

Research Article

Halophytic Plants as Promising Agents for Alleviating Fructose-Induced Metabolic Syndrome in Rats

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Abstract

Objectives: Metabolic syndrome (MetS) is a complex and multifactorial disorder characterized by a constellation of metabolic abnormalities, including insulin resistance, dyslipidemia, hypertension, and central obesity, which collectively increase the risk of cardiovascular disease and type 2 diabetes mellitus. Considering the growing interest in plant-derived bioactive compounds as alternative therapeutic agents, this study aimed to evaluate the protective effects of *Suaeda aegyptiaca* extract (SAE) and *Salsola imbricata* extract (SIE), two species from the Amaranthaceae family, compared with the standard antidiabetic drug canagliflozin (CANA), in a rat model of fructose-induced metabolic syndrome. **Materials and Methods:** A total of 30 male Wistar rats were allocated into five groups: a normal control, a fructose control, and three treatment groups receiving CANA (30 mg/kg/day), SAE (200 mg/kg/day), or SIE (500 mg/kg/day). To evaluate the preventive potential of the extracts, all treatments were administered daily in parallel with the fructose solution throughout the six-week study period. Physiological, biochemical, histopathological, and immunohistochemical markers of hepatic tissue were evaluated to determine treatment efficacy. **Results:** SAE and SIE exhibited significant prophylactic effects against the development of fructose-induced metabolic syndrome when administered concurrently with fructose. Both extracts effectively attenuated weight gain, hyperglycemia, and hypertension, improved lipid profiles, and reduced elevated liver enzymes, alanine aminotransferase (ALT) and aspartate aminotransferase (AST). Both treatments significantly reduced elevated myeloperoxidase (MPO) levels and enhanced glutathione peroxidase (GPX) activity, without significantly altering neutrophil activation protein 3 (NAP3), superoxide dismutase (SOD), or catalase (CAT) levels. Histopathological examination demonstrated restoration of near-normal hepatic architecture in the treated groups. These structural improvements were corroborated by immunohistochemical analysis, which revealed that both extracts markedly suppressed the pronounced hepatic expression of tumor necrosis factor- α (TNF- α). **Conclusions:** SAE and SIE demonstrated significant protective effects against fructose-induced metabolic disturbances, likely mediated through anti-inflammatory and antioxidant mechanisms. Their diverse phytochemical profiles may underlie these multifaceted actions, supporting their potential as complementary prophylactic agents for managing metabolic syndrome.

Keywords: metabolic syndrome; canagliflozin; hypoglycemic agents; oxidative stress; inflammation; halophytes; *Suaeda aegyptiaca*; *Salsola imbricata*

1. Introduction

Metabolic syndrome (MetS) is a multifactorial condition characterized by a cluster of metabolic abnormalities, including central obesity, insulin resistance, hypertension, and atherogenic dyslipidemia. It is widely recognized as a major risk factor for cardiovascular disease [1,2]. The global burden of MetS has increased significantly in recent years, largely due to the growing prevalence of obesity and the strong association between overnutrition and chronic non-communicable diseases [3,4].

Studies have shown that hypertension, dyslipidemia, and abdominal obesity are more prevalent in individuals with prediabetes and MetS. Moreover, the coexistence of prediabetes and MetS further exacerbates the risk of elevated blood pressure, postprandial hyperglycemia, and increased low-density lipoprotein (LDL) levels [5,6]. Fructose-fed rodents are a reproducible and cost-effective experimental model for investigating MetS [7].

Management of MetS remains challenging and often requires multiple pharmacological agents, highlighting the



need for alternative multi-target therapeutic approaches [3]. Although more than 1000 medicinal plants have been traditionally used to manage MetS, only a limited number have undergone rigorous scientific evaluation to validate their efficacy [8].

Canagliflozin (CANA), a sodium–glucose co-transporter 2 (SGLT2) inhibitor, has demonstrated cardiometabolic benefits beyond glycemic control, including improvements in blood pressure, lipid profile, renal function, and cardiovascular outcomes, making it an appropriate reference drug in experimental MetS studies [9].

Halophytic plants are increasingly regarded as promising sources of bioactive compounds due to their adaptation to saline environments through mechanisms such as ion homeostasis and enhanced antioxidant defenses [10,11]. These adaptations frequently lead to the biosynthesis of diverse secondary metabolites with significant pharmacological potential. *Suaeda aegyptiaca* and *Salsola imbricata* (Amaranthaceae) are two halophytes traditionally used in Saudi Arabian folk medicine. *S. aegyptiaca* exhibits anti-inflammatory, antidiabetic, antimicrobial, and antioxidant activities and contains flavonoids, tannins, alkaloids, saponins, sterols, triterpenes, and polyphenols that may contribute to the management of oxidative stress, hyperglycemia, and dyslipidemia [12,13,14,15,16,17,18,19]. Similarly, *S. imbricata* demonstrates significant hypoglycemic activity through the inhibition of α -amylase [20,21,22,23,24,25], supported by a rich phytochemical profile comprising phytosterols, fatty acids, flavonoids, phenolic acids, cerebrosides, and several novel metabolites including salisomide and salisoflavan [21,25,26,27,28,29,30,31]. Collectively, these findings highlight the metabolic diversity of *S. imbricata* and support the potential of halophytes as promising sources of bioactive agents for metabolic disorders. Therefore, this study aimed to investigate and compare the effects of *S. imbricata* and *S. aegyptiaca* methanolic extracts on fructose-induced metabolic syndrome in rats and to explore their potential metabolic, antioxidant, anti-inflammatory, and organ-protective effects.

2. Materials and Methods

2.1 Plants and Extracts

2.1.1 Plant Collection and Preparation

Aerial parts of the two plant species, *Suaeda aegyptiaca* and *Salsola imbricata* (family Amaranthaceae), were collected from the Qassim area. The plants were taxonomically identified by Mr. Ibrahim Aldubayan, a botanical expert in the region. Voucher specimens with accession numbers QPP-105 (*S. imbricata*) and QPP-110 (*S. aegyptiaca*) were deposited in the College of Pharmacy, Qassim University, KSA. The plants were air-dried and then ground into a fine powder using an electric grinder.

2.1.2 Preparation of Extracts

The powdered aerial parts of each plant (500 g) were extracted separately by maceration at room temperature ($22 \pm 2^\circ\text{C}$) in 80% methanol (1000 mL) with continuous shaking on an orbital shaker (ColeParmer™ Stuart™ Orbital Shaker, Thermo Scientific, Waltham, MA, USA), 100 rpm for 24 h. An 80% methanol solution was selected for its high efficiency in extracting a broad spectrum of phytochemicals with varying polarities, including phenolic compounds, flavonoids, and other bioactive constituents. After filtration, the marc was re-extracted using the same procedure for four consecutive days. The collected filtrates were pooled and concentrated under reduced pressure on a rotary evaporator at temperatures not exceeding 50°C , then dried to constant weight to ensure complete removal of residual solvent, yielding crude hydroalcoholic extracts: *Suaeda aegyptiaca* extract and *Salsola imbricata* extract (SAE and SIE, respectively).

2.2 Phytochemical Analysis

2.2.1 Preliminary Phytochemical Screening

An aliquot of 1 g from each extract was dissolved in 50 mL of distilled water and subsequently subjected to qualitative phytochemical screening tests to detect the main classes of secondary metabolites. The procedure was conducted as described previously [32].

2.2.2 Determination of Total Phenolic and Total Flavonoid Contents

The total phenolic content (TPC) and total flavonoid content (TFC) were determined using the Folin–Ciocalteu and aluminum chloride (AlCl_3) methods, respectively, as reported previously [32].

2.2.3 High-Performance Liquid Chromatography Analysis

An Agilent 1260 series chromatograph was used for high-performance liquid chromatography (HPLC) analysis. Separation was performed on a Zorbax Eclipse Plus C8 column (5 μm particle size, 4.6 mm $\times$ 250 mm) at 40°C . The mobile phase comprised water (A) and acetonitrile containing 0.05% trifluoroacetic acid (B). The flow rate was adjusted to 0.9 mL/min, and linear gradient programming of the mobile phase was performed as follows: 0–1 min (82% A); 1–11 min (82–75% A); 11–18 min (75–60% A); 18–24 min (60% A). The multi-wavelength detector was monitored at 280 nm. The injection volume was 5 μL for each sample solution.

2.3 Toxicological and Safety Evaluation Studies in Rats

A total of Forty-two adult male Wistar rats (8–10 weeks old, 110–170 g) were obtained from the Animal House of Qassim University and randomly divided into 14 groups ($n = 3/\text{group}$), including seven dose groups for each plant extract. All experimental procedures were approved by the Animal Care Committee of the Department of

Pharmacology, College of Pharmacy. Animals were maintained under standard laboratory conditions (20–22 °C, 12 h light/dark cycle) with free access to standard chow and drinking water. In the fructose-treated groups, MetS was induced by administration of fructose-enriched drinking water according to the experimental protocol. Animals were acclimatized for one week before the experiment. Methanolic SAE or SIE extracts were administered orally as single doses of 10, 100, 500, 1000, 5000, 10,000, and 20,000 mg/kg, dissolved in distilled water. The selected dose range was based on previously published acute toxicity studies of plant extracts [33]. Animals were observed continuously for the first 6 h and monitored for 24 h for signs of toxicity, including tremors, impaired coordination, respiratory changes, excitation, impaired righting reflex, and muscle spasms [34]. Median lethal dose (LD₅₀) values were estimated using the Karber arithmetic method. Since no mortality or obvious toxic manifestations were observed at any tested dose up to 20,000 mg/kg, the LD₅₀ values for both extracts were considered to be greater than 20,000 mg/kg, classifying them as “practically non-toxic” according to the Hodge and Sterner toxicity scale [35]. However, this classification is limited to preliminary observations of acute toxicity within 24 h, and the absence of hematological and histopathological evaluations remains a limitation of the study. All procedures were conducted in accordance with the ethical guidelines of the Qassim University Medical Ethics Committee and with international ethical and regulatory standards for animal research in laboratory settings [36]. Animals were treated in accordance with the National Research Council Guide for the Care and Use of Laboratory Animals [37]. The Research Ethics Committee of Qassim University approved the research protocol (approval number 21-12-33).

2.4 Drugs, Chemicals, Reagents, Kits, and Antibodies

■ D-fructose (≥99% purity; Sigma-Aldrich, St. Louis, MO, USA) was used for the induction of MetS.

■ CANA (Invokana® 100 mg tablets; Janssen Pharmaceutical Co., New Cairo, Egypt) was dissolved in distilled water before administration.

■ Folin–Ciocalteu reagent, gallic acid, quercetin, aluminum chloride, sodium bicarbonate, sodium nitrite, sodium hydroxide, acetonitrile, formic acid, and HPLC-grade water were obtained from Sigma-Aldrich (St. Louis, MO, USA).

■ Rat neutrophil activation protein-3 (NAP3) ELISA kit (Cat. No. SEA041Ra; Cloud-Clone Corp., Katy, TX, USA).

■ Rat Myeloperoxidase (MPO) ELISA kit (Cat. No. SEA601Ra; Cloud-Clone Corp., Katy, TX, USA).

■ Superoxide Dismutase (SOD) Diagnostic kit (Cat. No. SD2521; Biodiagnostic Co., Dokki, Giza, Egypt).

■ Catalase (CAT) Diagnostic kit (Cat. No. CA2517; Biodiagnostic Co., Dokki, Giza, Egypt).

■ Glutathione Peroxidase (GPX) Diagnostic kit (Cat. No. GP2524; Biodiagnostic Co., Dokki, Giza, Egypt).

■ Rabbit monoclonal anti-TNF- α antibody [EPR20972] (Cat. No. ab215188; Abcam, Cambridge, UK).

■ Mouse and Rabbit Specific HRP/DAB Detection IHC kit, including DAB chromogen and Mayer’s hematoxylin (Cat. No. ab64264; Abcam, Cambridge, UK).

2.5 Experimental Design

Experimental animals were allocated to one of five treatment groups (n = 6 per group) using a stratified randomization process based on body weight. Randomization was performed using random numbers to ensure comparable baseline weight distributions among groups. To minimize bias, histological and immunohistochemical assessments were conducted by an investigator blinded to the experimental group assignments. Rats were divided into the following groups: Group 1 was the normal control group (NC), which received distilled water daily via oral gavage. Group 2, the fructose control group (fructose-drinking rats, FDRs), received a 20% fructose solution in their drinking water to induce MetS [7]. Group 3 (fructose + CANA) received canagliflozin (30 mg/kg/day) [38], dissolved in distilled water and orally administered each morning. Groups 4 and 5 were orally administered SAE at 200 mg/kg/day [39] and SIE at 500 mg/kg/day [27], respectively. All therapeutic interventions (CANA, SAE, and SIE) were initiated simultaneously with fructose administration and maintained for the full six-week duration.

2.6 Hemodynamic Measurements

2.6.1 Body Weight

The body weight of all animals was measured at the start and at the end of the experiment.

2.6.2 Blood Pressure

Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured at the start and the end of the experiment using a noninvasive blood pressure recorder (Biological Research Apparatus, Via G.Borghesi 43, 21025 Comerio-Varese, Italy) from the tail of conscious rats by the tail-cuff technique. The average of at least three blood pressure measurements was recorded on each occasion [40].

2.7 Sample Collection and Tissue Preparation

At the end of the experimental period, rats were anesthetized with thiopental sodium (50 mg/kg, intraperitoneally) to achieve deep anesthesia, confirmed by loss of pedal withdrawal reflex. Blood samples were collected from the facial (submandibular) vein, and serum was separated and stored at –80 °C until biochemical analysis; before analysis, samples were thawed at room temperature. Subsequently, animals were euthanized via cervical dislocation under deep anesthesia in accordance with established

animal welfare guidelines [41]. Liver tissues were then harvested and fixed in 10% neutral buffered formalin for 48 hours for histopathological examination [41,42].

2.8 Biochemical Analysis

2.8.1 Determination of Blood Glucose and Lipid Profile

Random blood sugar (RBS) levels were measured at both the beginning and the end of the experiment in all groups. Serum glucose, total cholesterol, triglycerides, and high-density lipoprotein (HDL) levels were determined calorimetrically using commercially available diagnostic kits (Crescent Diagnostics, KSA). Absorbance was measured at 546 nm using a UV spectrophotometer (Apel Company, Japan).

2.8.2 Determination of Liver Function

The enzymatic activities of alanine transaminase (ALT) and aspartate aminotransferase (AST) were measured using the kinetic method. Serum levels of total protein and albumin were measured by colorimetric assay. Reagents were purchased from Crescent Diagnostics Test Company, KSA, and the UV spectrophotometer was purchased from Apel Company, Japan.

2.8.3 Determination of Kidney Function

The serum creatinine level was determined by the fixed-time kinetic method using the Jaffe reaction, which is based on the alkaline picrate reaction. Blood urea was measured by the colorimetric method. Reagents were purchased from Crescent Diagnostics Test Company, KSA, and the UV spectrophotometer was from Apel Company, Japan.

2.8.4 Assessment of Inflammatory Biomarkers and Oxidative Stress

2.8.4.1 Inflammatory Markers (NAP3 and MPO). Serum levels of neutrophil activation protein 3 (NAP3) and MPO were determined using enzyme-linked immunosorbent assay (ELISA) kits, following the manufacturer's protocols. Optical density was measured at 450 nm using a microplate reader, and concentrations were calculated using a standard curve. The kits were provided by Cloud-Clone Corp., Katy, Texas (Houston area), USA, with Cat. No: SEA041Ra for NAP3 and SEA601Ra for MPO.

2.8.4.2 Antioxidant Enzymes (SOD, CAT, and GPX). **Superoxide dismutase (SOD) and catalase (CAT)**

Serum concentrations were quantified using specific colorimetric diagnostic kits. SOD and CAT levels were determined based on the inhibition of specific chromogenic reactions and the degradation rate of hydrogen peroxide, respectively. Reagents were purchased from Biodiagnostic Co., Dokki, Giza, Egypt, with Cat. No. SD2521 for SOD and Cat. No. CA2517 for catalase.

Glutathione peroxidase (GPX)

The enzymatic activity of GPX was measured by monitoring the oxidation of NADPH to NADP⁺ in the presence

of glutathione reductase and reduced glutathione. The decrease in absorbance was recorded at 340 nm using a UV-visible spectrophotometer. The activity was calculated and expressed in international units per liter (IU/L). Reagents were provided by Biodiagnostic Company Dokki, Giza, Egypt, with Cat. No: GP2524.

2.9 Histological Examination

Liver specimens were fixed in 10% buffered formalin-saline and processed into paraffin blocks using routine protocols. Sections with a thickness of 5 μ m were stained with hematoxylin and eosin (H&E) [43] to evaluate the histological structures. Immunohistochemical staining was performed using a monoclonal antibody against tumor necrosis factor- α (TNF- α). The 5 μ m-thick liver sections were placed on polylysine-coated slides before being deparaffinized, rehydrated, and rinsed in phosphate-buffered saline (PBS). Endogenous peroxidase activity was inhibited by incubation with 0.3% hydrogen peroxide for 30 minutes. After antigen retrieval in a pH 6.0 citrate buffer for 25–30 minutes, samples were washed three times for a total of 3 minutes. The tissue was then treated with a blocking agent at non-specific binding sites. TNF- α antibody was used at a dilution of 1:300 and incubated overnight at 4 °C in a humid chamber. Slides were then incubated for 1 hour with the secondary antibody, followed by 40 minutes at room temperature with the streptavidin-biotin enzyme complex. Finally, the chromogen DAB was applied. Sections were then counterstained with Mayer's hematoxylin. The TNF- α antibody showed cytoplasmic immunoreactivity, and the positive control was a normal rat stomach (as provided by the manufacturer). Additional liver specimen slides were treated with buffer solutions instead of the primary antibody as the negative control. Initial image visualization was performed using a light microscope (Olympus BX50F4, Shinjuku-ku, Tokyo, Japan), and images were captured using a camera-based computer system (AmScope digital camera MU500, Irvine, CA, USA).

Quantitative Morphometric Study

The mean area percentage of TNF- α immunohistochemical staining was determined using the "ToupView" image analyzer computer system (China) at a magnification of $\times 100$. Digitized images were captured from 10 randomly chosen non-overlapping fields from each section. Microscopic examination and morphometric analysis were conducted in the Histology and Cell Biology Department, Faculty of Medicine, Fayoum University.

2.10 Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics software (version 28.0.1; International Business Machines Corporation, Armonk, NY, USA). Data distribution and normality were verified using the Shapiro-Wilk test, and equality of variances was assessed via Levene's

test. Results are expressed as the mean $\pm$ standard deviation (SD). Differences between the five experimental groups were analyzed using one-way analysis of variance (ANOVA) followed by Tukey's HSD post hoc test for multiple comparisons. For parameters measured at multiple time points (baseline vs. endpoint), such as body weight and blood pressure, a paired-samples *t*-test was employed to evaluate within-group longitudinal changes. The *p*-values < 0.05 were considered statistically significant.

3. Results

3.1 Phytochemical Analysis

Extraction yield: Alcohol-derived extraction of *S. aegyptiaca* yielded 52 g of a greenish-black semisolid residue (SAE), with a drug-to-extract ratio (DER) of 1:0.10 and an extraction yield of 10.4%. In comparison, extraction of *S. imbricata* produced 47 g of a solid greenish-brown extract residue (SIE), corresponding to a DER of 1:0.09 and an extraction yield of 9.4%.

Preliminary phytochemical screening: Qualitative analysis of the metabolic content in SIE and SAE revealed that both extracts contain carbohydrates, sterols/triterpenes, and flavonoids, whereas alkaloids, anthraquinones, and cardiac glycosides were absent in both extracts. Saponins were detected only in SAE, while tannins were identified exclusively in SIE.

The TPC and TFC of the methanolic extracts of SIE and SAE were quantified as milligrams of gallic acid equivalent (mg GAE/g extract) and quercetin equivalent (mg QE/g extract), respectively. SIE exhibited a higher TPC (146.12 ± 0.09 mg GAE/g) than SAE (81.20 ± 0.30 mg GAE/g). In contrast, TFC was slightly higher in SAE (67.60 ± 0.18 mg QE/g) than in SIE (63.80 ± 0.20 mg QE/g).

HPLC analysis was conducted to screen and quantify a panel of 18 phenolic compounds, mainly phenolic acids and flavonoids, in the total alcoholic extracts (SAE and SIE) of the two plant species. Phenolic acids were the predominant chemical class in both extracts (Table 1). In SAE, gallic acid showed the highest concentration (988.74 μ g/g), while caffeic acid, chlorogenic acid, and rosmarinic acid were present at moderate concentrations of 117.30, 115.42, and 111.53 μ g/g, respectively. In SIE, higher levels of phenolic acids were quantified, with syringic acid (44,462.06 μ g/g) being the most abundant compound among all detected metabolites, followed by ferulic acid (11,308.73 μ g/g), caffeic acid (3140.03 μ g/g), and p-coumaric acid (1843.19 μ g/g). Chlorogenic acid and gallic acid were detected at relatively lower concentrations (408.07 and 180.17 μ g/g, respectively). These findings indicate that SIE is particularly rich in substituted and methoxylated phenolic acids compared with SAE. Additionally, other phenolic compounds, such as ellagic acid and vanillin, were identified in both extracts but at notably higher levels in SIE (3101.64 and 1528.44 μ g/g, respectively) than in SAE (156.39 and 276.66 μ g/g, respectively).

Table 1. High-performance liquid chromatography (HPLC) analysis of the crude *S. aegyptiaca* extract (SAE) and *S. imbricata* extract (SIE).

Phenolic compound	Conc. (μ g/g)	
	SAE	SIE
Gallic acid	988.74	180.17
Chlorogenic acid	115.42	408.07
Catechin	216.97	10,606.78
Methyl gallate	22.65	11.21
Caffeic acid	117.30	3140.03
Syringic acid	70.29	44,462.06
Rutin	62.43	0.00
Ellagic acid	156.39	3101.64
Coumaric acid	87.61	1843.19
Vanillin	276.66	1528.44
Ferulic acid	75.36	11,308.73
Naringenin	82.69	2314.33
Rosmarinic acid	111.53	698.40
Daidzein	156.04	12.30
Quercetin	154.59	4205.80
Cinnamic acid	6.35	257.83
Kaempferol	22.40	322.18
Hesperetin	0.00	3125.26

Alternatively, flavonoids in SAE were detected at moderate concentrations, with catechin (216.97 μ g/g) and quercetin (154.59 μ g/g) being the most abundant among the tested flavonoids. In contrast, naringenin (82.69 μ g/g), kaempferol (22.40 μ g/g), and rutin (62.43 μ g/g) were present in lower concentrations. Notably, hesperetin was not detected in SAE. Conversely, SIE displayed a markedly higher flavonoid content, with catechin, quercetin, hesperetin, and naringenin detected at concentrations of 10,606.78, 4205.80, 3125.26, and 2314.33 μ g/g, respectively. Kaempferol was detected at a relatively low concentration of 322.18 μ g/g, and rutin was not detected in SIE.

3.2 Body Weight

Initial and final body weights were measured for all experimental groups: NC, FDRs, and FDRs treated with CANA, SAE, or SIE. Relative to the NC group, the FDR group exhibited a significant increase in body weight ($p = 0.0002$). Treatment with CANA, SAE, or SIE significantly attenuated fructose-induced weight gain compared with the FDR group ($p = 0.0001$, $p = 0.003$, and $p = 0.007$, respectively). However, body weight remained significantly higher than in the NC group, indicating that none of the interventions fully restored body weight to normal control levels. Within-group comparisons revealed a significant increase in final versus initial body weight for every cohort except the NC group (Fig. 1). Overall, the treated groups exhibited significantly lower weight gain than un-

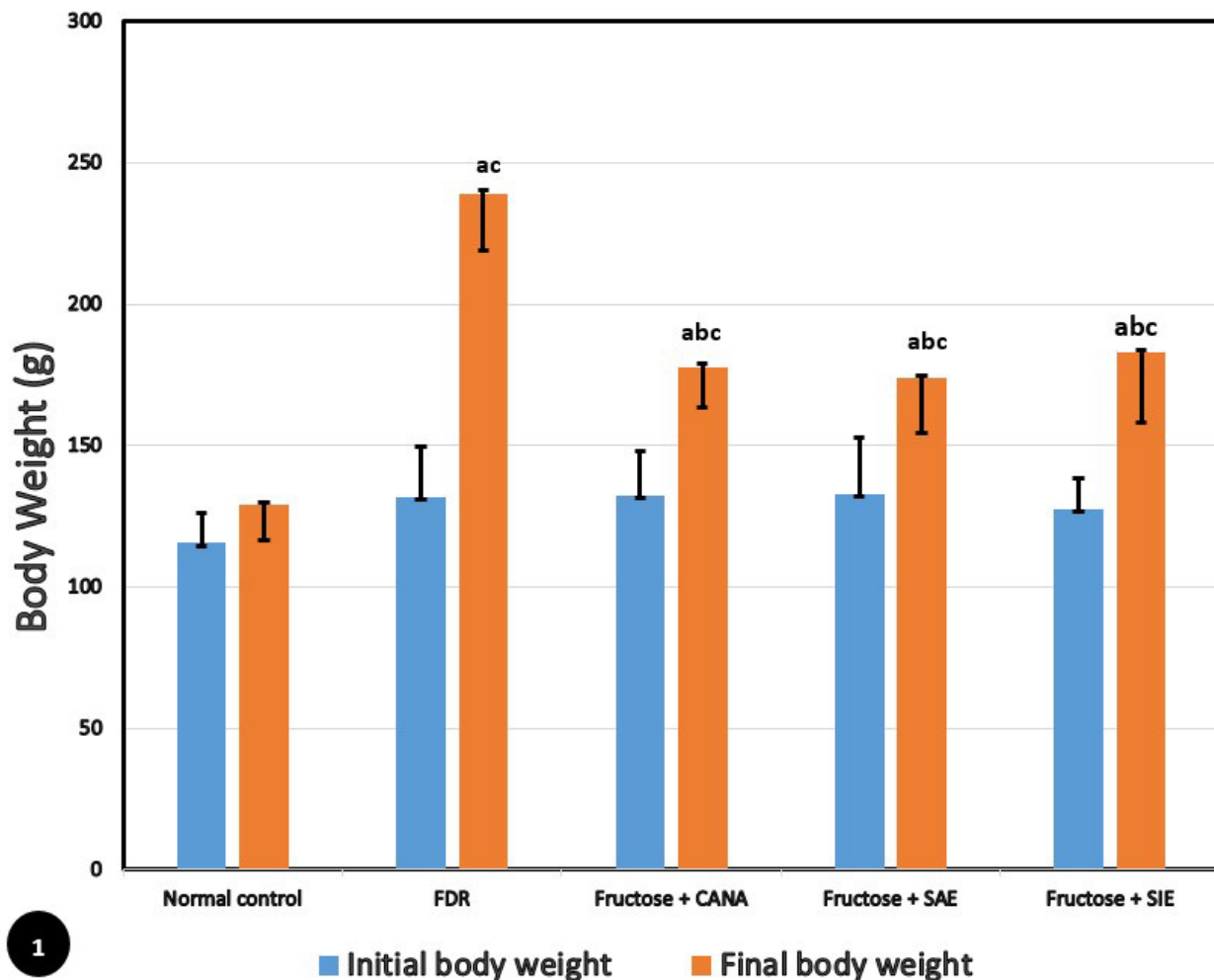


Fig. 1. Mean changes in body weight. FDRs, fructose-drinking rats; CANA, canagliflozin; SAE, *Suaeda aegyptiaca* extract; SIE, *Salsola imbricata* extract. Data are presented as the mean $\pm$ standard deviation (SD). ^a Significant compared with the normal control. ^b Significant compared with the FDR group. ^c Significant difference within the same group before and after treatment. Values were considered significant at $p < 0.05$.

treated FDRs, confirming the partial protective effect of CANA, SAE, and SIE against fructose-induced obesity.

3.3 Blood Pressure

SBP and DBP were assessed in all groups at both the beginning and end of the experiment. At baseline, no significant differences in SBP or DBP were observed among the groups. By the end of the study, the FDR group exhibited significantly higher SBP and DBP than the NC group ($p = 0.0001$). Treatment with CANA, SAE, or SIE significantly reduced SBP compared with the untreated FDR group ($p = 0.0001$ for all comparisons). However, SBP remained significantly higher than that of the NC group ($p = 0.0001$). Similarly, DBP was significantly increased in the FDR group relative to the NC group ($p = 0.0001$). Administration of CANA, SAE, or SIE significantly lowered DBP compared with the FDR group ($p = 0.0001$ for all comparisons); nevertheless, DBP values remained significantly

elevated compared with those of the NC group ($p = 0.0001$) (Table 2).

3.4 Random Blood Sugar

RBS levels were measured at both the beginning and end of the experiment across all groups (Fig. 2). At baseline, no significant differences were observed. By the end of the study, the FDR group exhibited a significant increase in RBS levels compared with the NC group ($p = 0.0001$). Treatment with CANA, SAE, or SIE significantly attenuated the fructose-induced elevation in RBS, yielding values significantly lower than those observed in the untreated FDR group ($p = 0.0001$ for all comparisons). Longitudinal analysis revealed a significant increase in RBS from baseline to the end of the study in all experimental groups ($p = 0.0001$). In contrast, the NC group showed no significant change throughout the study period.

Table 2. Blood pressure changes in all groups (n = 6).

Blood pressure (mmHg)	NC	FDR	Fructose + CANA	Fructose + SAE	Fructose + SIE
SBP at the start of experiment	107 ± 5	111 ± 5	109 ± 6	109 ± 6	111 ± 7
SBP at the end of experiment	111 ± 7	162 ± 7 ^{a,c}	132 ± 13 ^{a,b,c}	138 ± 7 ^{a,b,c}	137 ± 4 ^{a,b,c}
DBP at the start of experiment	76 ± 6	72 ± 5	70 ± 3	72 ± 7	74 ± 8
DBP at the end of experiment	72 ± 7	99 ± 2 ^{a,c}	81 ± 2 ^{a,b,c}	85 ± 4 ^{a,b,c}	84 ± 5 ^{a,b,c}

NC, normal control; FDRs, fructose-drinking rats; CANA, canagliflozin; SAE, *Suaeda aegyptiaca* extract; SIE, *Salsola imbricata* extract; SBP, systolic blood pressure; DBP, diastolic blood pressure. Data are presented as the mean ± SD. ^a Significant difference compared with the normal control. ^b Significant difference compared with the FDR group. ^c Significant difference within the same group before and after treatment. Values are considered significant at $p < 0.05$.

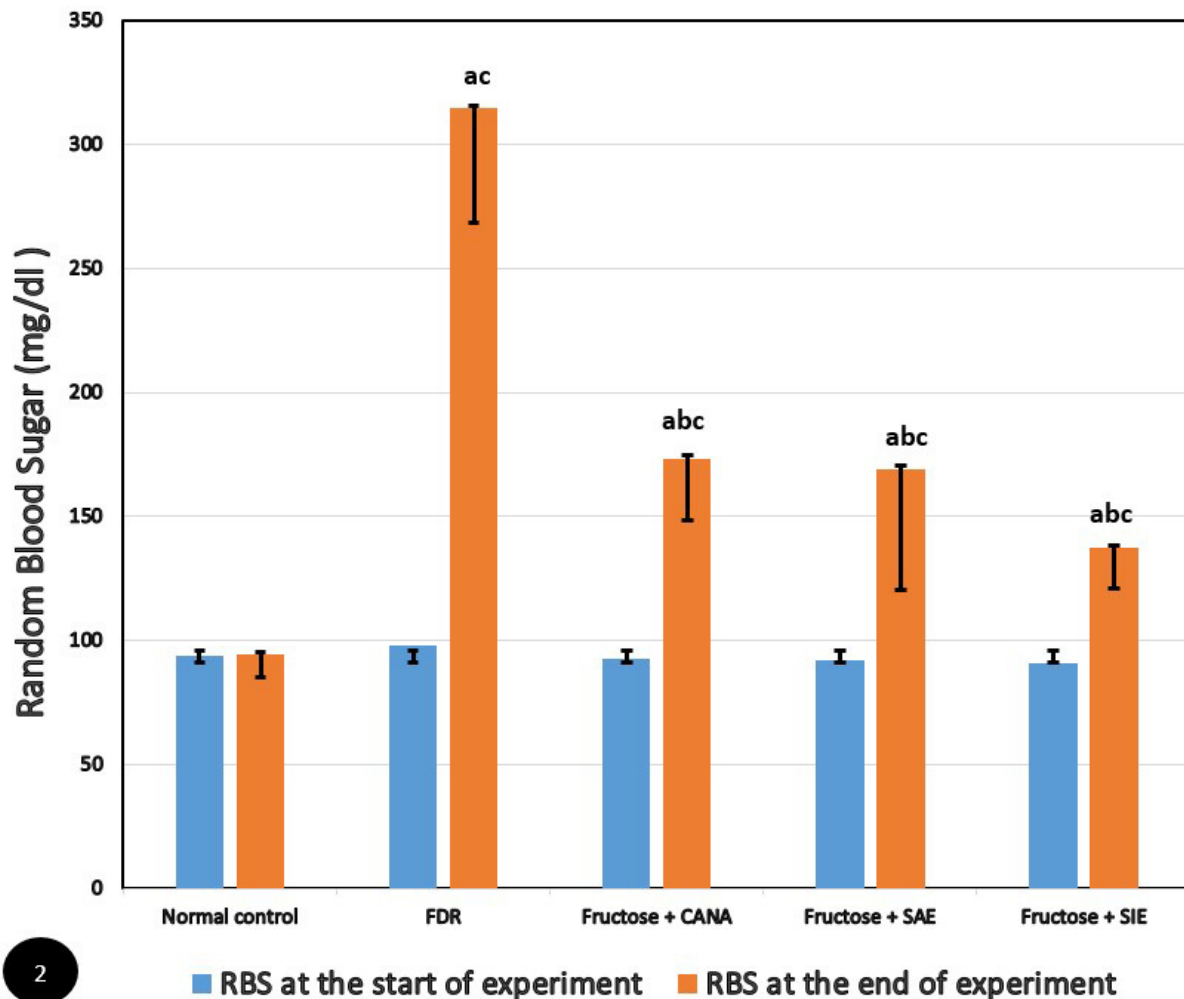


Fig. 2. Mean changes in random blood sugar (RBS) levels. FDRs, fructose-drinking rats; CANA, canagliflozin; SAE, *Suaeda aegyptiaca* extract; SIE, *Salsola imbricata* extract. Data are shown as mean ± SD. ^a Significant compared with normal control. ^b Significant compared with the FDR group. ^c Significant difference within the same group before and after treatment. Values are considered significant at $p < 0.05$.

3.5 Lipid Profile

Table 3 summarizes the effects of fructose feeding and treatment with CANA, SAE, or SIE on serum cholesterol, triglyceride (TG), and HDL levels. The FDR group exhibited a significant increase in serum cholesterol compared

with the NC group ($p = 0.0001$). Treatment with CANA, SAE, or SIE significantly reduced serum cholesterol levels relative to the untreated FDR group ($p = 0.0001$ for all comparisons). Notably, cholesterol levels in all treated groups were significantly lower than those observed in the

Table 3. Mean changes in cholesterol, triglycerides, and high-density lipoprotein in all groups (n = 6).

	NC	FDR	Fructose + CANA	Fructose + SAE	Fructose + SIE
Cholesterol (mmol/L)	2.29 ± 0.10	3.99 ± 0.06 ^a	1.45 ± 0.29 ^{a,b}	1.77 ± 0.30 ^{a,b}	1.93 ± 0.13 ^{a,b,c}
Triglycerides (mmol/L)	1.63 ± 0.03	3.64 ± 0.63 ^a	2.06 ± 0.03 ^b	2.00 ± 0.29 ^b	2.38 ± 0.17 ^{a,b}
High-density lipoproteins (mmol/L)	1.22 ± 0.09	0.70 ± 0.09	0.94 ± 0.47	1.07 ± 0.61	1.11 ± 0.58

NC, normal control; FDRs, fructose-drinking rats; CANA, canagliflozin; SAE, *Suaeda aegyptiaca* extract; SIE, *Salsola imbricata* extract.

Data are shown as the mean ± SD. ^a Significant difference compared with the normal control. ^b Significant difference compared with the FDR group. ^c Significant difference compared with the fructose + CANA group. Values are considered significant at $p < 0.05$.

NC group ($p = 0.0001$, 0.002 , and 0.038 , respectively). Similarly, TG levels were significantly higher in the FDR group than in the NC group ($p = 0.0001$). Treatment with CANA and SAE significantly reduced TG concentrations compared with the FDR group ($p = 0.001$ and 0.002 , respectively), restoring TG levels to values that did not differ significantly from those of the NC group ($p = 0.184$ and 0.297 , respectively). Although SIE treatment also significantly decreased TG levels relative to the FDR group ($p = 0.003$), TG concentrations remained significantly higher than those of the NC group ($p = 0.004$). In contrast, no significant differences in HDL levels were detected among the experimental groups ($p > 0.05$).

3.6 Liver and Kidney Function

Liver and kidney function parameters were assessed across all experimental groups (Table 4). The FDR group showed significantly elevated serum AST and ALT levels compared with the NC group, indicating hepatic injury. Concurrent treatment with CANA, SAE, or SIE protected against fructose-induced hepatic injury, maintaining AST and ALT levels comparable to those of the NC group. Regarding total protein levels, all experimental groups, including the FDR and treatment groups, showed a significant reduction compared with the NC group. In contrast, albumin levels did not differ significantly among any of the groups. For renal function markers, the FDR group exhibited significantly higher serum creatinine and urea levels than the NC group. Although treatment with CANA, SAE, or SIE resulted in lower creatinine and urea values than those observed in the FDR group, these reductions did not reach statistical significance ($p > 0.05$).

3.7 Oxidative Stress and Inflammatory Biomarkers

No significant differences were observed in NAP3, SOD, or CAT levels among the NC, FDR, CANA-, SAE-, and SIE-treated groups ($p > 0.05$; Table 5). In contrast, GPX levels were significantly higher in all treatment groups than in the FDR group ($p < 0.05$), suggesting enhanced antioxidant defense. Moreover, the FDR group exhibited a significant increase in MPO levels compared with the NC group ($p < 0.05$). Treatment with CANA, SAE, or SIE significantly reduced MPO levels compared with the untreated

FDR group ($p < 0.05$), indicating attenuation of fructose-induced inflammatory and oxidative stress responses.

3.8 Histological Results

3.8.1 Hematoxylin and Eosin Staining

H&E-stained liver sections from the control group showed normal hepatocyte architecture, with hepatocytes exhibiting vesicular nuclei radiating from the central veins and portal areas (containing branches of the portal vein, hepatic artery, and bile duct) located at the corners of the lobules (Fig. 3A,B). In contrast, the FDR group exhibited disrupted lobular architecture (Fig. 4A,B). Extensive vacuolated hepatocytes surrounding central veins, as well as a widespread distribution of hepatocytes with dark acidophilic cytoplasm and pyknotic nuclei, were evident. Portal vein dilatation and congestion, along with marked erythrocyte extravasation, were observed adjacent to the dilated, congested portal vein and between hepatocytes. Prominent inflammatory cell infiltration was also detected in the vicinity of portal areas. In the treated groups: Fructose + CANA group (Fig. 5A,B), fructose + SAE group (Fig. 6A,B), and fructose + SIE group, many hepatocytes with vesicular nuclei radiating from central veins were observed (Fig. 7A,B). In the fructose + CANA group, only a few vacuolated hepatocytes and hepatocytes with dark acidophilic cytoplasm and pyknotic nuclei were present, accompanied by mild inflammatory cell infiltration. In the fructose + SAE group, portal vein dilatation and congestion were still noticeable. In contrast, the fructose + SIE group showed numerous hepatocytes with dark acidophilic cytoplasm and pyknotic nuclei, which surrounded portal areas, along with extravasated erythrocytes between hepatocytes.

3.8.2 Immunohistochemical Staining for TNF- α

In the normal control group (Fig. 8A), hepatocytes showed negative TNF- α immunoreactivity. The fructose group exhibited strong cytoplasmic TNF- α expression (Fig. 8B). In the fructose + CANA group, most hepatocytes showed negative TNF- α immunoreactivity (Fig. 8C). The fructose + SAE group exhibited diminished cytoplasmic immunoreactivity (Fig. 8D), whereas the fructose + SIE group showed mild cytoplasmic immunoreactivity for TNF- α (Fig. 8E).

Table 4. Effects of fructose feeding and treatment with CANA, SAE, and SIE on liver and kidney functions (n = 6).

	NC	FDR	Fructose + CANA	Fructose + SAE	Fructose + SIE
AST (IU/L)	56.04 ± 3.31	227.52 ± 61.43 ^a	49.18 ± 27.54 ^b	59.98 ± 29.37 ^b	74.16 ± 33.18 ^b
ALT (IU/L)	20.5 ± 2.88	230.55 ± 102.43 ^a	43.91 ± 7.11 ^b	43.39 ± 19.25 ^b	69.66 ± 22.15 ^b
Total protein (g/dL)	7.42 ± 0.36	5.01 ± 0.39 ^a	5.63 ± 0.59 ^a	5.62 ± 0.49 ^a	5.56 ± 0.27 ^a
Albumin (g/dL)	4.14 ± 0.04	3.46 ± 0.57	3.71 ± 0.35	3.81 ± 0.3	3.92 ± 0.72
Creatinine (mg/dL)	0.61 ± 0.38	1.05 ± 0.22 ^a	0.88 ± 0.18	0.82 ± 0.14	0.92 ± 0.15
Urea (mg/dL)	26.94 ± 9.12	44.34 ± 9.82 ^a	34.07 ± 8.51	36.39 ± 3.98	34.36 ± 5.52

NC, normal control; FDRs, fructose-drinking rats; CANA, canagliflozin; SAE, *S. aegyptiaca* extract; SIE, *S. imbricata* extract; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Data are shown as the mean ± SD. ^a Significant difference compared with the normal control. ^b Significant difference compared with the FDR group. Values are considered significant at $p < 0.05$.

Table 5. Effects of fructose feeding and treatment with CANA, SAE, and SIE on oxidative stress and inflammatory markers (n = 6).

	NC	FDR	Fructose + CANA	Fructose + SAE	Fructose + SIE
NAP3 (ng/mL)	3.22 ± 0.89	4.77 ± 2.61	4.19 ± 1.33	2.97 ± 1.13	3.61 ± 1.45
SOD (IU/L)	19.15 ± 7.25	14.04 ± 0.59	17.08 ± 4.95	20.07 ± 10.17	18.92 ± 4.82
CAT (IU/L)	31.84 ± 1.15	30.05 ± 4.55	31.37 ± 6.40	33.04 ± 2.53	32.61 ± 2.85
GPX (IU/L)	526.19 ± 105.19	469.81 ± 101.52	724.53 ± 50.02 ^{a,b}	673.59 ± 137.19 ^b	803.25 ± 65.02 ^{a,b}
MPO (ng/mL)	26.15 ± 6.83	45.84 ± 19.91 ^a	23.73 ± 7.77 ^b	19.64 ± 6.79 ^b	18.88 ± 8.00 ^b

NC, normal control; FDRs, fructose-drinking rats; CANA, canagliflozin; SAE, *S. aegyptiaca* extract; SIE, *S. imbricata* extract; NAP3, neutrophil activation protein 3; SOD, superoxide dismutase; CAT, catalase; GPX, glutathione peroxidase; MPO, myeloperoxidase.

Data are shown as the mean ± SD. ^a Significant difference compared with the normal control. ^b Significant difference compared with the FDR group. Values are considered significant at $p < 0.05$.

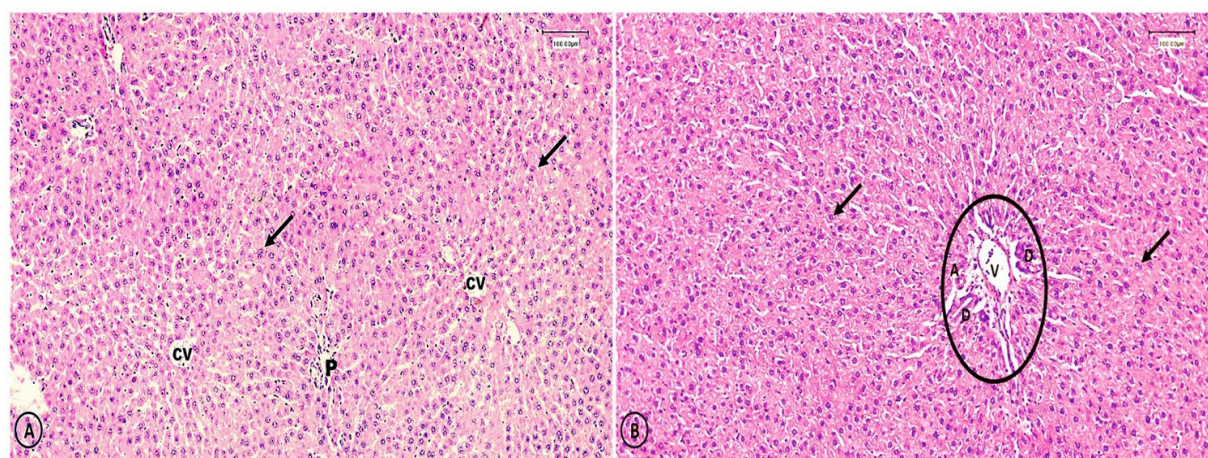


Fig. 3. Photomicrographs of hematoxylin and eosin (H&E)-stained liver sections from the control rat group. (A) shows normal hepatic architecture. Hepatocytes with vesicular nuclei (arrows) radiate from the central veins (CV). Portal areas (P) are located at the corners of hepatic lobules. (B) shows portal areas (encircled), containing branches of the portal vein (V), hepatic artery (A), and bile duct (D). The majority of hepatocytes have vesicular nuclei (arrows). (H&E stain; scale bar = 100 μm; 200×).

3.8.3 Statistical Analysis of TNF-α Immunoreactivity

A significant increase in TNF-α immunoreactivity was observed in the FDR group compared with the control group (Fig. 8F); all treated groups showed a significant decrease relative to the FDR group ($p < 0.05$). A significant increase was observed in all treated groups compared

with the control group ($p < 0.05$), except for the fructose + CANA group, which was comparable to the control group. Meanwhile, a significant decrease was noted in TNF-α immunoreactivity in the fructose + CANA group compared with both the fructose + SAE and fructose + SIE groups, as well as a significant difference between the fructose + SAE and fructose + SIE groups ($p < 0.05$).

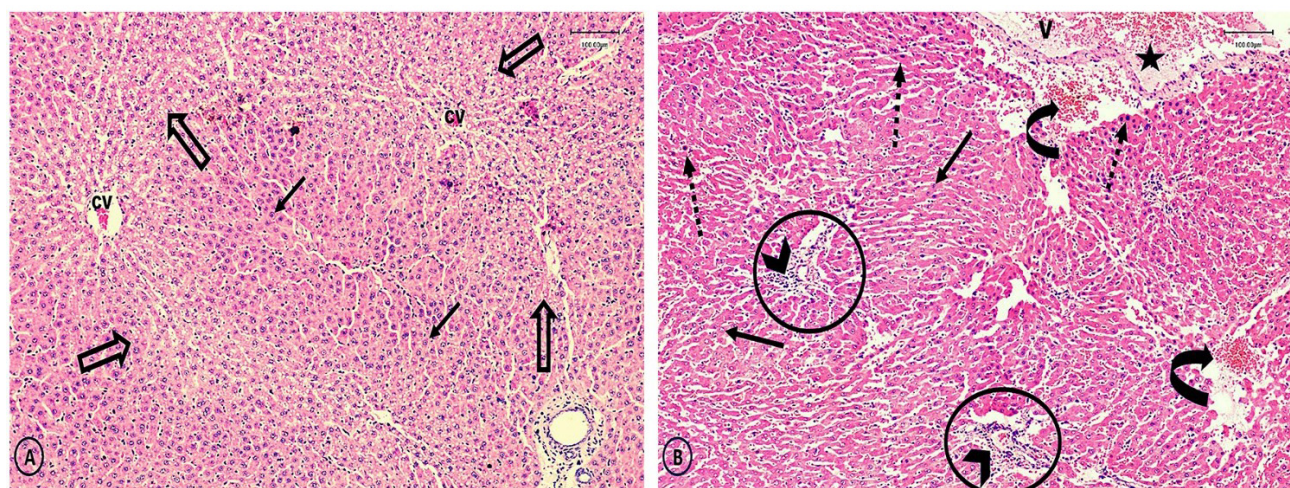


Fig. 4. Photomicrographs of hematoxylin and eosin-stained liver sections from the FDR group. (A) and (B) exhibit disrupted hepatic architecture. Hepatocytes with vesicular nuclei (arrows). Extensive vacuolated hepatocytes (hollow arrows) surrounding the CVs, as well as a widespread distribution of hepatocytes with dark acidophilic cytoplasm and pyknotic nuclei (dotted arrows), are evident. Portal vein (V) dilatation and congestion (star), in addition to marked erythrocyte extravasation (curved arrows), are also detected adjacent to the dilated, congested V and between hepatocytes. Obvious inflammatory cell infiltrates (arrowheads) in the vicinity of portal areas (encircled) are observed (H&E stain; scale bar = 100 μ m; 200 $\times$).

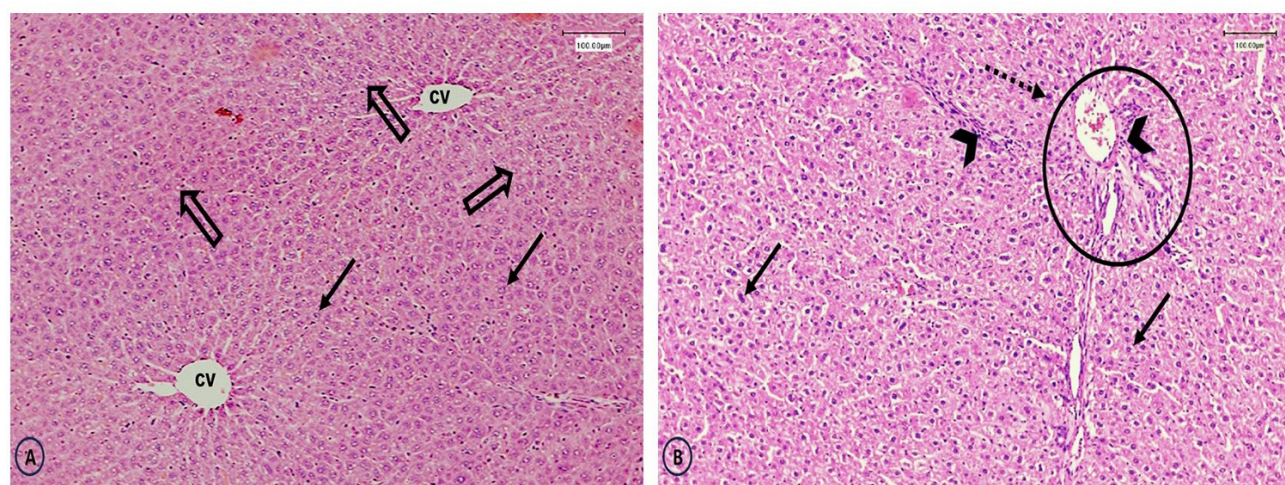


Fig. 5. Photomicrographs of hematoxylin and eosin-stained liver sections from the fructose + CANA group. (A,B) Numerous normal hepatocytes with vesicular nuclei (arrows) radiate from CVs. A few vacuolated hepatocytes (hollow arrows), as well as hepatocytes with dark acidophilic cytoplasm and pyknotic nuclei (dotted arrows), are observed. Inflammatory cell infiltrates (arrowheads) in the vicinity of portal areas (encircled) and between hepatocytes are also evident (H&E stain; scale bar = 100 μ m; 200 $\times$).

4. Discussion

This study investigated the metabolic and organ-specific effects of administering 20% fructose in drinking water to rats, focusing on body weight, blood pressure, random blood glucose, lipid profile, and liver and kidney function parameters. Furthermore, the prophylactic potential of CANA and the botanical SAE and SIE was assessed in preventing fructose-induced MetS.

Quantitative phytochemical analysis indicated that SIE is richer in TPC, whereas SAE exhibits slightly higher

TFC. Our data fell within the range reported in previous studies; however, some differences were observed, which may be attributed to extraction conditions, harvesting season, or methodological variations. In the present work, the TPC of SIE was quantified as 146.12 ± 0.09 mg GAE/g extract, which is lower than the value reported by Al-Omar et al. [44] (360.0 mg GAE/g). Conversely, it is higher than other previous reports, in which the TPC was calculated relative to the whole plant material rather than the crude extract [27]. Regarding the TFC, the current findings reported

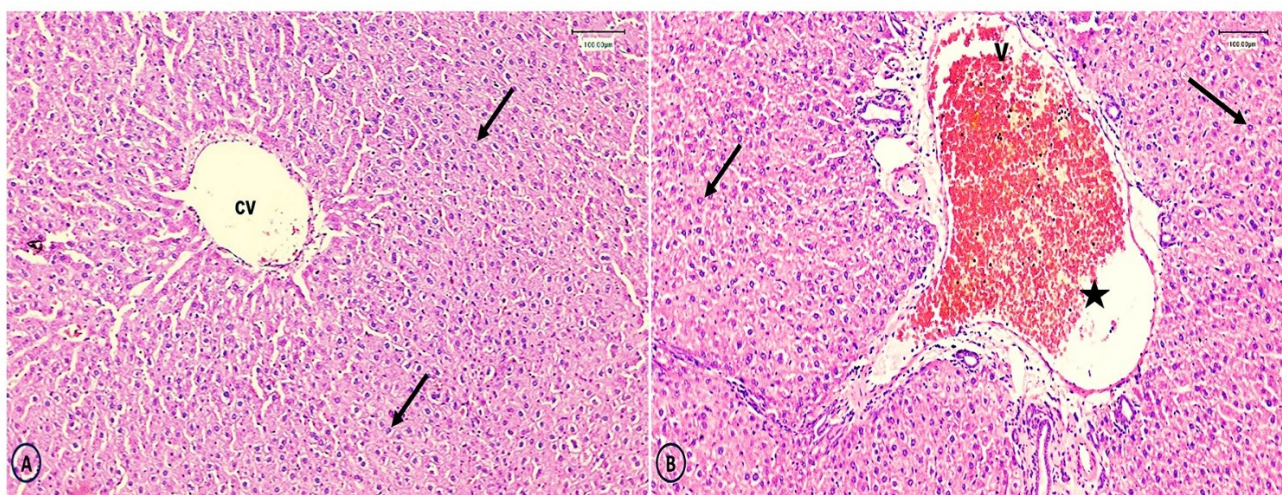


Fig. 6. Photomicrographs of hematoxylin and eosin-stained liver sections from the fructose + SAE group. (A,B) Most cells appear as normal hepatocytes with vesicular nuclei (arrows) radiating from the CVs. Dilatation and congestion (star) of the V can also be observed (H&E stain; scale bar = 100 µm; 200×).

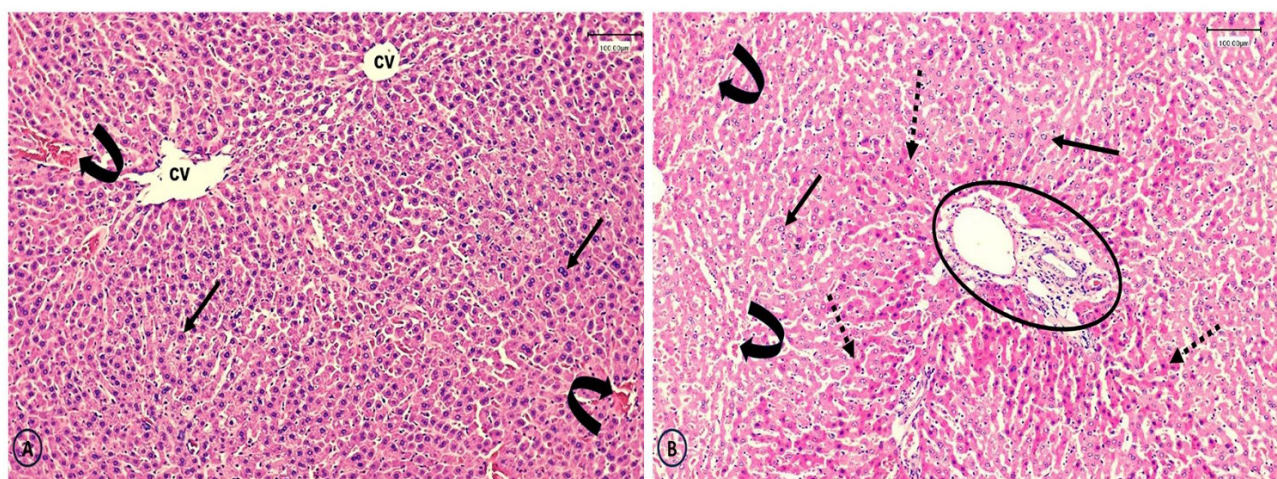


Fig. 7. Photomicrographs of hematoxylin and eosin-stained liver sections from the fructose + SIE group. (A,B) Numerous normal hepatocytes with vesicular nuclei (arrows) radiate from the CVs. Residuals of hepatocytes with dark acidophilic cytoplasm and pyknotic nuclei (dotted arrows) that surround the portal area (encircled) are observed. Areas of extravasated erythrocytes are also noted between hepatocytes (curved arrows) (H&E stain; scale bar = 100 µm; 200×).

a TFC for SIE (63.80 ± 0.20 mg QE/g extract) that exceeds a previous report [27] and is comparable to the value reported by Al-Omar et al. [44] (70.50 mg RE/g). For SAE, the present TPC and TFC values (81.20 ± 0.30 mg GAE/g extract and 67.60 ± 0.18 mg QE/g extract, respectively) are notably higher than those reported in earlier studies [45].

Comparative targeted HPLC profiling revealed distinct phenolic compositions for both extracts and confirmed that each extract possesses a characteristic phenolic profile relevant to the management of MetS. Notably, this is the first report describing the phenolic profile of SAE. The analysis identified gallic acid as the predominant phenolic acid, accompanied by moderate levels of chlorogenic, caffeic, coumaric, ferulic, and rosmarinic acids. The flavonoid

fraction was characterized by catechin, quercetin, naringenin, and rutin.

In contrast, the SIE profile was notably enriched in phenolic acids, particularly syringic and ferulic acids, as well as the flavonoids catechin and quercetin. A previous HPLC analysis of the hydrolyzed methanol extract of *S. imbricata* reported 21 phenolic acid and flavonoid constituents, among which coumaric acid and quercitrin were the most prevalent [27]. Remarkably, several of the identified phenolic acids, particularly gallic acid, ferulic acid, and caffeic acid, have been reported to be effective in managing MetS [46,47]. Similarly, the detected flavonoids, including catechin and quercetin, have been reported to have therapeutic potential in alleviating key manifestations of MetS

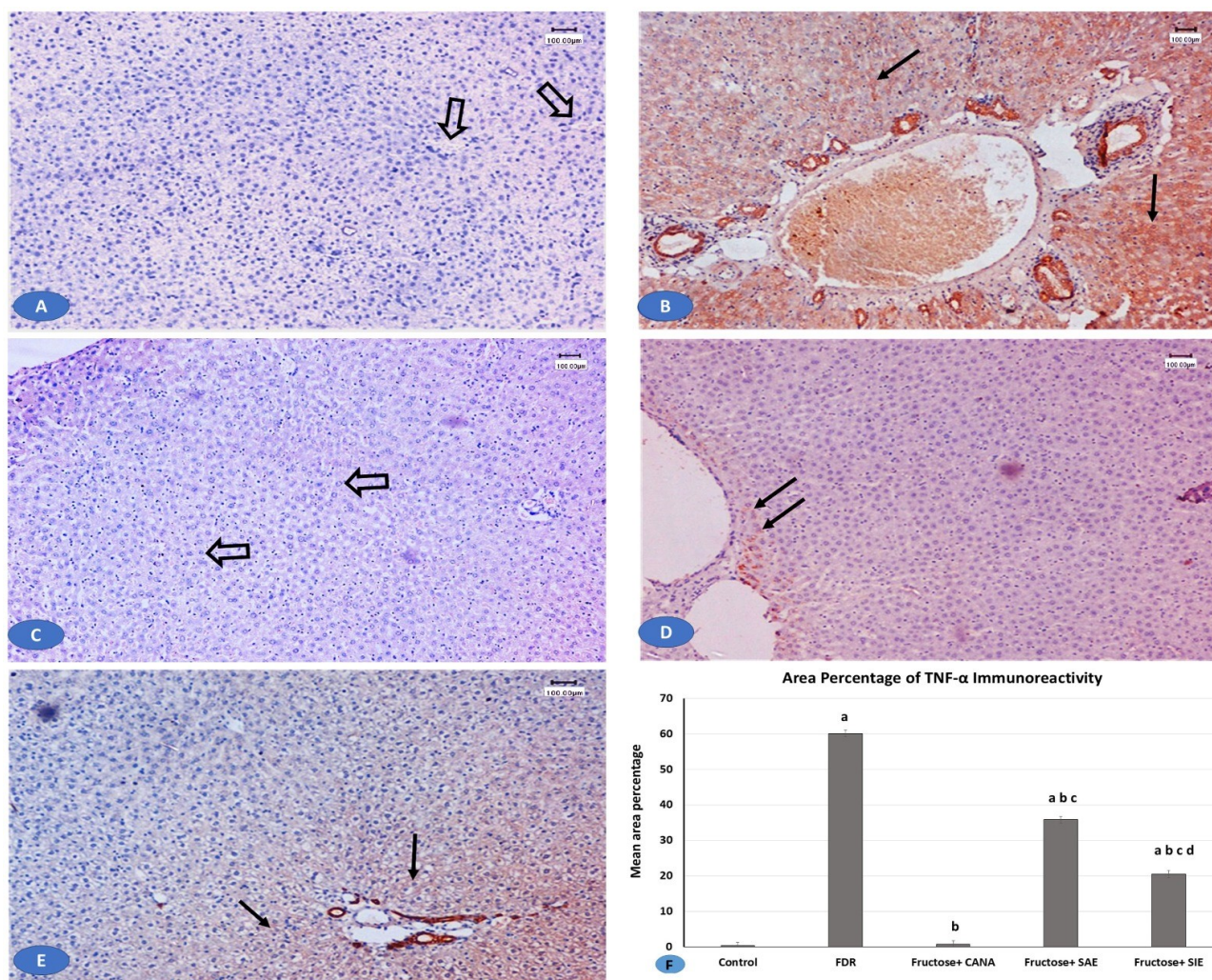


Fig. 8. Photomicrographs of immunohistochemical staining for tumor necrosis factor- α (TNF- α) in the different experimental groups. The normal control group (A) shows negative immunoreactivity in hepatocytes (hollow arrows). The fructose group (B) exhibits strong cytoplasmic immunoreactivity for TNF- α (arrows). The fructose + CANA group (C) shows negative hepatic immunoreactivity for TNF- α (hollow arrows) in the majority of hepatocytes. The fructose + SAE group (D) shows diminished cytoplasmic immunoreactivity (arrows). The fructose + SIE group (E) shows mild cytoplasmic immunoreactivity for TNF- α (arrows) (TNF- α immunohistochemical stain; scale bar = 100 μ m; 200 $\times$). Comparison of the mean area percentage $\pm$ SD of TNF- α immunoreactivity in all experimental groups (F). The histogram shows a significant increase in TNF- α immunoreactivity in the FDR group compared with the control group, and a significant decrease in all treated groups compared with the FDR group ($p < 0.05$). A significant increase was observed in all treated groups compared with the control group ($p < 0.05$), except for the fructose + CANA group, which was comparable to the control group. A significant decrease in TNF- α immunoreactivity in the fructose + CANA group compared with both the fructose + SAE and fructose + SIE groups, as well as a significant difference between the fructose + SAE and fructose + SIE groups, was also observed ($p < 0.05$). ^a Significant difference compared with the normal control. ^b Significant difference compared with the FDR group. ^c Significant difference compared with the fructose + CANA group. ^d Significant difference compared with the fructose + SAE group. Values are considered significant at $p < 0.05$.

[48]. Collectively, these phytochemical profiling results suggest that the observed bioactivities of both extracts may be attributed to the synergistic actions of their rich and diverse phenolic constituents.

Contrary to studies suggesting no significant effect of fructose on body weight in mice [49] or rats [50], our results demonstrated significant weight gain in the FDRs,

consistent with previous reports [51,52]. Treatment with CANA significantly reduced weight gain, consistent with previous reports [53,54]. FDRs developed hypertension, demonstrated by elevated SBP and DBP; this aligns with reports linking high fructose intake to activation of sodium–chloride transporters, suppression of vasodilators, and stimulation of the renin–angiotensin system [55,56,57]. The

CANA-treated group exhibited significant reductions in blood pressure compared with the FDR group, consistent with previous reports [58,59].

A significant increase in RBS was observed in the FDR group, reflecting fructose-induced insulin resistance and glucose intolerance [52]. Treatment with CANA significantly improved glycemic control, consistent with prior studies reporting the antidiabetic potential of CANA [60,61]. FDRs also exhibited significant dyslipidemia, consistent with the previously reported lipogenic and insulin resistance-promoting effect of fructose [62,63]. These lipid abnormalities were significantly improved by all treatments. Although some earlier findings did not detect changes in lipid profile in fructose-fed rats [64], our results are consistent with more recent evidence. The lipid-lowering effect of CANA observed here is also aligned with clinical studies reporting improved lipid profiles in T2DM patients [65,66]. Significant elevations in ALT, AST, creatinine, and urea were detected in the FDR group, indicating hepatic and renal dysfunction and aligning with earlier studies [67,68,69,70,71]. However, some studies have reported that short-term fructose overfeeding does not alter AST or ALT [72]. Treatment with CANA reduced these biomarkers. The hepatoprotective effect of CANA and the improvement in kidney function observed in the CANA-treated group are consistent with previous reports [73,74,75].

Natural products from plant and animal sources represent powerful tools for combating multifactorial diseases such as MetS. The versatile bioactive constituents in herbal medicines and their multiple mechanisms of action support their potential use in evidence-based management of several disorders [76,77]. Notably, to our knowledge, this is the first study to evaluate the efficacy of SAE and SIE in managing MetS. A review of the available literature revealed no prior reports examining the pharmacological effects of SAE or SIE on body weight or blood pressure in MetS models. Nevertheless, *S. imbricata* (syn. *S. baryosma*), along with other *Salsola* species such as *S. collina* and *S. richteri*, has traditionally been used to manage hypertension. Our findings provide supportive scientific evidence for these traditional uses of SIE [78]. The disturbed lipid profile observed in the FDR group was notably alleviated by both SAE and SIE. To our knowledge, this is the first report investigating the effects of these two plant species on dyslipidemia. With respect to kidney and liver function parameters, the extracts were found to mitigate only the elevated ALT and AST levels. These observations are consistent with previous studies documenting the hepatoprotective effects of *S. imbricata* [79,80].

Oxidative stress plays an important role in the development and progression of MetS [81,82,83,84,85,86,87]. Fructose overfeeding increases reactive oxygen species (ROS) production, while chronic hyperglycemia and dyslipidemia further enhance superoxide generation [87]. In the present study, FDRs exhibited reduced SOD levels, con-

sistent with previous reports [88,89]. In contrast, CAT and GPX activities did not differ significantly from those of the NC group, in contrast to previously reported findings [90]. MPO levels were significantly elevated in the FDR group, further supporting the role of high-fructose diets in promoting oxidative stress and inflammation [91].

Treatment with CANA resulted in non-significant increases in SOD and CAT activities compared with the FDR group, whereas GPX activity was significantly increased and MPO levels were significantly reduced. These findings suggest partial attenuation of fructose-induced oxidative stress. Previous studies have reported that CANA reduces free radical production and enhances antioxidant enzyme activities, including SOD, CAT, and GPX [92,93]. The discrepancy between those reports and the present results may be due to differences in experimental design, treatment duration, dosage, or disease model. Nevertheless, the observed increase in GPX activity and decrease in MPO levels in the current study support the antioxidant and anti-inflammatory properties of CANA. Furthermore, CANA has been shown to reduce oxidative stress, inflammation, arterial stiffness, blood pressure, and body weight, suggesting potential cardiovascular and renal protective effects [94,95].

Similarly, SAE and SIE treatment produced non-significant increases in SOD and CAT activities, while significantly increasing GPX activity and reducing MPO levels compared with the FDR group. These findings support the antioxidant and anti-inflammatory potential of *S. imbricata* extracts and are consistent with previous reports demonstrating their protective effects against oxidative damage and inflammation [80]. In addition, methanolic extracts of *S. imbricata* have been shown to inhibit lipopolysaccharide-induced nitric oxide release from macrophages, further supporting their antioxidant activity [10,11]. Although the present study did not directly investigate the underlying mechanisms, these properties may have contributed to the observed effects and warrant further investigation.

The observed differences among antioxidant enzymes may reflect selective modulation of specific antioxidant pathways. GPX is closely associated with glutathione metabolism, whereas SOD and CAT primarily regulate the detoxification of superoxide and hydrogen peroxide, respectively [96]. Therefore, the significant increase in GPX activity observed in the CANA-, SAE-, and SIE-treated groups may indicate preferential activation of glutathione-dependent antioxidant defenses. Concurrently, the reduction in MPO levels suggests attenuation of oxidative stress-associated inflammatory responses.

Collectively, the three interventions demonstrated broadly comparable protective effects against fructose-induced oxidative stress by enhancing GPX activity and suppressing MPO levels. No significant differences in NAP3 levels were observed among the experimental

groups. This finding may reflect the absence of acute tissue injury in the present model. Furthermore, MPO release has been reported to inhibit neutrophil migration and accumulation within inflamed tissues, which may have contributed to the unchanged NAP3 levels observed in this study [97]. As NAP3 was evaluated as an exploratory biomarker, further studies are warranted to clarify its role and clinical relevance in MetS.

Histopathological examination revealed extensive cell death and cytoplasmic vacuolation, marked dilation and congestion of portal veins, erythrocyte extravasation, and inflammatory infiltration, in addition to strong cytoplasmic immunoreactivity for TNF- α in FDRs. These findings are consistent with several previous reports [98,99]. In contrast, CANA treatment exerted a clear ameliorative effect, in which the portal vein gradually returned to its original size, hemorrhage diminished, hepatocytes restored their normal appearance with normal nuclei, and hepatic TNF- α immunoreactivity became almost negative. This is consistent with earlier work indicating that CANA attenuates fructose-induced hepatic damage [53].

Noticeable improvements in hepatocyte morphology were also observed in fructose + SAE-treated animals, including reduced inflammation, decreased TNF- α expression, and normal hepatocyte regeneration. These findings align with those published previously [39]. SIE treatment restored the normal appearance of hepatocytes, with reduced inflammatory infiltration, few apoptotic hepatocytes, limited erythrocyte extravasation, and mild cytoplasmic TNF- α immunoreactivity. Similar results have been reported previously [80], highlighting the significant anti-inflammatory effects of SIE in acrylamide-induced hepatic inflammation.

5. Conclusion

To our knowledge, this study is the first *in vivo* comparative evaluation of the MetS-modulating effects of SAE and SIE in a fructose-induced rat model. Fructose administration successfully induced a MetS-like state characterized by metabolic, oxidative, and histopathological alterations. CANA, SAE, and SIE each exhibited protective effects against fructose-induced metabolic disturbances and oxidative stress. The antioxidant effects of the tested interventions were evidenced by significant increases in GPX activity and reductions in MPO levels. Collectively, the findings suggest that these interventions exert primarily preventive rather than therapeutic effects against the development of MetS and support the potential value of SAE and SIE as natural agents for mitigating metabolic and oxidative abnormalities associated with this condition.

6. Limitations and Future Directions

The present study has several limitations. First, the sample size was relatively small, and only male rats were used, which may limit the generalizability of the findings.

Second, key metabolic parameters, such as insulin levels and Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), were not assessed. Third, only a single dose of each extract was evaluated, precluding dose-response analysis. In addition, food intake was not monitored; therefore, its potential contribution to the observed metabolic changes could not be evaluated. Moreover, correlation analyses between biochemical, oxidative stress, and histopathological findings were beyond the scope of the present study. Hematological and histopathological toxicity assessments were not conducted, and acute toxicity evaluation was limited to 24 hours. Although HPLC characterization of the extracts was performed, further studies are needed to isolate and identify the active metabolites and elucidate the underlying molecular mechanisms.

Abbreviations

ALT, Alanine Aminotransferase; ANOVA, Analysis of Variance; AST, Aspartate Aminotransferase; CANA, Canagliflozin; CAT, Catalase; DBP, Diastolic Blood Pressure; FDR, Fructose-Drinking Rats; GPX, Glutathione Peroxidase; H&E, Hematoxylin and Eosin; HDL, High-Density Lipoprotein; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; HPLC, High-Performance Liquid Chromatography; LD₅₀, Median Lethal Dose; MPO, Myeloperoxidase; MetS, Metabolic Syndrome; NAP3, Neutrophil Activation Protein 3; NC, Normal Control; RBS, Random Blood Sugar; ROS, Reactive Oxygen Species; SAE, *Suaeda aegyptiaca* Extract; SBP, Systolic Blood Pressure; SD, Standard Deviation; SIE, *Salsola imbricata* Extract; SOD, Superoxide Dismutase; TFC, Total Flavonoid Content; TGs, Triglycerides; TNF- α , Tumor Necrosis Factor Alpha; TPC, Total Phenolic Content.

Availability of Data and Materials

The datasets generated during and analyzed during the current study are not publicly available but are available from the corresponding authors on reasonable request.

Author Contributions

Conceptualization: ESS, RAA, and EA; methodology: LMA, ARA, and AME; formal analysis: ESS, HOA, and AME; investigation: AHM, AYB HOA, and HMA; writing, original draft preparation: LMA, ARA, RAA, and AME; writing, review and editing: ESS, and EA; supervision: ESS. All authors have read and agreed to the published version of the manuscript. All authors contributed to editorial changes in the manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

All procedures were conducted in accordance with the ethical guidelines of the Qassim University Medical Ethics

Committee and with international ethical and regulatory standards for animal research in laboratory settings. Animals were treated in accordance with the National Research Council Guide for the Care and Use of Laboratory Animals. The Research Ethics Committee of Qassim University approved the research protocol (approval number 21-12-33). The study was carried out in accordance with the ARRIVE guidelines.

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Conflicts of Interest

The authors declare no conflicts of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at <https://doi.org/10.31083/IJP52146>.

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