spirit and then cut with a lancet. Blood was immediately collected into four pre-warmed glass tubes maintained at 37°C. The tubes were placed in a 37°C water bath. A stopwatch was started, and after 30 seconds, the tube ends were cut. The time when blood became gelatinous (clotted) was recorded. CT was calculated as the average clotting time across the four tubes.

3. Statistical Analysis

Data are presented as mean ± standard deviation (SD). Data were organized using Microsoft Excel 2016 and analyzed using one-way ANOVA followed by Tukey's post-hoc test to compare groups (Minitab Inc., State College, PA). Differences were considered statistically significant at $P \leq 0.05$ (Duncan *et al.*, 1977).

RESULTS AND DISCUSSIONS

1. Effect of treatment with Samwa ethanolic extract (SEE) on BWG, FI and FER of alloxan-diabetic rats

Table 1. Effect of a 28-days treatment with Samwa ethanolic extract (SEE) on BWG, FI and FER of alloxan-diabetic rats

Group	Body weight gain (BWG, %)		Feed intake (FI, g/day/rat)		Feed efficiency ratio (FER)	
	Mean ±SD	Percent of change (%)	Mean ±SD	Percent of change (%)	Mean ±SD	Percent of change (%)
Negative control (Normal)	1.043±0.009 [a]	-----	12.22±0.65 [a]	-----	0.087 ±0.005 [a]	-----
Positive control (Diabetes)	0.811±0.021 [c]	-22.24	9.84±0.78 [b]	-19.48	0.067 ±0.017 [b]	-22.99
T1, Treated with SEE (100 mg/kg bw/day)	0.831±0.007 [c]	2.47	9.98±0.45 [b]	1.42	0.070 ±0.009 [b]	4.48
T2, Treated with SEE (200 mg/kg bw/day)	0.865±0.011 [bc]	6.66	10.43±0.52 [b]	6.00	0.074 ±0.011 [ab]	10.45
T3, Treated with SEE (300 mg/kg bw/day)	0.911±0.056 [b]	12.33	10.97±0.39 [ab]	11.48	0.080 ±0.008 [a]	19.40
T4, Treated with SEE (400 mg/kg bw/day)	0.943±0.062 [b]	16.28	11.35±0.30 [a]	15.35	0.082 ±0.012 [a]	22.39

Values are mean ±SD (n= 6). Means under the same column denoted by a different letter indicate significant differences between treatments ($p \leq 0.05$). Negative control, normal rats without treatment; Positive control, alloxan-induced diabetic rats without treatment; SEE, Samwa aerial part ethanolic extract; T1, T2, T3 and T4, diabetic groups treated with SEE, bw, body weight. Percentage of change (%) for the diabetes group is calculated compared to the normal group, while it is calculated for the SEE treated groups compared to the diabetes group.

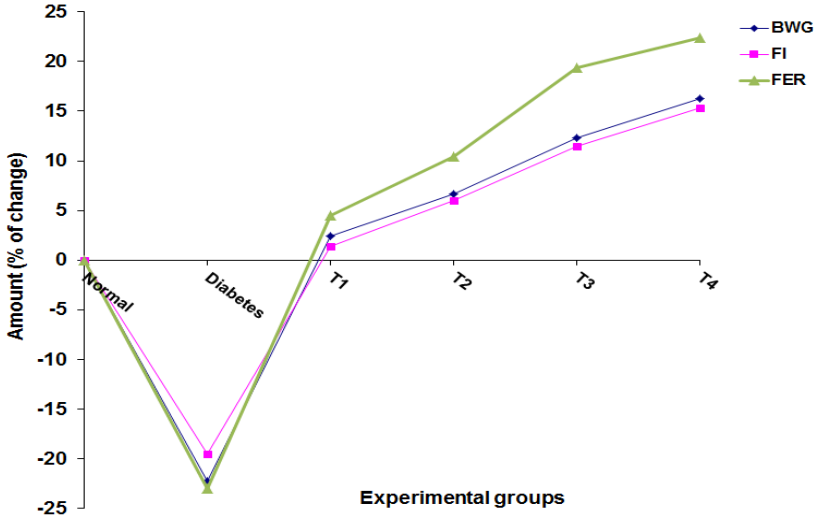

Figure 1. Effect of a 28-days treatment with Samwa ethanolic extract (SEE) on BWG, FI and FER of alloxan-diabetic rats

The guides of the experimental groups are shown in Table (1).

The effects of a 28-days treatment with Samwa ethanolic extract (SEE) on BWG, FI, and FER in alloxan-diabetic rats are presented in Table (1) and Figure (2). The data reveal a significant decrease in BWG, FI, and FER in alloxan-treated rats, with reductions of -22.24%, -19.48%, and -22.99%, respectively, compared to normal rats. However, treating diabetic rats with SEE (100, 200, 300, and 400 mg/kg body weight/day) for 28-days significantly ($p \leq 0.05$) increased these parameters in a dose-dependent manner. The observed increases in BWG were 2.47%, 6.66%, 12.33%, and 16.28%, in FI were 1.42%, 6.00%, 11.48%, and 15.35%, and in FER were 4.48%, 10.45%, 19.40%, and 22.39%, respectively, relative to the diabetic control group. These findings align with previous studies (Abou Haleka *et al.,* 2023 and Elhassaneen *et al.,* 2024a). Similarly, Helal *et al.* (2015) reported significant weight reduction in diabetic rats, which returned to near-normal levels following SEE treatment. Furthermore, Hashem and Shehata (2021) found that adding Samwa shoot powder to rabbit diets increased body weight due to enhanced feed intake. The current findings also corroborate studies using other plant powders/extracts with similar bioactive secondary metabolites (El-Khateb, 2015; Elhassaneen *et al.,* 2016a, b; Younis, 2016; El-Barbary, 2019; Yasin, 2021; Abd El-Rahman, 2021; Badawy, 2022; El-Hawary, 2023 and Mahmoud, 2023). The observed improvements in BWG, FI, and FER with SEE treatment may be attributed to the bioactive secondary metabolites present in Samwa, which exhibit various biological activities. Diabetes often induces liver dysfunction, leading to reduced body weight and food intake. Elhassaneen *et al.* (2016a) and Mansour (2017) noted that CCl_4-induced hepatotoxicity and diabetes significantly reduced body weight in rats. Consuming plant-based bioactive compounds, similar to those found in Samwa, restored body weight to near-normal levels. Additionally, diabetes and liver disorders are major contributors to malnutrition, as affected individuals often experience symptoms such as reduced feed intake, malabsorption, maldigestion, metabolic imbalances, and impaired nutrient storage (Morresion & Hark, 1999; Elhassaneen *et al.,* 2014; El-Khateb, 2015; Sayed Ahmed *et al.,* 2016; Aly *et al.,* 2017; Younis, 2016; Yasin, 2021; El-Hawary, 2023 and Elhassaneen *et al.,* 2023).

2. Effect of treatment with Samwa ethanolic extract (SEE) on liver functions of alloxan-diabetic rats

Table 2. Effect of a 28-days treatment with Samwa ethanolic extract (SEE) on liver functions of alloxan-diabetic rats

Group	Serum Aspartate aminotransferase activity (AST, U/L)		Serum alanine aminotransferase activity (ALT, U/L)		Serum alkaline phosphatase (ALP,U/L)	
	Mean ±SD	Percent of change (%)	Mean ±SD	Percent of change (%)	Mean ±SD	Percent of change (%)
Negative control (Normal)	48.42±2.76 [b]	------	33.65±1.56 [b]	----	126.37±6.51 [c]	----
Positive control (Diabetes)	67.43±7.14[a]	39.26	49.09±4.09 [a]	45.88	169.65±9.88 [a]	34.25
T1, Treated with SEE (100 mg/kg bw/day)	65.87±6.21[a]	-2.31	44.87±2.82 [a]	-8.60	161.43±7.41 [a]	-4.85
T2, Treated with SEE (200 mg/kg bw/day)	61.78±5.91 [ab]	-8.38	41.90±1.17 [ab]	-14.65	149.88±10.03 [b]	-11.65
T3, Treated with SEE (300 mg/kg bw/day)	55.89±4.17 [b]	-17.11	40.64±2.11 [ab]	-17.21	145.98±8.17 [b]	-13.95
T4, Treated with SEE (400 mg/kg bw/day)	55.01±4.98 [b]	-18.42	38.87±3.02 [b]	-20.82	139.67±6.42 [bc]	-17.67

The guides of the experimental groups are shown in Table (1).

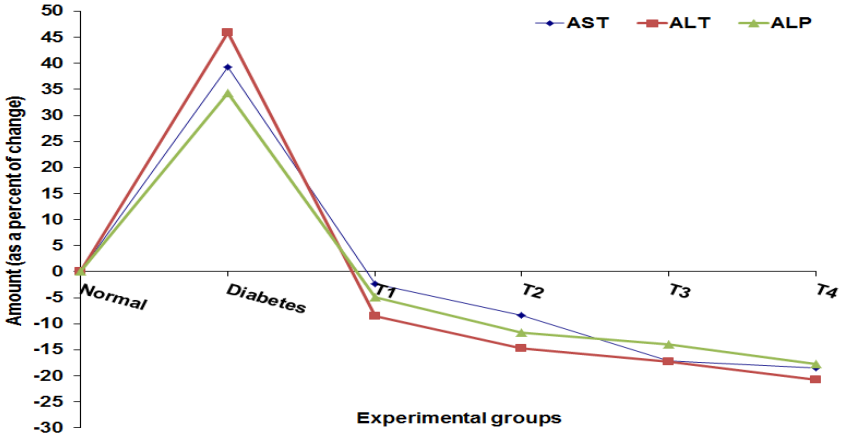

Figure 2. Effect of a 28-days treatment with Samwa ethanolic extract (SEE) on liver functions of alloxan-diabetic rats

The guides of the experimental groups are shown in Table (1).

The effect of a 28-days of treatment with Samwa ethanolic extract (SEE) on liver functions of alloxan-diabetic rats is shown in Table (2) and Figure (2). From such statistics, it is possible to observe an enormous increase in AST, ALT and ALP levels in alloxan-treated rats by a rate of 39.26, 45.88 and 34.25% compared with that of normal rats, respectively. However, treatment of the diabetic rats with SEE (100, 200, 300 and 400 mg/kg bw/day) for 28-days led to a significant ($p \leq 0.05$) decrease in the activities of these enzymes by the rate of -2.31, -8.38, -17.11 and -18.42%, -8.60, -14.65, -17.21 and -20.82%, and -4.85, -11.65, -13.95 and -17.67 % compared to the diabetic animals, respectively. Also, SEE treatment dose-dependently decreased the AST, ALT and ALP of rats. In general, aminotransferase enzymes (ALT and AST) plus ALP are typically found inside cells. The recorded high activities of AST, ALT and ALP in the serum clarified damage to cells rich in these enzymes including to the liver cells. Such data are in accordance with that reported by Ahmed *et al.* (2001) who examined the impact of Samwa ethanol extract on liver functions and found that the transaminase, AST and ALT, were dramatically raised in alloxan-induced diabetes. Treatment with Samwa extract resulted in a significant dose-dependent decrease in elevated levels of liver enzymes (transaminases) in rats. Also, Abou Haleka *et al.* (2023) found that Samwa methanolic extract pretreatment significantly decreased AST, ALT and ALP of rats exposed to adrenaline. Furthermore, El-Khawaga *et al.* (2010) reported that diabetes-induced liver disorders and other transaminases including a decrease in the levels of hepatic glycogen content and glucose 6 phosphate dehydrogenase (G6PD), increase in glucose 6 phosphatase (G6Pase). Transaminases in general are enzymes that catalysis a transamination reaction between an amino acid and an α-keto acid. Thus, are important in the synthesis of amino acids, which form proteins. A long time ago, measuring the level activities of various transaminases in the blood was important in the diagnosing and diseases many tracked (Ladue *et al.*, 1954 and Karmen *et al.*, 1955). They reported that the presence of elevated transaminases can be an indicator of liver and cardiac damage. Also, several authors reported that liver and pancreas disorders such as those found in diabetes probably cause cell lysis resulting in release the of intracellular enzymes into the blood (Pagana & Pagana, 1997; El-Khawaga *et al.*, 2010; Sayed-Ahmed *et al.*, 2020 and Elhassaneen *et al.*, 2022b). Data from the present study demonstrated that SEE exhibited hepatoprotective effect (s) in alloxan-induced diabetics. These effects may be ascribed to its high amount of active secondary metabolites including phenolics, carotenoids, flavonoids, anthocyanins, polysaccharides, terpenoids, triterpenoids, alkaloids and glycosides (Abdel-Kader *et al.*, 2009; Aboushoer *et al.*, 2010; Abdel Motaal *et al.*, 2011; Muhaidat *et al.*, 2015; Korkor *et al.*, 2022; Elhassaneen *et al.*, 2024a). All of those bioactive substances are known for their activity, which includes antioxidant and scavenging properties, as well as inhibition of lipid oxidation immune and inflammatory responses modulation and Gut Microflora improvement which, plays an important role in protecting the liver from many complications resulting from many diseases including diabetes (Elbasouny *et al.*, 2019; El-Barbary, 2019; Elhassaneen *et al.*, 2021a, c; 2022b; 2024a; Hashem & Shehata, 2021; Abd Elalal *et el.*, 2022; El-Hawary, 2023 and Mahmoud, 2023). With the same context, many studies indicated that plant parts contain phenolics, carotenoids, anthocyanins, polysaccharides and terpenoids such as those present in

SEE, which demonstrated protection against liver injuries induced by toxic chemicals (Ibrahim *et al.*, 2004; Mohamed *et al.*, 2013; Elhassaneen & Abd Elhady, 2014; Elhassaneen & Kamal, 2014; Elhassaneen *et al.*, 2016b; Sayd-Ahmed *et al.*, 2020; Mahran & Elhassaneen, 2023 and Elhassaneen & Mahrran, 2024). Data from the current study with the others concluded the protective effects of SEE against liver disorders induced by diabetes could be passed through one or more proposed mechanisms including increasing the liver's antioxidant capability, decreasing bilirubin levels, blocking the hepatocellular uptake of bile acids, modulating of the immunity responses, modulating of the hepatic Phase I and II metabolizing enzymes, scavenging of the reactive oxygen species, inhibiting of the lipid oxidation and declining the apoptosis process (Elhassaneen, 1996; Gao *et al*., 2003; Beattic *et al*., 2005; El-Nashar, 2007; Aly *et al*., 2017; Mahran *et al*., 2018; Sayed-Ahmed *et al.*, 2020; Elhassaneen *et al*., 2023; Mahran & Elhassaneen, 2023 and Elhassaneen & Mahran, 2024).

3. Effect of treatment with Samwa ethanolic extract (SEE) on blood glucose, insulin and leptin levels of alloxan-diabetic rats

Table 3. Effect of a 28-days treatment with Samwa ethanolic extract (SEE) on blood glucose, insulin and leptin levels of alloxan-diabetic rats

Group	Blood glucose ($mg.dl^{-1}$)		Insulin level ($\mu U.ml^{-1}$)		Leptin ($ng.ml^{-1}$)	
	Mean ±SD	Percent of change (%)	Mean ±SD	Percent of change (%)	Mean ±SD	Percent of change (%)
Negative control (Normal)	90.97 ±5.02 ^{f}	-----	-----	-----	4.97 ±0.36	-----
Positive control (Diabetes)	305.76 ±8.63 ^{a}	236.12	6.99 ±0.59 ^{b}	-----	8.32 ±0.59 ^{a}	67.40
T1, Treated with SEE (100 mg/kg bw/day)	267.56 ±9.70 ^{b}	-12.49	7.94 ±0.44 ^{b}	13.59	8.18 ±0.44 ^{a}	-1.68
T2, Treated with SEE (200 mg/kg bw/day)	236.89 ±6.98 ^{c}	-22.52	8.99 ±0.68 ^{ab}	28.61	8.04 ±0.27 ^{a}	-3.37
T3, Treated with SEE (300 mg/kg bw/day)	184.88 ±9.43 ^{d}	-39.53	10.24 ± 0.73 ^{a}	46.49	7.09 ±0.36 ^{b}	-14.78
T4, Treated with SEE (400 mg/kg bw/day)	163.85 ±7.34 ^{e}	-46.41	11.19 ±0.81 ^{a}	60.09	6.96 ±0.1 ^{b}	-16.35

The guides of the experimental groups are shown in Table (1).

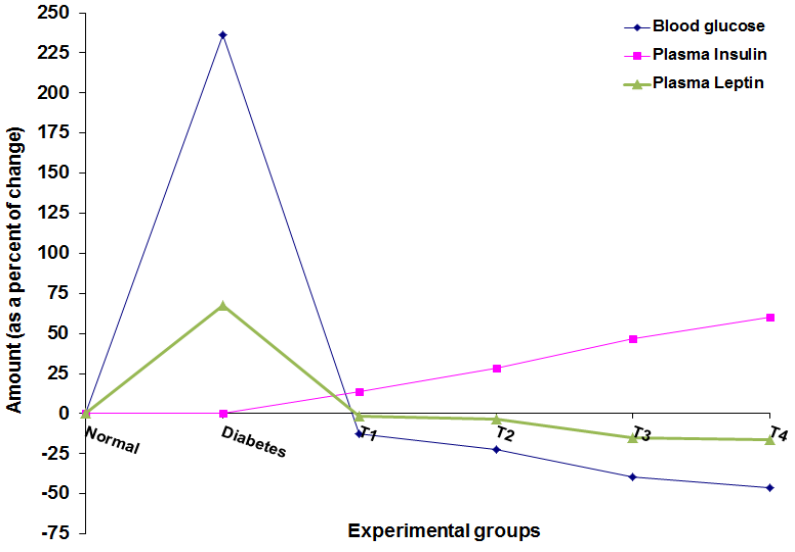

Figure 3. Effect of 28 days treatment with Samwa ethanolic extract (SEE) on blood glucose, insulin and leptin levels of normal and alloxan-diabetic rats

The guides of the experimental groups are shown in Table (1).

The impact of a 28-days treatment with Samwa ethanolic extract (SEE) on blood glucose, insulin, and leptin levels in alloxan-diabetic rats is presented in Table (3) and Figure (3). The data reveal a significant ($p \leq 0.05$) increase in blood glucose and serum leptin levels in alloxan-treated rats, with rates of 236.12% and 67.40%, respectively, compared to normal rats. However, treatment with SEE (100, 200, 300, and 400 mg/kg body weight/day) significantly ($p \leq 0.05$) reduced blood glucose levels by -12.49%, -22.52%, -39.53%, and -46.41% and serum leptin levels by -1.68%, -3.37%, -14.78%, and -16.35%, respectively, compared to diabetic controls. Conversely, serum insulin levels were significantly elevated with SEE treatment in a dose-dependent manner. These findings are consistent with previous studies on Samwa extracts and powders (Abdel Motaal *et al.,* 2011; Abdelfattah *et al.,* 2019; Abdel Maksoud *et al.,* 2020 and Ismail, 2022). The hyperglycemic state induced by alloxan is linked to the production of ROS, which cause DNA strand breaks in pancreatic β-cells, ultimately leading to cell death (Pusztai *et al.,* 1996; Lenzen, 2008; Arafa, 2021 and Elhassaneen *et al.,* 2021c). The loss of β-cells impairs glycogenolysis and enhances gluconeogenesis and hepatic glucose production (Gold, 1970; Caro, 1990; Raju *et al.,* 2001 and Beck-Nielsen, 2002). In the current study, the hypoglycemic effects of SEE were evident, as glucose levels decreased and insulin levels increased in diabetic rats treated with SEE. These effects are likely due to the high concentration of bioactive compounds in SEE, including phenolics, carotenoids, polysaccharides, terpenoids, alkaloids, and glycosides, which exhibit antioxidant and free radical scavenging activities and inhibit lipid oxidation (Aboushoer *et al.,* 2010; Abdel-Kader *et al.,* 2009; Abdel Motaal *et al.,* 2011; Aparadh *et al.,* 2012; Muhaidat *et al.,* 2015; Panicker *et al.,* 2020; Korkor *et al.,* 2022 and Elhassaneen *et al.,* 2024a). These properties contribute to improved glucose metabolism and alleviation of metabolic dysregulation associated with insulin resistance and type 2 diabetes (Elhassaneen *et al.,* 2014, 2015, 2024a; Sayed Ahmed *et al.,* 2016; Elmaadawy *et al.,* 2016; Aly *et al.,* 2017; Elbasouny *et al.,* 2019 and Abd El-Rahman, 2021). Leptin, primarily produced by adipose tissue but also synthesized in other organs such as the liver, stomach, and skeletal muscles, regulates energy balance by suppressing appetite, stimulating thermogenesis, and reducing glucose and body fat (Margetic *et al.,* 2002 and Meek & Morton, 2012). Leptin also interacts with insulin and other energy-regulating hormones, indirectly influencing glucose metabolism (Kraemer *et al.,* 2020). In the current study, leptin levels were elevated in alloxan-induced diabetic rats. Previous studies have shown that leptin can improve insulin resistance and glucose and lipid imbalances in diabetic mouse models (Toyoshima *et al.,* 2005). Additionally, insulin levels may contribute to the pathogenesis of leptin and its effects on glucose metabolism and hyperglycemia (Amitani *et al.,* 2013). Furthermore, leptin has been shown to reduce insulin synthesis by inhibiting pre-proinsulin mRNA expression in β cells (Kumar *et al.,* 2020). The decline in leptin levels in alloxan-diabetic animals treated with SEE was recorded which may be attributed to its different bioactive compounds content with their several biological roles (Panicker *et al.,* 2020; Korkor *et al.,* 2022 and Elhassaneen *et al.,* 2024a). Such biological roles could be affected by reducing the SEE through many mechanisms including mediation of the impacts of insulin, insulin-like growth factor, growth hormone, cytokines glucocorticoids, and metabolites (Margetic *et al.,* 2002).

4. Effect of treatment with Samwa ethanolic extract (SEE) on serum lipid profile parameters of alloxan-diabetic rats

Table 4. Effect of a 28-days treatment with Samwa ethanolic extract (SEE) on serum lipid profile parameters of alloxan-diabetic rats

Group	Triglycerides (TGs, mmol.$^{-1}$)		Total cholesterol (TC, mmol.$^{-1}$)		High density lipoprotein-Cholesterol (HDL-c, mmol.$^{-1}$)		Low density lipoprotein-Cholesterol (LDL-c, mmol.$^{-1}$)	
	Mean ±SD	Percent of change (%)	Mean ±SD	Percent of change (%)	Mean ±SD	Percent of change (%)	Mean ±SD	Percent of change (%)
Negative control (Normal)	0.71± 0.09 ^{c}	----	4.59± 0.19 ^{c}	----	2.11± 0.02	----	2.71± 0.17 ^{c}	----
Positive control (Diabetes)	1.42± 0.12 ^{a}	100.00	6.63± 0.29 ^{a}	44.44	1.21± 0.09	-42.65	3.65± 0.27 ^{a}	34.69
T1, Treated with SEE (100 mg/kg bw/day)	1.31± 0.10 ^{a}	-7.75	6.29± 0.31 ^{ab}	-5.13	1.31± 0.10	8.26	3.49± 0.22 ^{b}	-4.38
T2, Treated with SEE (200 mg/kg bw/day)	1.22± 0.07 ^{ab}	-14.08	6.03± 0.11 ^{b}	-9.05	1.40± 0.07	15.70	3.18± 0.31 ^{bc}	-12.88
T3, Treated with SEE (300 mg/kg bw/day)	1.14± 0.09 ^{b}	-19.72	5.26± 0.22 ^{bc}	-20.66	1.54± 0.2	27.27	2.98± 0.18 ^{c}	-18.36
T4, Treated with SEE (400 mg/kg bw/day)	1.03± 0.05 ^{bc}	-27.46	5.01± 0.14 ^{c}	-24.43	1.59± 0.20	31.40	2.88± 0.17 ^{c}	-21.10

The guides of the experimental groups are shown in Table (1).

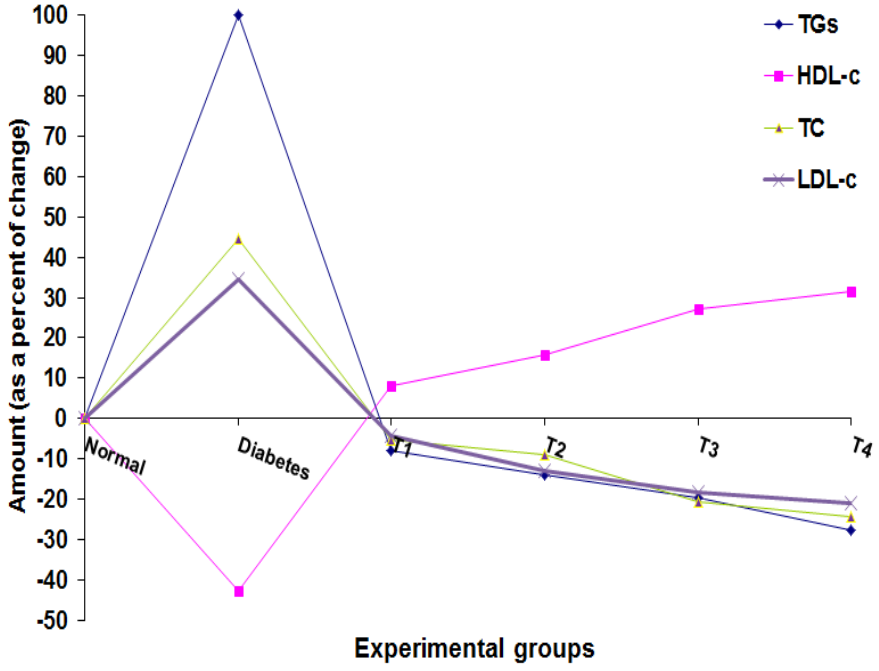

Figure 4. Effect of a 28-days treatment with Samwa ethanolic extract (SEE) on serum lipid profile parameters of alloxan-diabetic rats

The guides of the experimental groups are shown in Table (1).

The impact of a 28-days treatment with Samwa ethanolic extract (SEE) on serum lipid profile parameters of alloxan-diabetic rats is pointed out in Table (4) and Figure (4). The data indicates that a significant ($p \leq 0.05$) increase in serum triglycerides (TGs), total cholesterol (TC) and low-density lipoprotein- cholesterol (LDL-c) levels were observed in alloxan- treated rats by a rate of 100.00, 44.44 and 34.69% compared with that of normal rats, respectively. However, treatment of the diabetic rats with SEE (100,

200, 300 and 400 mg/kg bw/day) for 28 days led to significantly ($p \leq 0.05$) reduced TGs, TC and LDL-c levels by the rate of -7.75, -14.08, -19.72 and -27.46%, -5.13, -9.05, -20.66 and -24.43%, and -4.38, -12.88, -18.36 and -21.10% % compared to the diabetic animals, accordingly. The opposite direction was observed with high-density lipoprotein- cholesterol (HDL-c). Also, SEE treatment dose-dependently decreased the serum TG, TC and LDL-c levels and raised HDL-c levels in rats. The current data are consistence with those acquired by several authors (Pari & Latha, 2002; El-Khawaga *et al.,* 2010 and Elhassaneen *et al.,* 2024a). An increase in serum lipids (TG's, TC and LDL-c) of alloxan-diabetic rats could be ascribed to an elevation in the rate of lipolysis with a decline in lipogenesis which drives to release of more fatty acids into the blood circulation (Agardh *et al.,* 1999 and Elhassaneen *et al.,* 2022b). The elevation of fatty acid levels may participate in triglyceride biosynthesis (Seifter and England, 1982). On the other side, the insulin deficiency which was reported in alloxan-diabetic rats will lead to a decrease in lipoprotein lipase activity and an increase in the metabolism of free fatty acids from peripheral fat depots (Ahmed *et al.,* 2001 and El-Khawaga *et al.,* 2010). Such observations interpreted the formation of hyperlipidemic and hypercholesterolemic states associated with alloxan-induced diabetes in rats. Such phenomena, raised the serum bad lipid particles (TGs and TC) and decreased the serum good lipid particles (HDL-c), which was improved by SEE treatment. Several previous *in vivo* and *in vitro* studies exhibited the same behavior with the varied plant parts other than samwa (Elhassaneen *et al.,* 2021b, 2022a, 2024a; Shalaby & Elhassaneen, 2021; Aboraya *et al.,* 2022 and Gharib *et al.,* 2022). In general, hyperlipidemic and hypercholesterolemic states are well-established **risk** factors for several diseases including carcinogenesis, CVD, fatty liver, atherosclerosis, and peripheral vascular disease (Nelson, 2013 and Alloubani *et al.,* 2021). Several decades ago, synthetic oral antihyperlipidemic and antihypercholesterolemic drugs became popular but almost all of them exhibited adverse side effects. Data from the current study approved the effectiveness of SEE in enhancing the disturbance in serum lipid profiles of diabetes induced by alloxan in rats without side effects. The antihyperlipidemic and antihypercholesterolemic impact of SEE may be attributed to several mechanisms. These include inhibition of acyl-CoA cholesterol acyltransferase, a key enzyme in lipid metabolism. This inhibition can reduce intestinal cholesterol absorption. Additionally, SEE may stimulate the production of hepatic LDL receptors, enhancing the clearance of plasma LDL. Furthermore, SEE may raise the conversion of endogenous cholesterol to bile acids, and the polymeric structure of some SEE bioactive compounds (polyphenols, polysaccharides, terpenoids, triterpenoids, alkaloids, glycosides etc.) which potentially bind to cholesterol and bile acids. All of such data and observations could represent the mile stone towards the using of SEE in CVD treatment such as atherosclerosis through its hypolipidemic/ hypocholesterolemic effects.

5. Effect of a 28-days treatment with Samwa ethanolic extract (SEE) on plasma antioxidant enzymes (paraoxonase and Arylesterase, PON1) activities of alloxan-diabetic rats

Table 5. Effect of a 28-days treatment with Samwa ethanolic extract (SEE) on plasma antioxidant enzymes (paraoxonase and Arylesterase, PON1) activities of alloxan-diabetic rats

Group	Paraoxonase activity ($U.L^{-1}$)		Arylesterase activity ($kU.L^{-1}$)	
	Mean ±SD	Percent of change (%)	Mean ±SD	Percent of change (%)
Negative control (Normal)	111.98±3.88	-----	129.94±6.23	-----
Positive control (Diabetes)	54.83±4.13	-51.04	85.09±4.29	-34.52
T1, Treated with SEE (100 mg/kg bw/day)	61.89±2.17	12.88	89.23±2.89	4.87
T2, Treated with SEE (200 mg/kg bw/day)	73.64±4.55	34.31	96.17±5.87	13.02
T3, Treated with SEE (300 mg/kg bw/day)	81.02±5.11	47.77	108.78±6.05	27.84
T4, Treated with SEE (400 mg/kg bw/day)	89.75±3.12	63.69	111.65±5.17	31.21

The guides of the experimental groups are shown in Table (1).

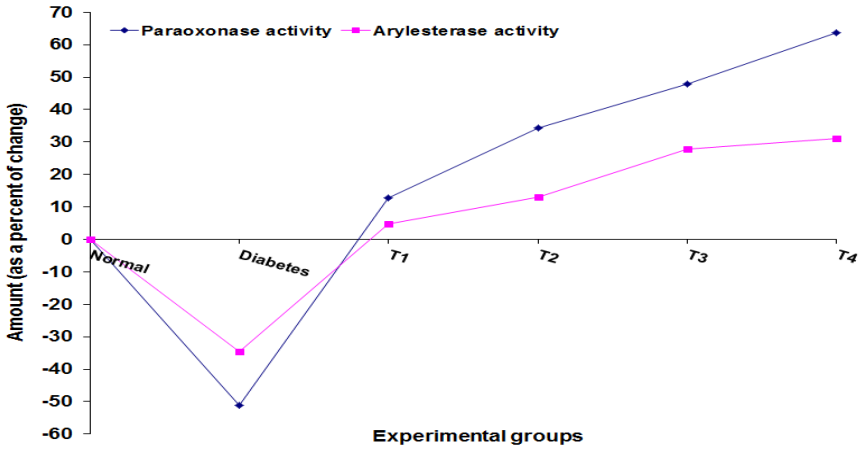

Figure 5. Effect of a 28-days treatment with Samwa ethanolic extract (SEE) on plasma antioxidant enzymes (paraoxonase and Arylesterase) activities of alloxan-diabetic rats
The guides of the experimental groups are shown in Table (1).

The effect of a 28-days treatment with Samwa ethanolic extract (SEE) on plasma antioxidant enzymes (paraoxonase and Arylesterase, PON1) activities of alloxan-diabetic rats is pointed out in Table (5) and Figure (5). The data shows a significant ($p \leq 0.05$) decrease in serum PON1 activities were observed in alloxan- treated rats by a rate of -51.04 and -34.52% compared with that of normal rats, respectively. However, treatment of the diabetic rats with SEE (100, 200, 300 and 400 mg/kg bw/day) for 28 days led to significant ($p \leq 0.05$) increases in PON1activities by the rate of 12.88, 34.31, 47.77 and 63.69%, and 4.87, 13.02, 27.84 and 31.21%, compared to the diabetic animals, respectively. Also, SEE treatment dose-dependently increased the serum PON1 activity levels in rats. These findings align with previous research in human and rat models demonstrating similar observations (Wegner *et al.*, 2011; Aviram & Vaya, 2013; Sibel *et al.*, 2014 and Aboraya *et al.*, 2022). Serum paraoxonase 1 (PON1) is a calcium-dependent enzyme that hydrolyzes various substrates, including lipid peroxides. Synthesized in the liver and associated with high-density lipoprotein (HDL), PON1 plays a crucial role in atheroprotection (Kumar *et al.*, 2020). Numerous studies have reported decreased PON1 activity in diseases characterized by oxidative stress, including diabetes (Boemi *et al.*, 2001; Amine *et al.*, 2011; Sibel *et al.*, 2014 and Aboraya *et al.*, 2022). This reduction in diabetic individuals may be attributed to hyperglycemia and/or oxidative stress, potentially through glycoxidation of HDL and subsequent enzyme inhibition. Moreover, glycosylation or oxidative modifications of transcription factors or nucleic acids can impair enzyme synthesis. The PON1 gene is activated by peroxisome proliferator-activated receptor gamma (PPAR-γ), leading to increased synthesis and release of PON1 from the liver, thereby reducing atherosclerosis (Khateeb *et al.*, 2010). The atheroprotective effects of PON1 are likely mediated through its lipid-modifying, antioxidant, anti-thrombotic, anti-apoptotic, anti-inflammatory, and anti-adhesion properties (Grzegorzewska *et al.*, 2021). Also, numerous studies have shown that the decrease in PON1 activity contributes significantly to high plasma levels of homocysteine-thiolactone, which damages proteins by homocysteinylation and involves vascular disease (Yilmaz, 2012). Serum PON1 activity was increased with the treatment of SEE which might be related to the direct stimulating effect of SEE on PON1 and/or its biological activities (Elhassaneen *et al.*, 2024a). In a similar study, Aboraya *et al.* (2022) reported the same results with other plant parts extract (*Ganoderma lucidum*) which have almost the same bioactive compound found in SEE. Such bioactive compounds measured in SEE recorded several biological compounds including antioxidant and scavenging activities, and inhibition of lipid oxidation (Elhassaneen *et al.*, 2024b). With the same context, Sibel *et al.* (2014) reported a rise in PON1 activities with the applied of other antioxidants i.e. vitamin B_6 in diabetic rats. These findings suggest that treatment with SEE may protect PON1 from inactivation and/or degradation, thereby mitigating oxidative stress and potentially improving diabetic conditions and their associated complications.

6. Effect of a 28-days treatment with Samwa ethanolic extract (SEE) on serum ROS and MDA levels of alloxan-diabetic rats

Table 6. Effect of 28-days treatment with Samwa ethanolic extract (SEE) on serum ROS and MDA levels of alloxan-diabetic rats

Group	Hydrogen peroxide (H_2O_2, mmol.l^{-1})		Malondialdehyde (MDA, nmole.mL^{-1})	
	Mean ±SD	Percent of change (%)	Mean ±SD	Percent of change (%)
Negative control (Normal)	38.93 ± 0.13 ^{d}	-----	6.51±0.09 ^{c}	-----
Positive control (Diabetes)	65.87 ± 0.27 ^{a}	69.20	10.42±0.23 ^{a}	60.06
T1, Treated with SEE (100 mg/kg bw/day)	59.43 ± 0.11 ^{ab}	-9.78	9.78±0.11 ^{a}	-6.14
T2, Treated with SEE (200 mg/kg bw/day)	54.84 ± 0.16 ^{b}	-16.75	8.74±0.17 ^{ab}	-16.12
T3, Treated with SEE (300 mg/kg bw/day)	49.73 ± 0.09 ^{bc}	-24.50	7.85±0.31 ^{b}	-24.66
T4, Treated with SEE (400 mg/kg bw/day)	46.63 ± 0.12 ^{c}	-29.21	7.29±0.19 ^{bc}	-30.04

The guides of the experimental groups are shown in Table (1).

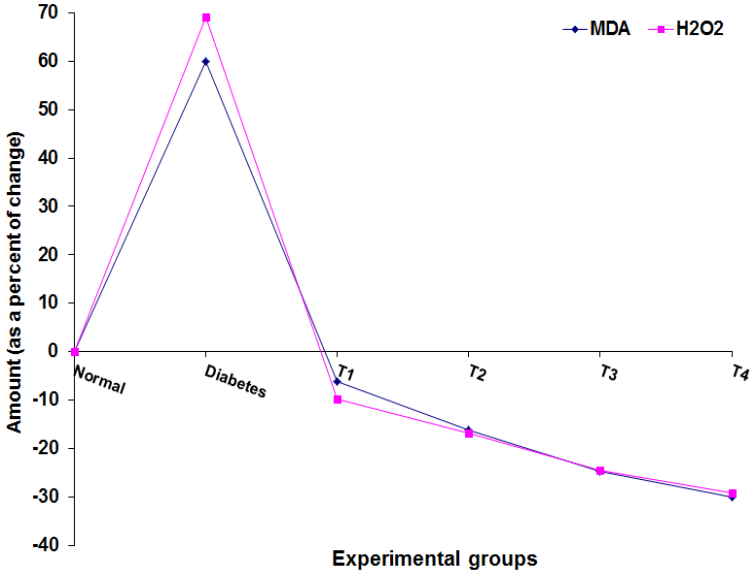

Figure 6. Effect of a 28-days treatment with Samwa ethanolic extract (SEE) on hepatic ROS and MDA levels of alloxan-diabetic rats

The guides of the experimental groups are shown in Table (1).

The effect of 28 days treatment with Samwa ethanolic extract (SEE) on plasma oxidants (ROS and MDA) levels of alloxan-diabetic is pointed out in Table (6) and Figure (6). The data shows a significant ($p \leq 0.05$) increase in serum ROS and MDA levels in alloxan- treated rats by a rate of 69.20 and 60.06% compared with that of normal rats, respectively. However, treatment of the diabetic rats with SEE (100, 200, 300 and 400 mg/kg bw/day) for 28-days led to significantly ($p \leq 0.05$) reduced ROS and MDA levels by the rate of -9.78, -16.75, -24.50 and -29.21%, and -6.14, -16.12, -24.66 and -30.04%, compared to the diabetic animals, respectively. Also, SEE treatment dose-dependently decreased the serum ROS and MDA levels in rats. Data in the current study found that alloxan-injection produced a significant reduction in serum antioxidant enzyme activities associated with a significant rise in H_2O_2 and MDA contents in comparison to the typical control animal. Such these observations are relatively in consistent with several previous studies (El-Khawaga *et al.*, 2010; Arafa, 2021 and Elhassaneen *et al.*, 2021a, c, 2024a). The increasing of MDA levels induced in the alloxan group might be

attributed to the hypoinsulinemia recorded. Hypoinsulinemia stimulates the activity of fatty acyl coenzyme -A -oxidase, which takes action on the β-oxidation of fatty acids that leads to lipid peroxidation (Schlaepfer and Joshi, 2020). As reviewed by Baynes (1991), increased lipid peroxidation disturbance the cell membrane functions by lowering membrane fluidity, which alters the activities of membrane-bound enzymes and receptors (Baynes, 1991). These lipid peroxidation products are highly cytotoxic and react with the cell of organelles such as mitochondria, lysosomes and cell wall membrane (Esterbauner *et al.,* 1992; Elhassaneen & Abd Elhady, 2014; Elhassaneen *et al.,* 1996, 2016a,b and Badawy, 2017). In the same context, Grune *et al.* (1997) found that MDA is a modulator of signal transduction pathways that disturb cellular activities. For example, the raised levels of ROS and/or MDA might decrease the antioxidant activities such super oxide dismutase (SOD) in alloxan-diabetic rats (Elhassaneen *et al.,* 2021a, c, 2023; El-Hawary, 2023 and Ismail *et al.,* 2024). The study of Abou-Seif and Youssef (2004) reported that Hyperglycemia triggers several glucose auto-oxidation and protein kinase C activation, leading to increased production of oxidants such as superoxide ($O_2^{\cdot-}$) and hydroxyl (·OH) radicals as well as hydrogen peroxide (H_2O_2) which decrease the SOD activity (Abou-Seif and Youssef, 2004). On the other side, official sources suggest that MDA-induced mutagenic and carcinogenic effects (Shamberger *et al.,* 1974). Data from the current investigation showed that treatment of the allopxan-diabetic rats with SEE removed some metabolic abnormalities caused by diabetes in different cells by decreasing the ROS (H_2O_2) and the MDA formation. Such observation is in partial agreement with that mentioned by several authors (Devi *et al.,* 2010; Nagy & Amin, 2015 and Abdullah *et al.,* 2016). Therefore, our data suggested that the CEE probably can treat the hyperglycemic effect by improving insulin sensitivity, at least in part, by boosting lipid metabolism and reducing oxidative stress in diabetic rats.

7. Effect of a 28-days treatment with Samwa ethanolic extract (SEE) on haemostasis process parameters of alloxan-diabetic rats

Table 7. Effect of a 28-days treatment with Samwa ethanolic extract (SEE) on bleeding time of alloxan-diabetic rats

Group	Bleeding time (Minutes)			
	Day 7	Day 14	Day 21	Day 28
Negative control (Normal)	5.97 ±0.25 ^{abA}	4.21 ±0.29 $^{c\ B}$	4.02 ±0.40 $^{c\ C}$	3.70 ±0.44 ^{dD}
Positive control (Diabetes)	6.71 ±0.28 $^{a\ A}$ (12.40)	5.34 ±0.35 $^{ab\ B}$ (26.84)	4.53 ±0.29 ^{bcC} (12.57)	4.09 ±0.56 ^{cD} (10.58)
T1, Treated with SEE (100 mg/kg bw/day)	5.39 ±0.41 ^{bB} (-19.74)	6.01 ±0.11 $^{a\ A}$ (12.55)	4.90 ±0.13 $^{b\ C}$ (8.26)	5.28 ±0.51 $^{a\ BC}$ (29.02)
T2, Treated with SEE (200 mg/kg bw/day)	5.01 ±0.19 $^{bc\ AB}$ (-25.34)	4.90 ±0.22 $^{bc\ B}$ (-8.30)	5.36 ±0.22 $^{a\ A}$ (18.38)	4.51 ±0.42 ^{bC} (10.09)
T3, Treated with SEE (300 mg/kg bw/day)	5.41 ±0.31 $^{b\ A}$ (-19.36)	5.08 ±0.24 $^{b\ AB}$ (-4.95)	4.50 ±0.31 $^{bc\ C}$ (-0.56)	4.29 ±0.55 $^{bc\ C}$ (4.93)
T4, Treated with SEE (400 mg/kg bw/day)	4.94 ±0.19 $^{c\ A}$ (-26.38)	5.23 ±0.30 $^{b\ A}$ (-2.15)	3.34 ±0.20 $^{d\ B}$ (-26.14)	3.39 ±0.29 $^{d\ B}$ (-17.13)

Means in the same column denoted by different small superscript letters indicate significant differences between treatments ($p \leq 0.05$). Means in the same raw denoted by different capital superscript letters indicate significant differences bleeding time periods ($p \leq 0.05$). Data in parentheses represent the percentage of change (%), for the diabetes group is calculated compared to the normal group, while it is calculated for the SEE treated groups contrasted to the diabetes group. The guides of the experimental groups are shown in Table (1).

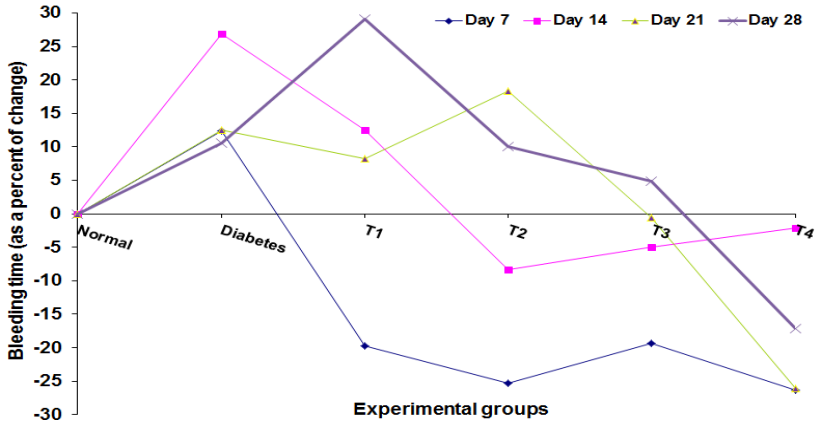

Figure 7. Effect of a 28-days treatment with Samwa ethanolic extract (SEE) on bleeding time of alloxan-diabetic rats

Values are mean (n= 6). The percentage of change (%) for the diabetes group is calculated compared to the normal group, while it is calculated for the SEE treated groups contrasted to the diabetes group. The guides of the experimental groups are given in Table (1).

Table 8. Effect of a 28-days treatment with Samwa ethanolic extract (SEE) on clotting time of alloxan-diabetic rats

Group	Clotting time (Minutes)			
	Day 7	Day 14	Day 21	Day 28
Negative control (Normal)	7.81±0.34 $^{a\ A}$	6.93±0.23 $^{b\ B}$	5.96±0.17 $^{ab\ C}$	4.81±0.22 $^{ab\ D}$
Positive control (Diabetes)	8.11±0.18 $^{a\ A}$ (3.89)	8.01±0.40 $^{a\ A}$ (15.55)	6.10±0.12 $^{a\ B}$ (2.38)	5.14±0.19 $^{a\ C}$ (6.77)
T1, Treated with SEE (100 mg/kg bw/day)	5.78±0.24 $^{b\ A}$ (-28.73)	5.66±0.29 $^{bc\ A}$ (-29.30)	4.64±0.45 $^{b\ B}$ (-24.01)	4.61±0.33 $^{b\ B}$ (-10.24)
T2, Treated with SEE (200 mg/kg bw/day)	5.28±0.3 $^{c\ A}$ (-34.86)	3.98±0.12 $^{d\ C}$ (-50.31)	4.47±0.52 $^{bc\ B}$ (-26.82)	3.86±0.28 $^{bc\ C}$ (-24.95)
T3, Treated with SEE (300 mg/kg bw/day)	6.32±0.52 $^{ab\ A}$ (-22.01)	6.12±0.22 $^{b\ B}$ (-23.60)	6.11±0.22 $^{a\ A}$ (-0.13)	3.54±0.30 $^{c\ B}$ (-13.50)
T4, Treated with SEE (400 mg/kg bw/day)	5.98±0.42 $^{b\ A}$ (-26.26)	5.28±0.30 $^{c\ B}$ (-34.02)	3.82±0.18 $^{c\ C}$ (-35.74)	3.70±0.18 ^{cC} (-25.69)

The guides for the experimental groups are shown in Table1 and for the statistical analysis are shown in Tables 7.

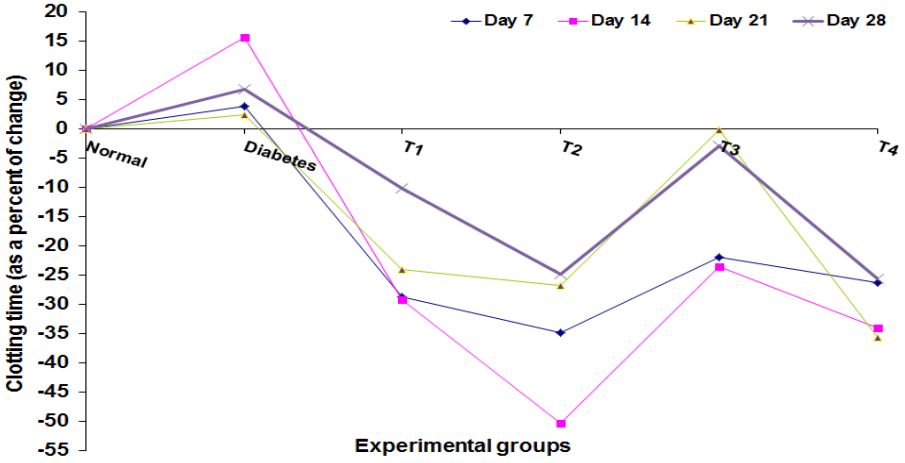

Figure 8. Effect of a 28-days treatment with Samwa ethanolic extract (SEE) on clotting time of alloxan-diabetic rats

The guides of the experimental groups are shown in Table (1).

Tables (7 and 8) and Figures (7 and 8) present the effects of a 28-days of Samwa ethanolic extract (SEE) treatment on hemostasis parameters in alloxan-diabetic rats. In diabetic rats, bleeding and clotting times were significantly increased compared to controls at 7, 14, 21, and 28 days ($p \leq 0.01$), with increases of 12.40%, 26.84%, 12.57%, and 10.58% for bleeding time and 3.89%, 15.55%, 2.38%, and 6.77% for clotting time, correspondingly. Treatment with SEE (100, 200, 300, and 400 mg/kg bw/day) for 28 days significantly decreased these parameters in diabetic rats compared to controls ($p \leq 0.05$). This effect exhibited a partial dose-dependent relationship. Hemostasis involves a complex interplay of processes that maintain blood fluidity while controlling bleeding from injured vessels. As described by Dapper *et al.* (2007) and Tanko *et al.* (2012), this intricate process includes vasoconstriction, thrombin activation, platelet adhesion and activation, fibrin formation, and subsequent inactivation of coagulation. This study focused on the effects of SEE on bleeding and clotting times, key parameters reflecting vascular and platelet responses (bleeding time) and the function of clotting factors in the intrinsic pathway (clotting time) (Ochei & Kolhatkar, 2000 and Dapper *et al.*, 2007). The significant reduction in clotting time observed with SEE treatment suggests an enhancement of certain clotting factors involved in the intrinsic pathway. Such a date is in accordance with that reported by several studies carried out with plant parts other than Samwa. For example, Tanko *et al.* (2012) and Aboraya *et al.* (2022) found that aqueous extracts of *Ganoderma lucidum* improved hemostasis, specifically reducing, i.e., bleeding and clotting times in normal rats. Similarly, Okoli *et al.* (2007) and Bamidele *et al.* (2010) observed similar effects with extracts of *Ageratum conyzoides* and *Aspilia africana*. The photochemistry study of *Samwa ariel part* indicated that it has included a high content of active secondary metabolites such polyphenols, polysaccharides, flavonoids, alkaloids and carotenoids which demonstrated numerous biologically active effects including, antioxidant activity, free radical scavenging, and lipid oxidation inhibition (Elhassaneen *et al.*, 2024a). Also, some of such active secondary metabolites, polyphenols and alkaloids, have been linked to plant hemostatic activity by intercepting the bleeding of harm vessels by precipitating the proteins to form vascular plugs (Okoli *et al.*, 2007). Therefore, the haemostatic mechanism of the SEE could probably be regarding the presence of these active secondary metabolites with their different biological roles.

8. Correlation studies

The correlation between biological oxidant (H_2O_2 and MDA), lipid fractions (HDL and LDL-c), and enzymatic antioxidants in alloxan-diabetic rats treated with Samwa ethanolic extract (SEE) for 28 days is indicated in Table (9). When all treatments were considered in the statistical analysis, significant differences were discovered among redox status parameters i.e. oxidative stress and antioxidant defense systems. PON was negatively correlated with MDA (r= - 0.8063, p=0.001), HDL-c (r=- 0.8243, p= 0.001) and H_2O_2 (r= - 0.7312, p=0.01), and positively correlated with HDL-c (r= + 0.8789, p=0.001). The same behavior was exhibited with ARE. Also, MDA was negatively correlated with HDL-c (r= - 0.8215, p=0.001) and positively correlated with LDL-c (r= + 0.7638, p=0.01). The same behavior was exhibited with H_2O_2. These correlations suggest that significant elevations in MDA and H_2O_2 would be unlikely in diabetic rats without concurrent alterations in antioxidant defense systems, including PON and ARE. This observation aligns with findings by Aviram and Vaya (2013), who demonstrated that the addition of PON to HDL significantly prolonged the lag phase of lipid oxidation and reduced the formation of HDL peroxides and aldehydes in human serum. This inhibitory effect was most pronounced when PON was added before the onset of oxidation. Furthermore, Aviram *et al.* (1998) showed that PON effectively prevents the accumulation of oxidized lipids during induced oxidation and can even degrade preformed oxidized lipoproteins. These effects are likely attributed to PON's ability to hydrolyze specific lipoprotein peroxides during lipid oxidation. Supporting these findings, Shalaby (2014) reported an inverse relationship between plasma MDA levels and antioxidant enzyme activity in diabetic rats. Similarly, Elhassaneen *et al.* (2021a) observed significant differences in plasma MDA levels and antioxidant enzyme activity in diabetic rats treated with *Catharanthus roseus* extracts. Furthermore, Elhassaneen *et al.* (2024a) showed important associations between plasma MDA and antioxidant enzyme levels in diabetic rats treated with *Ganoderma lucidum* extract. All of these extracts often contain many of the active secondary metabolites that are found in the extract understudy. As shown in Figure (9), oxidative stress, hyperglycemia, hyperlipidemia and hemostasis degradation, as represent risk factors for diabetic disease, can be treated by Samwa ethanol extract (SEE) through many intracellular pathways.

Table 9. Correlation between biological oxidant (H_2O_2 and MDA) and lipid fractions (HDL and LDL-c), and enzymatic antioxidant in alloxan-diabetic rat's treated with Samwa ethanolic extract (SEE) for 28-days

Parameters	*r*	Parameters	*r*
MDA/PON	- 0.8063**	MDA /ARE	- 0.7632 **
HDL-c/PON	+ 0.8789**	HDL-c/ARE	+ 0.7659 **
LDL-c/PON	- 0.8243**	LDL-c/ARE	- 0.7856*
H_2O_2/PON	- 0.7312*	H_2O_2/ARE	- 0.6947 *
MDA/HDL-c	- 0.8215**	H_2O_2/HDL-c	- 0.7395**
MDA /LDL-c	+ 0.7638 *	H_2O_2/LDL-c	+ 0.6769 *

* P ≤ 0.05 ** P ≤ 0.01

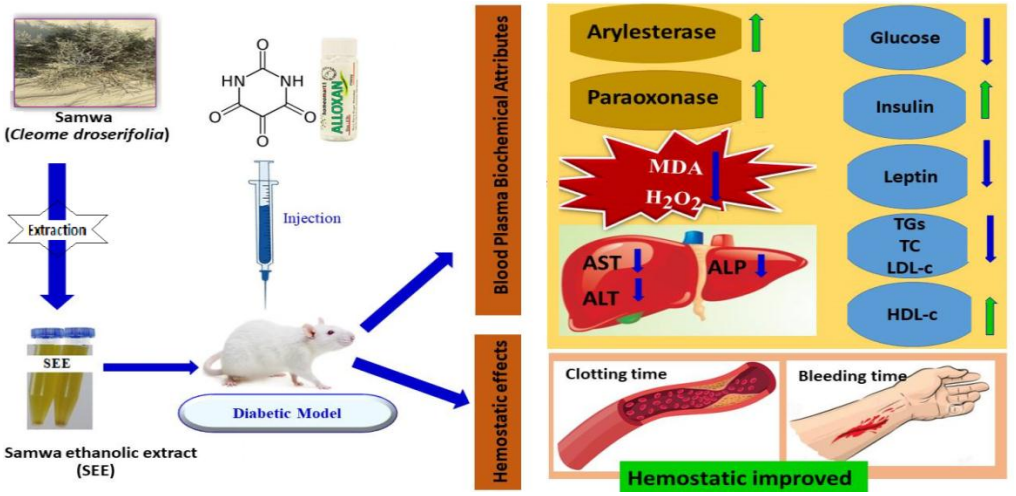

Figure 9. Graphical summary demonstrating the effect of Samwa ethanolic extract (SEE) on diabetes complications induced by alloxan

CONCLUSION

Type 2 diabetes is a chronic condition characterized by persistently high blood glucose levels resulting from insufficient insulin production or the body's ineffective response to insulin. Beyond these primary factors, oxidative stress plays a pivotal role in the development and progression of diabetic complications. The findings from the present investigation demonstrate the efficacy of Samwa ethanolic extract (SEE) in partially ameliorating type 2 diabetes and its associated complications in alloxan-induced diabetic rats. These complications include hyperglycemia reduction, increased insulin levels, enhanced serum antioxidant enzyme activities (paraoxonase and arylesterase), reduced serum oxidants (MDA and H_2O_2) levels, and improved hemostatic effects in diabetic rats.

These results provide a promising basis for considering SEE as a therapeutic agent in the management of type 2 diabetes and its complications. Consequently, the inclusion of SEE in pharmacological formulations for patients with type 2 diabetes is recommended, though further research is necessary to substantiate and expand upon these findings.

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Conflicting interests

The authors acknowledge that this is not present in the article for the possibility of publishing it.

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الملخص العربي

الإجهاد التأكسدي، ارتفاع سكر الدم، ارتفاع الدهون، واضطراب التوازن الدموي كعوامل خطر لمرض السكري في الفئران: دراسة الفعالية العلاجية لنبات الساموا (*Cleome droserifolia*)

نيفين سيوفى اسماعيل، يوسف عبد العزيز الحسانين، دعاء عمر محمد جودة

هدفت الدراسة الحالية إلى تقييم الفعالية المحتملة لاستخلاص الإيثانول من نبات الساموا (*Cleome droserifolia*) كعامل خافض للسكر في الدم، خافض للدهون، ومضاد للأكسدة، بالإضافة إلى دوره في تعزيز التأثيرات المساعدة على التوازن الدموي في الفئران المصابة بالسكري من النوع الثاني المُعتمدة على الألوكسان. تم توزيع ٣٦ فأر على مجموعتين رئيسيتين: المجموعة الأولى (المجموعة ١، ٦ فئران، والتي تمثل المجموعة الضابطة السالبة/الطبيعية وتم تغذيتها على نظام غذائي أساسي (BD)، بينما تم استخدام المجموعة الثانية (٣٠ فأر) لتحفيز السكري من النوع الثاني وتقسيمها إلى خمس مجموعات فرعية متساوية. كانت هذه المجموعات الفرعية كما يلي: المجموعة ٢: فئران مصابة بالسكري وتم تغذيتها فقط على النظام الغذائي الأساسي (المجموعة الضابطة الموجبة). المجموعات ٣-٦ :فئران مصابة بالسكري تم تغذيتها على النظام الغذائي الأساسي وتم إعطاؤها مستخلص الساموا الإيثانولي (SEE) بجرعات ١٠٠، ٢٠٠، ٣٠٠، و٤٠٠ ملغ/كجم من وزن الجسم يوميًا لمدة ٢٨ يومًا .أدى تحفيز السكري باستخدام الألوكسان إلى زيادة كبيرة ($p \leq 0.05$) في مستويات الجلوكوز في الدم، الدهون الثلاثية، الكوليسترول الكلي، كوليسترول البروتين الدهني منخفض الكثافة (LDL-C)، المالونالديهيد (MDA)، بيروكسيد الهيدروجين (H_2O_2)، واللبتين، حيث كانت الزيادات على التوالي ٢٣٦,١٢%، ١٠٠,٠٠%، ٤٤,٤٤%، ٣٤,٦٩%، ٦٠,٠٦%، ٦٩,٢٠%، و٦٧,٤٠% مقارنة بالمجموعة الطبيعية على التوالى. في المقابل، انخفضت مستويات كوليسترول البروتين الدهني عالي الكثافة (HDL-C) ، وفعالية إنزيمي الباراوكسوناز والأريليستيراز بنسبة ٤٢,٦٥%، ٥١,٠٤%، و٣٤,٥٢% على التوالي. بالإضافة إلى ذلك، تم تمديد زمن النزيف والتخثر عند عدة نقاط زمنية (٧، ١٤، ٢١، و٢٨ يومًا). أدت المعالجة بـ SEE لمدة ٢٨ يومًا إلى تحسين هذه المعايير بشكل كبير وبطريقة تعتمد على الجرعة. شملت التحسينات تقليص مستويات الجلوكوز، وصورة دهون الدم، وعوامل الإجهاد التأكسدي، وتطبيع المعايير المساعدة على التوازن الدموي. تشير هذه النتائج إلى أن SEE لديه إمكانات علاجية في إدارة مرض السكري من النوع الثانى ومضاعفاته المرتبطة به. بناءً على ذلك، يُوصى بإدراج SEEفي التركيبات الدوائية للأفراد المصابين بالسكري من النوع الثانى.

الكلمات المفتاحية: وظائف الكبد، اللبتين، الأنسولين، مالونالدهيد، باراوكسوناز، أريلستريز، أوقات النزيف والتخثر.